Updates in Hypertension and Cardiovascular Protection
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Pietro Amedeo Modesti
Francesco P. Cappuccio
Gianfranco Parati *Editors*

Ethnic Diversities, Hypertension and Global Cardiovascular Risk

ESH European Society of Hypertension

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Updates in Hypertension and Cardiovascular Protection

The aim of this series is to provide informative updates on both the knowledge and the clinical management of a disease that, if uncontrolled, can very seriously damage the human body and is still among the leading causes of death worldwide. Although hypertension is associated mainly with cardiovascular, endocrine, and renal disorders, it is highly relevant to a wide range of medical specialties and fields – from family medicine to physiology, genetics, and pharmacology. The topics addressed by volumes in the series *Updates in Hypertension and Cardiovascular Protection* have been selected for their broad significance and will be of interest to all who are involved with this disease, whether residents, fellows, practitioners, or researchers.

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Preface

This book, which is part of the series on "Hypertension and related sequelae" published by Springer with the official endorsement and collaboration of the European Society of Hypertension, is intended for health personnel interested in improving knowledge and skills on cardiovascular risk of ethnic minorities in Europe.

Over the last few decades, the possibility for European health professionals to see patients originating from non-European countries has greatly increased, whereas cultural training on health needs of minority groups remains often limited and likely biased. Cardiovascular prevention for these new populations requires novel approach models now perceived as essentials by stakeholders to achieve a future reduction of healthcare costs and health inequalities. This book is therefore aimed at both improving the skills of health professionals and encouraging research activities in this special field.

Our special thanks to everyone who has been involved in the development of the book, to health workers, and to communities of minority groups who are jointly actively contributing to fill these gaps.

Firenze, Italy — Pietro Amedeo Modesti

Contents

Part I Ethnicity in the European Context

1 Multinational Populations in Europe: Migration Policies and Classifications of Migrants 3
Stefano Becucci

2 Migration, Communicable, and Noncommunicable Diseases: Are We Witnessing a Paradigm Shift? 17
Francesco Castelli, Maria Lorenza Muiesan, and Issa El Hamad

3 Inequalities and Health Policies in the European Countries 27
Gavino Maciocco

Part II Ethnic Disparities in Cardiovascular Disease

4 Ethnic Disparities in Stroke 35
Charles Agyemang and Pietro Amedeo Modesti

5 Intracranial Atherosclerosis in Asian Populations 45
Pietro Amedeo Modesti, Maria Boddi, and Sergio Castellani

6 Coronary Heart Disease Among Non-Western Immigrants in Europe 61
Pietro Amedeo Modesti and Ugo Fedeli

7 Hypertension and the Heart in Africa 75
Albertino Damasceno, Angela Woodiwiss, and Mahamoud Sani

8 Ethnicity and Hypertension-Related Target Organ Damage 95
Stefano Perlini

9 Chronic Kidney Disease: Global Burden and Perspectives for Africa 105
Faical Jarraya

10 Ethnicity and Atrial Fibrillation: A Counterintuitive Phenomenon 125
Andrea Colella and Pietro Amedeo Modesti

Part III Drivers Predisposing Ethnic Minorities to Cardiovascular Disease

11 Disparities in Hypertension in the Ethnic Minority Groups: Beneficial Aspects of Minority Ethnic Group Cultures 139
Pietro Amedeo Modesti, Charles Agyemang, Francesco P. Cappuccio, and Gianfranco Parati

12 Type 2 Diabetes in Ethnic Minority Groups in Europe 155
Karlijn A. C. Meeks and Charles Agyemang

13 Health Needs and Global Cardiovascular Risk of Chinese First-Generation Migrants in Europe: Which Peculiarities? 169
Pietro Amedeo Modesti, Maria Calabrese, Giorgio Galanti, and Piergiuseppe Cala'

14 Overweight and Obesity in Ethnic Minorities: Ethnic-Specific Cut-off Values of Obesity Indices 183
Aletta Elisabeth Schutte

Part IV Ethnic Specific Issues for Prevention and Treatment of Hypertension and Global CV Risk

15 New Notions on Salt Sensitivity 191
Gert van Montfrans and Lizzy M. Brewster

16 Body Image Perception in Ethnic Minorities: Implications for Prevention 201
Emanuela Gualdi-Russo

17 Risk Assessment of Future Type 2 Diabetes and Implication for Prevention 207
Pietro Amedeo Modesti, Maria Calabrese, and Giorgio Galanti

18 Screening Strategies for Type 2 Diabetes and Risk Stratification in Minorities 217
Andre Pascal Kengne

19 Cardiovascular Risk-Assessment Models and Ethnicity: Implications for Hypertension Guidelines 235
Dong Zhao, Gianfranco Parati, and Pietro Amedeo Modesti

20 Antihypertensive Drug Therapy in Patients of African and South Asian Ethnicity: A Systematic Review 243
Lizzy M. Brewster, Gert A. van Montfrans, and Yackoob K. Seedat

21 Cardiovascular Risk Factors in Migrants: Beyond the First Generation 271
Mohamed Bamoshmoosh

22 Hypertension in Pregnancy and Related Health Outcomes in European Ethnic Minorities 299
Alessandra Modesti and Felice Petraglia

23 Ethnic Differences in Left Ventricular Remodelling in Athletes: Implications for Preparticipation Visit 309
Giorgio Galanti, Benedetta Tosi, and Pietro Amedeo Modesti

Part I

Ethnicity in the European Context

1 Multinational Populations in Europe: Migration Policies and Classifications of Migrants

Stefano Becucci

1.1 Introduction

This introductory chapter, written by someone who is not an expert in medical issues, aims to highlight three aspects. The first refers to a descriptive and interpretative representation of migratory processes that have affected the countries of the European Union in recent years. The second examines the presence of migrants not belonging to the European Union according to the terminology and conceptual categories existing in reference to current legislation and the sociology of the migrations. The third and final part seeks to highlight the social, economic and institutional factors which, with a degree of plausibility, can be connected to the manifestation of various types of health problems the migrant population encounters in the new country of residence, problems which perhaps find an environment that fosters their development in predisposed physical constitutions, but that then (also) have the opportunity to develop and assume greater intensity in relation to the new social environment in which each migrant comes to reside. The three parts into which the chapter is divided therefore concern migrants in the countries that make up the European Union, with a particular focus on non-EU citizens.

1.2 Migratory Processes Towards the European Union: Some Figures

The European Union, even before it expanded to include the countries of Eastern Europe between 2004 and 2007, held considerable appeal for populations from third countries. Here we cite some statistics distinguishing between foreigners from

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the European Union and those not belonging to the Union. But first, clarification should be provided on the method relating to the statistical survey sources. Only in recent years has Eurostat, the European agency that collects data from national statistics institutes, been able to compare data between different states of the European Union. Years ago, the statistical survey criteria followed by the states of the Union differed from each other considerably. They were based on one of the following recognition criteria: residence permits issued to citizens of other countries, the number of foreign residents present in the country and, finally, data from populations censuses [1].

Residence permits provide an updated snapshot of the foreign population present in a country, with the caveat, however, that there is always a time delay, depending on the red tape encountered in each country, between the moment a migrant requests a residence permit and when that request is received and then entered into each statistical category. For example, in Italy, a country on which we have more information, in limited cases even 8–10 months can go by before a residence permit is renewed. Another important aspect is that the number of residence permits issued by a member state, as the European Union has gradually expanded, does not allow us to understand the overall extent of the migratory phenomenon. This is because those who were once required to request an entry visa were no longer required to do so once their state became part of the European Union. In this sense, population registers are the most comprehensive, with the proviso however that they tend to underestimate the number of foreigners not belonging to the European Union. This is because not all those who have an entry visa (non-tourist) decide to register as resident at the registry offices of the country they are in. In this regard, population censuses are more reliable, the problem is though that they are not carried out each year but instead with intervals of years between each one.

Taking into consideration the limits just highlighted, the number of foreigners resident in a state other than their own, at the end of 2015, came to 35,140,213, corresponding to 7% of the 508,450,856 citizens of the 28 states of the European Union [2]. Among all the foreigners living in a new country of the European Union, again in 2015, those from countries outside the European Union numbered 19,837,930, representing 56% of the total.

With a population tending to be equally weighted in terms of gender, the states in the western area of the European Union host, as is to be expected, the largest number of foreigners, whether they belong to the European Union or not. In absolute values referred to 2015, most foreigners reside in the European countries of the original western area, that is, the EU15. They are located for the most part in 5 countries: in decreasing order, Germany hosts 7,539,774 people, the United Kingdom 5,422,094, Italy 5,014,437, Spain 4,454,354 and France 4,355,707. In percentage terms, Germany has 21.5%, the United Kingdom 15.4%, Italy 14.3%, Spain 12.7% and France 12.4%, giving these five countries 77.6% of all foreigners present in the European Union.

As regards those from non-EU countries, we find a very similar situation, however, with the difference that the order of the 5 countries changes: Germany 4,055,321 (20.4%), Italy 3,521,825 (17.8%), France 2,869,882 (14.5%), Spain

2,505,196 (12.6%) and the United Kingdom 2,434,022 (12.3%). These countries host 77.6% of the almost 20 million foreigners not belonging to the European Union on account of their nationality.

With the gradual expansion of the EU, the internal migratory processes and those from outside the territory of the Union have increased, with particular concentration, as we have seen, in the western states. To understand the growth trend, we can consider the historical series from the end of 2006 to 2015. In the first year of reference, the number of foreigners (EU and non-EU) was 29,733,543, 6% of the resident population (at the time the EU27) [3], which then in 2015 reached the values mentioned above, with 18% growth on 2006.

In the last decade, Italy has seen the highest growth, 71%, going from 2,938,922 in 2006 to 5,014,437 in 2015, followed by the United Kingdom (+ 48%), from 3,659,900 to 5,422,094; France (+ 19%), from 3,650,100 to 4,355,707; Germany (+ 4%), from 7,255,949 to 7,539,774; and finally Spain, down by 3%, from 4,606,474 to 4,454,354, a country that was affected by the financial crisis of 2008 more so than others, above all in the construction industry. Other countries in the western area, like Finland and Denmark, have significant growth percentages, respectively 80% and 52%, but with essentially contained values in absolute terms (in 2015 Denmark hosted 422,492 foreigners; Finland 218,803).

From 2006 to 2015, the countries of Eastern Europe had very high growth percentages: Romania (+ 241%), Bulgaria (+ 157%), Slovakia (+ 92%), Slovenia (+ 90%) and the Czech Republic (+ 54%). At the same time, however, in 2015 their values were contained in absolute terms. The presence of foreigners in the Eastern European countries includes the minimum value of 61,766 foreigners in Slovakia and the maximum value of 457,323 in the Czech Republic. Slovenia (101,533 people), Romania (88,771) and Bulgaria (65,622) are in intermediate positions. The eastern countries of the European Union have the highest percentages of migrant growth in their territories, but this is essentially due to the fact that since they joined the EU they have had extremely contained absolute values. Only in recent years have they seen the foreign population grow within their territories.

1.3 The Categories of Migrants

While at first glance it might seem simple to provide a thorough classification of migrants, in actual fact, with more careful examination, what causes definition problems is the very conceptual category of “migrant”. According to the official definition by the United Nations, migrants are those who “move from a country of habitual residence and reside in a new one for more than one year” [4]. This definition does not take account of all those who, for various reasons, move to a different country other than their own for less than 1 year, for example, in the case of seasonal workers. Moreover, together with a statistical distinction, we must take into account a sociological categorization which refers to the different social connotation attributed to the term “migrant”. In this sense, some categories of people, despite moving to and residing in the new country, will not fall under the category of migrant as that

figure is socially understood. This means that the statistical representation only partly reflects the social one attributed to the figure of the migrant.

Let us take as an example those who regularly spend a varying amount of time abroad over the course of a year, alternating months spent in the new country of residence with months spent in their habitual country. In this regard, Italian, French and English pensioners, as well as those from other countries of Northern Europe, move to states where the cost of living is significantly lower. Thanks to the pension acquired in their country of origin, they see their purchasing power and quality of life significantly increase. Then there are all those who spend a period of time abroad for health reasons, a stay which, depending on the cases, may last for months. Finally, let us take the case of footballers from South America who join European teams. These people are unlikely to be considered "migrants" and even less so "non-EU citizens".

Thanks to the possibility nowadays of travelling at low cost from one country to another, the category of migrant seems increasingly less appropriate to understand the movements of the population on a global scale. Moreover, only some of those who move from one country to another are socially defined as "migrants". Therefore, beyond a mere legal classification that distinguishes between nationals and foreigners, specific social meanings come into play which place some of the foreigners present in each European country under the social definition of "migrant". The latter, by definition, are also foreigners, but this does not mean that all foreigners are considered migrants.

In more detail, the category of migrant is usually associated with social representations that refer to negative connotations. There are various reasons for this negative connotation. Migrants are perceived by a part of the population of the host country as a potential threat to the status quo, as a destabilizing and disturbing element of the existing social order. Proof of this is the approval, aided by the fear sparked by terrorist attacks of Islamic origin that have occurred in various European countries in recent years, that parties with a xenophobic leaning have acquired lately in the European sphere. Similarly, Britain's decision to withdraw from the European Union following a referendum (referred to as Brexit) can largely be interpreted as a choice motivated by the fear represented by the arrival of new migrants in the country.

With the conceptual and interpretative limits just mentioned regarding a comprehensive classification, there are various categories of migrants. The first important distinction refers to the whether or not they are citizens of the European Union. In this sense, citizens of the European Union do not require entry visas within the territory of the Union, they have access to the same services provided for the citizens of another country, and, after 4 years of regular residence in the new country, they enjoy political rights at local level.

The second distinction refers, on the contrary, to citizens from countries that do not belong to the EU and, more specifically, from developing countries considered to have high migratory pressure. Foreigners from these areas are divided into different groups:

1. The so-called economic migrants, namely, those who move to another country in order to find work. These are then divided into seasonal workers and workers who have a residence permit for over 1 year. The latter group includes those who come under the category of workers specialized in specific production areas.
2. Migrants who come to the new country on a family reunification permit.
3. Those who transfer to the new country to study.
4. Those who come to the new country for health reasons.
5. Asylum seekers and refugees fleeing from war and persecution of various types.
6. Illegal immigrants who enter the new country through illegal means or, as more often happens, on a tourist permit and then remain in that country beyond the limit set by the tourist visa.

In light of the foregoing, we can detect a civic stratification of foreigners present in the European Union [4]. At the top are the citizen-migrants of the European Union who are guaranteed the same rights as nationals. These foreigners also have active and passive suffrage in local political elections.

They are followed by foreigners from developing countries, whose entry visa sets a time limit on access to the welfare system existing in each country. In other words, access to social services is as a rule provided for all those whose status is regular. Holders of temporary entry visas may access them with all the limitations relating to their short stay in the host country. On the contrary, foreigners not belonging to the European Union who have the status of permanent residents are equal to European citizens in terms of access to the welfare systems and, in various countries, they have the right to vote at local level.

As regards this latter aspect, most European countries, 21 out of 28, permit non-EU foreigners to participate in local political elections. The general condition is that the non-EU citizen must hold a permanent residence permit. This permit is granted after a certain period of time, which however varies considerably from country to country: from 10 years in Slovakia to a minimum of 6 months in Ireland. For many of these countries, in each case, the time frame of reference ranges between 2 and 3 years as a necessary condition to obtain a permanent residence permit. Moreover, the right to vote at local level is only guaranteed in some countries for foreigners of certain nationalities: Great Britain grants this right to citizens of Commonwealth countries, Pakistanis and Irish citizens; Finland to Scandinavians and Icelanders; Malta to British citizens; and Portugal to Portuguese-speaking foreigners from former colonies [3, 5, 6]. On the contrary, countries that do not allow any type of political participation at local level for non-EU citizens—therefore making the right to vote dependent on the acquisition of citizenship of the host country—represent a minority. They are Austria, Cyprus, Croatia, Poland, Greece, Italy and Romania.

While EU internal migrants are found at the top of this civic hierarchy, irregular migrants are at the bottom. According to recent evaluations developed by Frontex, the European agency tasked with tackling illegal immigration, at the end of 2015, there were 1,822,337 illegal entries of people within the territory of the European Union. Most of these people, over one million, arrived by sea along the two routes

of the eastern and central Mediterranean, while the rest travelled over land along the Balkan route. Many of these people, however, by admission of the same European agency, were fleeing their country in order to seek refuge and protection in the new European state [2].

Illegal migrants are those who by law have no access, due to their irregularity, to any type of institutional support or health service, with the exception of urgent medical care provided by emergency health services.

Out of the six categories of migrants mentioned above, the most important in terms of number and social significance are the so-called economic migrants and asylum seekers. We will focus our attention on these two categories.

As regards labour migrants, each member state has followed its own standards of conduct. In the early 2000s, Germany encouraged the recruitment of a skilled workforce, such as IT engineers from India. In parallel to this form of recruitment, like other countries of Western Europe, it has maintained the annual system of quotas aimed at inserting seasonal workers into the national production system. Among the countries of the western area, it was more decisive about choosing to recruit a skilled workforce, while other countries, in particular those in the southern area, based the recruitment of the workforce on the annual quota system of seasonal workers to be used in sectors such as agriculture, catering, tourism and the hotel industry. In a broader sense, the same bodies of the European Union, particularly the Commission, at the end of 2012 established a special entry visa known as the "blue card" aimed at recruiting a qualified workforce. However, due to resistance from each member state, preferring instead to manage the recruitment of the workforce within their national territories independently, the blue card system has not yet had appreciable results [2].

As regards those seeking asylum and refuge, according to the latest evaluations by the UN Refugee Agency [7], at the end of December 2015, there were 1,144,730 refugees in the 28 states of the European Union, while at the same time there were 647,767 people, that is, pending cases, that had applied for refugee status.

In part, factors that have led to a consistent increase in asylum applications in recent years in the European Union can be attributed to the changes that have occurred in some countries bordering the Mediterranean, such as Libya, and countries that are close to it, such as Syria. In 2011, the killing in Libya of the dictator Gaddafi by his opponents triggered the start of a civil war that saw various opposing factions fighting for control of the country. In the same year, a civil war broke out in Syria between the dictator Bashar al-Assad and rival military factions, in addition to the gradual settlement in the country of the fundamentalist Muslims of the so-called Islamic State. With the outbreak of armed conflict, almost 12 million people, amounting to half the Syrian population, were forced to move from their homes. Around seven million of them found refuge in neighbouring countries or, alternatively, they reached the countries of the European Union. According to estimates by the UN Refugee Agency [7], from April 2001 to November 2015, the countries of the European Union received 813,599 applications for asylum from Syrian asylum seekers: most of the arrivals within the European Union occurred in 2015, in that the previous year there were 138,000

applications. In any case, the approximately 800,000 asylum seekers present in EU countries represent no more than 10% of all the Syrians who found refuge in neighbouring countries. In 2015, Turkey took in 1.8 million, Libya 1.2 million, Jordan 684,000, Iraq 251,000 and Egypt 132,000.

More generally, the European states that host the highest number of refugees are, in descending order, France, 264,972 people (23% of the total number of refugees); Germany, 250,299 (22%); Sweden, 142,207 (12%); the United Kingdom, 117,234 (10%); Italy, 93,715 (8%); the Netherlands, 82,494 (7%); and Austria, which hosts 60,747 refugees (5% of the total). These seven countries, all in the western area of Europe, took in 87% of the refugees present in the EU28. Finally, the very high number of pending cases should be noted, with the people for the most part being hosted in Germany, which has single-handedly received 311,551 asylum seekers waiting to know whether or not their application will be accepted. This number alone represents 48% of all the pending cases within the EU28, evidencing, moreover, the attention the German state has long attributed to political refugees—attention that dates back to the time of the construction of the Berlin Wall in 1961 and that increased with its collapse in 1989 when Germany in a few years came to host around one million people, referred to as the "ethnic Germans" who hailed from the Soviet Union and other Eastern European countries. Germany provided these people with the same social and welfare protections (healthcare, unemployment benefits and access to social housing) that German citizens born and raised in the country were entitled to [8].

Other countries of the Southern Mediterranean have a relatively low number of both refugees, 7304 (Greece) and 5798 (Spain), and asylum seekers, 29,157 (Greece) and 11,020 (Spain). These numbers, essentially low, suggest that these countries were only partly involved in the illegal entry route of asylum seekers from the African continent. This is true for Spain, while Greece, despite having been as involved as Italy in the migratory phenomenon, has rather seen many of those who would go there but then do anything to reach other countries in the western area of Europe—all this in spite of the current agreements of the Dublin Regulation (at present subject to possible review within Europe) which sets an obligation for the asylum seeker to remain in the first country of entry, the country in which they submitted an application to obtain refugee status. In actual fact, these people did everything possible to reach the western European countries where they already had family ties that could guarantee them essential support during the new arrival phase or, in any case, where they presumed that once they had arrived, they would be able to find greater opportunities to improve their socio-economic condition.

1.4 Analysis of Some Western Countries of the European Union

Within the original countries of the European Union, that is, Europe comprised of 15 member states, there are different methods of entry and integration into the foreign population. In this sense, we can refer to a historical model of immigration represented by the countries of Northern Europe, and in particular Germany, France,

Great Britain and the Netherlands. These countries had some similarities and some specific differences, at least until a certain period, roughly speaking from the postwar era up to the 1970s.

Then, as some scholars have long pointed out, we have the Mediterranean model of immigration, which involves countries in the western area of the European Union, such as Portugal, Spain, Italy and Greece [9, 10]. Finally, there are the countries of Eastern Europe that have joined the EU in the last 10 years, which however, as we have seen, do not have significant numbers of migrants within their territories. For this very reason, in the following, we will highlight the main characteristics of the countries of Northern Europe listed previously and then go on to examine those of the Mediterranean area.

As regards the models of Northern Europe and the Mediterranean area, the analysis will focus on the different systems of entry and residence for migrants and the criteria for obtaining citizenship in the country in which they reside. These analyses will take into account distinct time phases which, from the postwar period onwards, distinguished the different approaches of European countries to immigration. Some periods will be covered in more detail: from the end of the Second World War to the early 1970s, when the first serious oil crisis occurred in 1971–1973 which led many countries in Northern Europe to review their migratory policies, to the end of the 1980s, when even the states of Southern Europe went from being, albeit modestly in the initial phase, labour-exporting countries to immigration countries, up to the current phase of the EU28.

Since the postwar period, France has been an immigration country. It has recruited, through government agencies set up for this specific purpose or by delegating the task to government-linked bodies, migrants from the countries of Southern Europe as a workforce to be employed in the reconstruction and industrialization of the country. Together with Italian, Spanish and Greek migrants, foreigners arrived in the country from Maghreb, or Tunisia, Algeria and Morocco. This is due to the colonial links France has with these countries and the type of French legislation that provided the possibility, as long as these countries were colonies, for Tunisians and Algerians to move to France and be able to reside there. The recruitment of migrants from Maghreb followed in the 1960s and 1970s, well after Algeria and Tunisia acquired independence from France. In fact, if we examine the foreign component present in France at the end of the 1990s, we can see that a considerable proportion come from North Africa, with Algerians making up, among migrants from Maghreb, the most numerous national group (614,200), while there were over 200,000 Tunisians [1].

The French system, due to the national history and culture dating back to the revolution of 1789, belonged to the "assimilationist" model, on the basis of which foreigners found it easy to acquire citizenship. The fact is, however, that they gradually lose their original specific cultural characteristics and assimilate, in cultural and social terms, into the new host society. This is a type of migrant integration that is largely described in terms of assimilation into the French society. The acquisition of citizenship is governed by the criterion of jus soli, a principle that guaranteed easy acquisition of French citizenship. Thanks to this opportunity, many migrants, in the

order of tens of millions of people, have become French citizens in a relatively short time due to the sole fact that they were born on French soil. It is no coincidence that around one quarter of the current French population has foreign origins, precisely due to the easy acquisition of citizenship [8].

It should be said that, to a large extent, this involves de jure more than de facto recognition, as the recurring revolts that occurred from the 1990s onwards in the outskirts of French metropolises highlighted. In view of a situation of socio-economic disadvantage concentrated in the outskirts of large cities, government agencies put in place non-specific social policies (that is not directly aimed at certain "foreign" communities) even if, in actual fact, they concerned the children of second and third generation migrants, that is, those who experienced problems in terms of educational attainment, professional success and generally speaking difficulty in starting an independent social promotion path.

Germany, on the contrary, represents the European example that most adheres to the so-called *Gastarbeiter* model, namely, the guest worker. Since the postwar period, it has also implemented a method of recruiting the workforce into the national manufacturing industries. However, this occurs under a migratory policy model that considers foreign workers as a temporary component of German society. Together with migrants from Italy, Greece and other Southern European countries, since the 1970s, the principal foreign community in terms of presence is the Turkish one, whose migrants arrived on German soil thanks to intergovernment agreements between Germany and Turkey. In 1998, there were over two million citizens, the most numerous group corresponding to 29% of all foreigners present in Germany [1].

Hence, according to an eminently functionalist conception of immigration in relation to the requirements of the German labour market, foreign workers are required to stay in the country for a limited period, corresponding to the duration of the employment contract which coincides with the duration of the residence permit. Housing provided thanks to a contribution from the employer was built for people expected to return to their country within a short period of time. Acquisition of citizenship, at least until the reform of this institution in 1999, was only possible through jus sanguinis, that is, through German descent or through marriage with a partner of German nationality. The intention of successive governments over the years was to establish a rotation model of immigration based on the continuous replacement of the workforce to be recruited from other countries, a model that establishes, in line with its initial assumptions, strong restrictions on family reunification and therefore on the possibility for foreign migrants to rebuild new nuclear families within German society. In fact, family reunifications were not permitted until 1981 when new regulations were introduced which on the contrary facilitated them [8].

This conception highlights its full limitations at the end of the last century when it did not take into account two easily foreseeable aspects. Firstly, that employers have a need to rely on workers they already know and who, through the work they have done up until then, have received training and are qualified from a professional point of view. The rotation of the workforce initially envisaged and regulated by the

provisions that govern the entry and residence of foreign workers ends up being counter-productive for the German entrepreneurs themselves. Secondly, "host workers", even with the limitations and difficult circumstances in which they find themselves, actually become stable: they put down roots in the host country where they establish new families and have children who grow up in the new country, thereby having all the requirements, at least potentially, to feel part of German society. Thereafter, with the citizenship reform which introduced the principle of jus soli and *jus domicile*, German policy and society finally seem to recognize that millions of foreigners who have lived in Germany for decades must be given equal national dignity.

The third reference model we can find in literature on migrations in Europe is referred to as "multiculturalism" or, another similar variant, "pluralist", which inspired the migratory policies of countries such as Great Britain and the Netherlands [8, 11]. Unlike the countries mentioned above, the reference model followed is geared, on the one hand, around stabilizing the presence of foreigners and, on the other, safeguarding their specific identity and cultural characteristics, hence access to forms of institutional support sanctioned by recognition of being a "minority to be protected". Specific social policies for migrants were implemented through programmes aimed at overcoming discrimination originating from xenophobia, which they could encounter in the host country. This approach was further confirmed in regard to religious freedom in the public sphere and the development of school programmes that account for the specific identities of the minorities present in the country. Moreover, the associations established by the corresponding immigrant community were the main point of reference for government agencies in the management and delivery of specific social policies targeting migrants belonging to that community.

However, it should not be forgotten that only thanks to institutional intervention, which in itself guides and selects the minorities to be protected, can a foreign community enjoy a sort of safeguarding of its cultural and religious identity. Moreover, the direct endorsement of social policies aimed at certain foreign communities implies the likely risk of considering the set of individuals belonging to that community as a homogeneous group. An aspect that does not take into account the individual requirements and needs of each individual. This approach also creates conditions that, based on social policies conceived with anti-discriminatory intentions, can result in forms of separation and the self-ghettoization of disadvantaged minorities.

Finally, let us briefly examine the main characteristics of the migrant integration model in Southern Mediterranean countries. This involves, on the one hand, Italy, Spain and Greece, and, on the other, an implicit model of the entry and integration of non-EU foreigners into the respective national territories. We speak of an "implicit" model because, as we shall see shortly, it has to do with a migratory phenomenon to which the arrival countries are subjected rather than one they have requested and regulate. In the first place, these countries became places of immigration rather late, that is, from the second half of the 1980s, in comparison

with other Northern European countries with a much longer migratory tradition. Secondly, the configuration of the national backgrounds of migrants clearly diverges in some respects from the countries of Northern Europe. While England and France, at least from the 1960s onwards, mainly received migrants from countries linked to their colonial past, for instance, Pakistanis, Indians and Bengalis for Great Britain, and Tunisians and Algerians for France, the countries of Southern Europe receive migrants who only partially had previous links with their country of destination.

Due to its previous colonial links with the countries of Central and South America, Spain establishes preferential entry channels for Spanish-speaking foreigners from these areas. Italy, on the contrary, is the main destination for migrants from North Africa and sub-Saharan Africa, as well as migrants from Eastern Europe. Greece, due to its geographic position, is the destination (and place of transit towards other European countries) for migrants who arrive by sea along the eastern route of the Mediterranean as well as over land from nearby Macedonia and Albania.

What these countries have in common, in addition to the fact, as mentioned, that they were the first countries of emigration and thereafter, in the last 30 years, of immigration, is the fact that they have approved a series of regularizations aimed at providing a pathway out of illegality for a great many foreigners who arrived illegally or who have overstayed in a country beyond the limit stated in their visa.

By way of example, we need only mention that, in around 40 years, from 1973 to 2005, of the 8 European countries for which we have data on the regularizations approved during this period, Belgium has approved 3 regularizations, bringing 65,500 people out of illegality, France has approved 4 involving 262,800 people, Greece 2 for a total of 722,000 people, the Netherlands 3 for 19,100 people, Portugal 3 for a total of 240,200, the United Kingdom 2 for 2200 people and Spain 6 for 4,003,500 people. Italy, in the same period, approved 6, providing a pathway out of illegality for 1,500,100 people, not to mention a subsequent regularization, again in Italy, dating back to 2009 aimed at those who could demonstrate they had an employment contract as a domestic assistant and carer for the elderly which involved around 300,000 people [9]. In comparison with other continental European countries, Southern European countries have systematically made use of the tool for the ex post regularization of irregular migrants. These countries, unlike those of Northern Europe that have a much longer migratory tradition, have essentially had to deal with the arrival on their territory of new migrants without being capable of regulating the flow. Nor have they been able to implement policies of recruiting qualified personnel from the countries of departure to be introduced into the respective national labour markets.

Another aspect the countries of Southern Europe have in common is the widespread use of unreported employment, a situation in which migrants, who are in legal terms weaker and more willing to accept salaries below the minimum permitted by law, find themselves. These jobs are distinguished by the "three Ds": *difficult, dangerous, dirty*. They correspond to labour-intensive manual work in small- and medium-size manufacturing enterprise;, commercial establishments in urban areas

with particularly demanding hours, such as bakeries; as well as domestic services and caring for people. Finally, in the agricultural sector, companies consistently rely on the workforce as technological innovations are impractical or not economically viable [12, 13].

Unlike Northern Europe, these countries were hit harder by the economic-financial crisis that struck in 2008. Portugal and Greece, subjected to economic bailouts by the European troika (the European Commission, the European Central Bank and the International Monetary Fund), had to follow budgetary manoeuvres aimed at restoring the deficit. The macro-economic adjustment led to drastic cuts to the national health service in terms of staff and the overall resources allocated to it. Between 2008 and 2012, the average per capita annual cuts to the health sector came to 12% in Greece, 8% in Portugal and 4% in Spain [14]. Spain, in the precrisis phase, guaranteed all migrants, irrespective of whether they were legal or illegal, full access to medical treatments. Afterwards, with the legislative reform in 2012, it established that illegal migrants can only access the national health system if they are under 18 years old, pregnant women or people who require urgent medical care that cannot be delayed [14].

Like Spain, Italy too, with the reform implemented by legislative provisions in 2008–2009, the so-called security package, implemented a series of legislative measures aimed at containing the presence of illegal migrants in the country. These also include the restriction for illegal migrants to just urgent medical treatment. Moreover, having also been hit by the economic crisis, it had to put in place structural adjustment economic manoeuvres to comply with the fiscal compact parameters decided at European level.

Within a welfare system characterized by territorial fragmentation and the differential segmentation of aid (Italy is one of the few European countries that does not provide national support for people living in poverty conditions), over the years it has drastically reduced the resources of the National Fund for Social Policies [15]. While in 2006 it amounted to 775 million euros, in 2010 it was 380 million [11], a sum that seems largely inadequate to implement incisive social policies faced with a growing proportion of the population in financial difficulty.

The absolute poverty (namely, the impossibility of accessing a set of basic needs) of families rose from 4.1% in 2007 to 7.9% in 2013, in numerical values, from 2.4 million people in absolute poverty in 2007 to 6,020,000 in 2013, while those who find themselves in a situation of relative poverty (based on the average standard of living measured by consumption and income) amount to 10,048,000 [16, 17]. Overall there are around 16 million people, Italian and foreigners, out of a population of 62 million, living in conditions of overt poverty or who are at risk of poverty.

In this framework, migrants are those who, more than others, are penalized by the reduction of social policies, in particular in two areas. Firstly, as regards support for housing policies, where there is a different distribution of property ownership between Italians and foreigners (72% of Italian families own a home with respect to 23% of foreigners) [11]. Secondly, the other risk factor is poverty. The income of foreign families in Italy is over one fifth lower than that of Italian families, and this is linked to the fact that foreigners are mainly employed in low-salary jobs [18].

Conclusions

To summarize, the more a country follows entry and residence policies geared towards the temporary model, the more migrants are susceptible, once their work permit expires, to having to return to their country or, rather, to entering a condition of illegality. This inevitably results in lower protection in terms of access to medical treatment and social services. On the other hand, the assimilationist model, despite involving, in cultural and identity terms, forms of the homogenization of migrants to the standards and values of the host society, is less discriminatory in terms of the set of universal protections provided by the host country. The multicultural model provides for specific social policies that benefit disadvantaged minorities. These policies can translate into greater access to social services and healthcare for those countries that take this line. At the same time, there is a risk that the emphasis placed on cultural differences to be preserved and the tendency of separation between the indigenous and foreign population may lead to forms of the encapsulation and self-ghettoization of the foreign community.

Ultimately, leaving aside differentiated approaches in terms of migratory policy models, other elements also influence the actual condition of migrants in the countries of the European Union. They include the economic conditions of the country, the quality of the resources allocated to facilitate the foreigner integration process, the actual social mobility opportunities, the existence or not of discriminatory and xenophobic impulses in the society and, finally, the economic positioning of the migrants. As in fact revealed by recent research, the migrants residing in Germany, France, Great Britain and the Netherlands have a higher than 50% chance of falling into the lowest social stratum of the social scale with respect to the corresponding national population [6]. Although there is a lack of detailed data, it is just as plausible, in light of what has been said above, that the same risk is also present in Southern European countries. In other words, we are dealing with a vicious circle that stems from economic insecurity, low salaries and unreported employment, the effects of which are then felt in terms of personal health [19].

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2 Migration, Communicable, and Noncommunicable Diseases: Are We Witnessing a Paradigm Shift?

Francesco Castelli, Maria Lorenza Muiesan, and Issa El Hamad

2.1 Introduction and Determinants of Migration

Migrants are people on the move. They are usually defined by the International Organization for Migration (IOM) as "any person who is moving or has moved across an international border or within a State away from his/her habitual place of residence, regardless of (1) the person's legal status, (2) whether the movement is voluntary or involuntary, (3) what the causes for the movement are or (4) what the length of the stay is." Over 244 million international migrants are estimated to live outside their country of birth nowadays, let apart the silent enormous number of internally displaced people who are forced to leave their home to reach other places within the same country.

The factors causing South-North migration are nowadays stronger than ever and include socioeconomic factors and environmental factors. Among social factors, *demographic increase* in the southern hemisphere as compared to aging and shrinking of the population in the northern countries is among the most powerful pushing factors, as it is *urbanization*, also favored by the sad phenomenon of *land grabbing* by multinational companies leaving rural people without land to cultivate. Wars and dictatorships are also to be numbered among social pushing factors. Among

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environmental factors, *climatic changes* caused by greenhouse emissions mainly by the industrialized North is causing desertification or, on the opposite, flooding in many poor economies. According to the United Nations, climate change is one of the leading causes of land degradation and migration, requiring urgent mitigation efforts [1]. It has recently been estimated that climate changes will force as many as 10% of the human population to move for resettlements from flooded areas by the year 2100 [2].

Often determinants of migration act together so that it is difficult to discriminate the most important one in the individual case. Altogether, they are causing nowadays the most relevant migration flow ever occurred in human history.

Quite schematically, migrants are divided into "economic" migrants (also including family reunification) and "forced migrants," often referred to as asylum seekers or refugees.

For the sake of this article, however, we will mainly refer to South-North "economic" migrants, representing 85 million people in 2015, although we are well aware that an even higher number of individuals (93 million) migrate from South to South or from North to North (55 million) according to the IOM [3].

2.2 The "Healthy-Migrant" Effect

The healthy-migrant effect, i.e., the fact that a selection mechanism toward youngest and healthiest individuals is operating among those who decide to migrate for economic reasons, is believe to play a role in defining the health profile of the economic migrant. However, the healthy-migrant effect is supposed to vanish with time, and new phenomenon such as family reunification and refugees escaping wars and dictatorships is progressively diluting such population health status. The healthy-migrant effect is now under discussion. Furthermore, second-generation migrants (i.e., the sons of those who first migrated) or relatives who joined them after resettlement may suffer from different diseases than the individual that originally left his/her place of residency.

If it is true that stroke and neoplasms are usually persistently lower in migrants if compared to the European population even 5–10 years after migration, the relative risk of TB reactivation and HIV is maintained higher (even if decreasing) even long after first arrival and the risk of cardiovascular disease is higher even shortly after reaching the destination country [4].

As stated at the beginning of the chapter, our analysis is limited to migrants from the resource-limited countries of the South to the affluent Northern countries. Even so, however, the definition of "migrant" remains vague, as the cultural and epidemiological features of the *country of origin* may have a great influence on the health profile of migrating individuals. At the same time, the *country of destination* also affects the health outcome of the migrant for regulatory (access to care), climatic, linguistic, and cultural reasons. Last but not least, the *reason for migration* is also to be considered, as an economic migrant, possibly benefiting from the healthy-migrant effect, may be affected by different illnesses if compared to a refugee who

has been force to leave his/her country. It is therefore not surprising that different studies may give origin to different, and even conflicting, evidence. When mortality rates in natives and migrants of different geographic origin were assessed, large variations in mortality patterns were found across migrant's population in different European countries [5].

2.3 Migration and Infectious Diseases

Infectious diseases have always been associated in the past, since ancient times, to travel and human mobility. After the siege of Naples by the French troops lead by Charles VIII in 1494, Girolamo Fracastoro from Verona wrote his masterpiece "*Syphilis sive* ***de morbo gallico***" (Syphilis, the French disease), and soon after smallpox, measles and typhoid fever were imported to South America from the European conquerors. The Venice Republic had already introduced the quarantine isolation in the previous century to protect the town from the Black Plague.

Therefore, it comes with no surprise that migration—especially from countries with high infectious disease endemic burden such as those in the African continent – has always been associated with a potential risk of infectious diseases and contagion. This is not without rationale, as the higher incidence of some infectious diseases (tuberculosis, HBV, HIV, Chagas disease, etc.) in origin countries leads to possible reactivation of latent infections in the host country in first-generation migrants. Furthermore, the marginalization and poverty conditions that migrants often experience after resettling certainly expose them to poverty-related infections such as, in particular, sexually transmitted infections (STIs) [6]. Of note, in fact, the proportion of HIV-infected migrants who acquired the infection in the host country after migration has recently been estimated to be as high as 66% [7]. Violence, promiscuity, and sex abuse during travel and at interception sites also contribute to the prevalence of sexually transmitted infections in migrants. However, infectious diseases are certainly not prevalent at arrival in hotspots [8] and after resettlement and are not usually considered to constitute a risk for the native population [9]. A comprehensive review of health problems of migrants at first arrival has been recently published by Pavli and Maltezou [10].

The bulk of literature on migrants' health after resettlement has been focused so far on infectious diseases, and consensus has been reached that the two mayor drivers of infectious diseases in southern migrants to industrialized countries are (1) the prevalence of a specific infection in origin country and (2) the marginalization status in the destination country.

It is therefore not surprising that migrants coming from West Africa have a higher prevalence of hepatitis B active infection (HBsAg) [11] or latent tuberculosis, while migrants from Egypt have a higher prevalence of HCV infection or latent schistosomiasis. Migrants from Southern African or Eastern European countries are more likely to suffer from latent tuberculosis, with a higher prevalence of MDR tuberculosis, and migrants from Latin America (especially from Bolivia) are at risk of Chagas disease [12]. Of note, migrants from malaria endemic areas returning to their country of origin (VFR, visiting friends and relatives) have a higher risk of

contracting malaria in the absence of preventive measures [13]. A comprehensive and geographically wide report of infectious diseases in resettled migrants has been recently offered by the GeoSentinel Network [14]. The question "*Unde venis*?" is therefore of the upmost importance when the clinical history of a migrant is obtained. It has been reported that the overall mortality in economic migrants from former USSR to Germany and Israel resulted to be lower than the general German population, except for specific infection-related causes, such as viral hepatitis, liver, and stomach cancers [15].

At the same time, as already pointed out, poor living conditions and social marginalization are the favoring background for sexually transmitted diseases, especially HIV [7] and tuberculosis reactivation among other. Migrant-friendly policies, such as limiting cultural and linguistic barriers and providing adequate access to care to poverty-related contagious diseases, are considered the best way to protect both the health of the migrant and the hosting community [16].

In recent years, the picture of migrants' health is becoming more complex and multifaceted due to the epidemiological transition now rapidly occurring in origin countries but also to the changing behavior and lifestyle that superimpose to genetic traits and cultural factors, giving rise to a shifting from the long-standing paradigm connecting human mobility and infection [17] to a scenario where aging and noncommunicable disease play an increasingly important role [18].

2.4 The Global Burden of Diseases in Low-Middle-Income Countries (LMIC)

The health profile of people is rapidly changing in low-middle-income countries (LMIC, where most of the migrants come from). The Global Burden of Disease Studies have shown a robust trend toward longer life expectancy in LMIC [19], accompanied by a trend to a decrease in rates of communicable, maternal, and child diseases and by an increased number of years of life lost (YLLs) due to noncommunicable conditions such as diabetes mellitus, cardiovascular diseases, neoplasm, and others [20]. In fact, most areas in the developing world are experiencing the so-called epidemiological transition, with a significant number of even premature deaths due to noncommunicable diseases such as obesity and hypertension, which are becoming a significant public health concern especially in urban residents [21].

Mental health is also being increasingly studied in migrants within low-middle-income countries. A recent report from India shows a high incidence of psychological distress in young migrants from rural areas to urban areas in India. This is especially true soon after migration, but higher incidence of psychological disturbances persists even long after resettlement [22].

Among others, the following are considered to be the leading drivers of this epidemiological transition: (1) demographic increase in developing countries, (2) aging, (3) better control of communicable diseases as a result of intense efforts, and (4) increasing proportion of chronic noncommunicable conditions leading to long disability periods.

2.5 Migration and Noncommunicable Diseases

The picture is less clear when the increasing burden of noncommunicable diseases is considered, as predisposing factors (genetic, cultural, behavioral, socioeconomic, etc.) are multiple and variably associated. According to some reports, a lower overall (and especially cardiovascular-linked) mortality rate has been reported in migrants living in Denmark when compared to an age- and sex-matched Danish population [23]. On the same line, a lower prevalence of hypertension in Bangladeshi migrants living in the UK or Moroccan and Turkish individuals living in the Netherlands [24] has been reported.

Conversely, other pieces of evidence are in favor of a higher prevalence of cardiovascular diseases [25], diabetes [26], and kidney diseases in foreign-born populations in most migrants' destination countries. A recent meta-analysis by Modesti et al. showed a higher systolic and diastolic blood pressure in migrants from sub-Saharan Africa to Europe than European residents, lasting for many years and refractory to preventive strategies. However, the opposite was true for migrants from Southern Asia, suggesting interethnic differences. Also, Muslim migrants showed lower blood pressure values, suggesting that also religion-bound alimentary habits play an important role [27].

The bulk of scientific evidence points to a higher incidence of diabetes in the migrant population compared to the destination country age-matched natives in all geographical areas [26]. Complications and mortality are also much higher, as demonstrated by the 90% higher mortality in males and 120% higher mortality in females belonging to 30 different groups in 7 European countries [28].

The key determinants of noncommunicable diseases in migrants are briefly reviewed below:

1. *Prevalence of Risk Factors and Diseases in the Country of Origin*

   The epidemiological transition in low-middle-income countries (LMIC) toward noncommunicable diseases – unfortunately often naccompanied by a significant reductionof the infectious diseases burden – has now been demonstrated by the Global Burden of Diseases Studies [20], as a result of urbanization, aging of the population, dietary habit changes, and persisting low access to quality prevention activities and care. This applies to hypertension [29], diabetes [30], and other noncommunicable diseases, especially in the urban setting. Unfortunately, the burden of noncommunicable diseases goes on top of the usual burden of infectious diseases (with particular regard to tuberculosis and HIV) in migrants from the rural to the urban environment in resource-limited countries [31], giving rise to the converging burden of communicable and noncommunicable diseases. An example of such convergence is provided by the predisposing role of diabetes in the reactivation and development of active tuberculosis in migrants [32].
2. *Genetic Factors*

   The role of genetics is obviously estimated to be important in defining the health profile of migrants exposed to a foreign environment. As an example, North Americans of African descent tend to suffer more from diabetes and

cardiovascular diseases than natives in the host countries, possibly linked to gene sequence variations [33]. Recently, the RODAM (Research on Obesity and Diabetes among African Migrants) study has elegantly demonstrated three loci (*CPT1A*, *NLRC5*, and *BCAT1*) possibly linked to both general adiposity and abdominal adiposity [34]. The precise definition of the weight to be attributed to genetic factors and changing lifestyle as determinants of noncommunicable diseases in migrants is however still to be assessed, and factors other than genetics also play a major role.

3. *Lifestyle and Behavior*

   Existing evidence demonstrates that many lifestyle habits, including diet, change progressively after migration to industrialized countries, especially in younger individuals, leading in general to an increase in energy and fat food, with lower intake of fiber, a phenomenon referred to as "nutrition transition." This has long been recognized in second-generation migrants, who are more likely to eat more fatty food than their matched counterparts in the origin country, leading to obesity, as elegantly demonstrated for Gujarati migrants in Britain [35]. This phenomenon has been clearly demonstrated in the RODAM study in first generation that pointed out how Ghanaian adult migrants to Europe were more likely to eat fatty and protein-rich food than Ghanaian adults living in urban and rural Ghana. An opposite trend was observed for carbohydrates [36]. The same RODAM study provides evidence of converging trend of the smoking habit between European population and the Ghanaian migrant population, which resulted to be more likely to smoke than their counterpart in Ghana [37]. Interestingly, the RODAM study provided contrasting results on the association of socioeconomic position and type 2 diabetes, which resulted to be directly associated with education in rural Ghana and inversely associated with education in urban Ghana and in Ghanaian's adult migrants living in Europe [38].

   As a matter of fact, it has been suggested that dietary and physical activity behaviors in ethnic minorities are most probably the result of a multifactorial game including social, cultural, material, and psychosocial factors [39], suggesting an integrated research approach to gain useful elements to inform public interventions. More sociologic and standardized studies are needed to assess the opposite evidence in a balanced manner.

4. *Cultural Factors*

   The attitude of first-generation migrants to retain cultural priorities and cultural identity of origin country may sometime act as a protective shield against Western dietary habits, even if the majority of evidence points to a progressive adaptation to Western dietary habits [40]. In addition, the protective effect on health of first-generation migrants often referred to as "healthy-migrant effect" may also be lost with time as the culturally protective habits are progressively lost, with worsening of the health profile in second-generation offsprings [41].

   Cultural factors such as gender roles, body image, cultural priorities, cultural identity, and explanatory model of disease may also make reciprocal comprehension between the patient and the health worker difficult as their respective cultural paradigms are different, possibly leading to dramatic misunderstandings [42].

5. *Access to Prevention and Care*

   Prevention and early access to care is pivotal to impede complications of both communicable and noncommunicable diseases to occur. This is beneficial from both the individual and the society perspectives regardless from the legal status of the migrant. However, most evidence suggests that migrants in Europe do not have access to care even when they are legally entitled to do so as it is the case for antenatal care [43] or for cultural reasons.

   Such phenomenon is at least partly culturally bound, but efforts are to be displayed to ensure that the receiving country health system offers inclusive services that may prevent long-term life-threatening and costly complications. This is the case for many noncommunicable conditions such as cardiovascular diseases, diabetes, hypertension, neoplastic diseases, and other metabolic illnesses.

   Even when migrants have access to drug treatment for chronic diseases, they discontinue more often the use of antihypertensive drugs and have a lower adherence, as compared to native residents in the same region [44].

This multifaceted and complex scenario requires sound scientific evidence to drive public health interventions, using a standardized methodological research approach to the issue of noncommunicable diseases in migrants. The HELIUS (*Healthy Life in an Urban Setting*) study in Amsterdam is aimed at assessing the association between genetic factors, country-specific culture, migration history, ethnic identity, and socioeconomic and discriminatory factors with the incidence of diseases within specific nosologic spheres: (1) cardiovascular (including diabetes), (2) mental health (depressive disorders and drug abuse), and (3) infectious diseases in four different ethnic groups: Suriname (both Afro-caraibic and Southern Asia individuals), Ghana, Turkey, Morocco, and Dutch natives. The study is intended to recruit 30.000 participants and its results are awaited soon [45].

Conclusions

As long as the determinants of migration (demographic increase, urbanization, land grabbing, economic disparities, climate changes, wars, dictatorships, etc.) will be operating, the migration flow from southern poor countries to northern affluent countries will continue to be unchanged and possibly increasing. This is not a new phenomenon, as it has been reported since ever, and some European destination countries, including Italy, Greece, Portugal, and Spain, have been once—during the last century—origin countries of migrants searching for a better life for themselves and their families. However, the dimension and the rapidity of nowadays migration flows are much higher and possibly difficult to manage. Western societies must be aware of such progressive structural change in their ethnic composition, adapting their social and schooling and health systems to cope with such rapidly evolving situation. With particular regard to health, the major drivers of infectious diseases in migrants are (1) epidemiology of the infection in the country of origin and (2) the marginalized social status in the destination country. It is generally assumed that the impact of such infections in the native population is null, when access to rapid prevention and care measures is assured. A shift toward noncommunicable diseases is being observed,

as a result of (1) the epidemiological transition now occurring in most origin countries and (2) the changing alimentary and lifestyle habits in the migrating population over time, with particular regard to second-generation migrants.

Many knowledge gaps are still present, urging social and health scientists to develop sound methodological approaches to proper collate scientific data on such a complex phenomenon to be offered to policy makers. Social and health workers in Western societies need to be adequately trained to the new challenges of migration medicine, and inclusive preventive and curative health and social policies should be put in place regardless of legal barriers.

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Inequalities and Health Policies in the European Countries

3

Gavino Maciocco

3.1 Socioeconomic Inequalities and Health

In 2005, WHO established the Commission on Social Determinants of Health (CSDH) chaired by Sir Michael Marmot and composed of 20 members of academics, former ministers of health and former heads of state, in order to gather information and evidence on the impact of social determinants on health and above all to transform the wealth of knowledge and experience acquired in possible effective and political interventions for governments around the world. After 3 years, in August 2008, the Commission published the final report of the work entitled "Closing the gap in a generation: Health equity through action on social determinants of health" [1]. At the heart of the report is the imperative for all governments to act on the social determinants of health in order to eliminate health inequalities between countries and within the countries themselves.

"Social justice is a matter of life and death – the final Report states. It affects the way people live, their consequent chance of illness, and their risk of premature death. We watch in wonder as life expectancy and good health continue to increase in parts of the world and in alarm as they fail to improve in others. A girl born today can expect to live for more than 80 years if she is born in some countries – but less than 45 years if she is born in others. Within countries there are dramatic differences in health that are closely linked with degrees of social disadvantage. Differences of this magnitude, within and between countries, simply should never happen. These inequities in health, avoidable health inequalities, arise because of the circumstances in which people grow, live, work, and age, and the systems put in place to deal with illness. The conditions in which people live and die are, in turn, shaped by political, social, and economic forces. (…) The poorest of the poor have high levels of illness and premature mortality.

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But poor health is not confined to those worst off. In countries at all levels of income, health and illness follow a social gradient: the lower the socioeconomic position, the worse the health. It does not have to be this way and it is not right that it should be like this. Where systematic differences in health are judged to be avoidable by reasonable action they are, quite simply, unfair. It is this that we label health inequity. Putting right these inequities – the huge and remediable differences in health between and within countries – is a matter of social justice. Reducing health inequities is, for the Commission on Social Determinants of Health, an ethical imperative "Social injustice is killing people on a grand scale".

In a previous report published in 2003 by WHO Regional Office for Europe ("The Solid Facts" [2]), Michael Marmot had stated:

> "Even in the most affluent countries, people who are less well off have substantially shorter life expectancies and more illnesses than the rich. Not only are these differences in health an important social injustice, they have also drawn scientific attention to some of the most powerful determinants of health standards in modern societies. They have led in particular to a growing understanding of the remarkable sensitivity of health to the social environment and to what have become known as the social determinants of health".

During the past decades, a widening of the relative gap in death rates between upper and lower socioeconomic groups has been reported for several European countries. In general, changes in cardiovascular disease mortality explain about half of the widening of the relative gap in total mortality. Mortality from cardiovascular diseases declined in all countries and all socioeconomic groups, but relative (percentage) mortality decline was usually faster in the upper socioeconomic groups [3].

To provide evidence-based recommendations for social determinants of health that are suitable for the diverse countries of the WHO European region, a European Review of Social Determinants and the Health Divide was commissioned in 2012 by the Regional Director for Europe [4].

3.2 The Report "Health Inequalities in the EU"

The Report "Health inequalities in the EU" was published in 2013 [5].

This report demonstrates marked differences in the social determinants of health across EU Member States and inequalities in health between social groups based on these determinants. To examine the extent of social differences in individual health across the EU, two analyses are presented in the report: (a) the relationship between self-reported health and levels of education, income and deprivation and (b) life expectancy and education.

(a) In 2010, whichever indicator of socioeconomic status is considered—education, income or material deprivation—reporting of poor or very poor general health and long-standing health problems tends to be infrequent in the most advantaged group and increasingly common as disadvantage worsens. The steepest social

gradients are those between material deprivation and adverse health outcomes. For both men and women at ages 25 and over, less than 1 in 20 of the least deprived fifth of the population reported poor or very poor general health. For the most deprived fifth of men and women, the reported levels exceeded 20%. For long-standing illness, the comparable ranges were from around a quarter of both men and women to approximately 40%. Women were more likely than men to report that their general health is poor or that they have a long-standing illness. This is partly attributable to women's lower socioeconomic status.

(b) The analysis of mortality in 2008–2009 by educational level was based on Member States for which mortality data are available by educational level. This indicated that educational gradients in life expectancy existed in all Member States but that they vary by sex, age and the overall level of survival. The steepest social gradients were those for male life expectancy at age 25 in Estonia, Czech Republic, Hungary, Bulgaria and Poland—Member States with some of the highest levels of mortality in the EU. For women aged 25 and men aged 65, inequalities in life expectancy according to level of education were smaller, but the same patterns are evident. Life expectancy at age 25 for men with tertiary education in Estonia was 17.8 years longer, or 50% higher, than life expectancy for men who did not complete secondary education; the corresponding figures for Hungary were 13.3 years and 34%. In contrast, in Malta, Norway, Sweden and Italy, the differences between the same two groups ranged from 3.2 to 5.2 years, which is 6–10%. Moreover, life expectancy at age 25 for highly educated men in Estonia was the same as life expectancy for poorly educated men in Italy, at 53 years. The variation in female life expectancy between Member States was smaller than for males. Similarly, educational gradients for women were less steep within Member States. At age 25, the difference between highly educated and poorly educated women ranged from 9.1 years in Estonia and 7.5 years in Bulgaria to 2.9 years in Italy and only 1.7 years in Malta. There is evidence from published studies reviewed for this report of an increase in health inequalities between social groups within countries, including some in the east of the EU (such as Hungary, Estonia, Lithuania and Poland), as well as in the Nordic countries. Action on health inequalities must therefore remain a public health priority for the EU. This review has identified the clear existence of inequalities by educational status for total mortality, cancer, ischaemic heart disease, general morbidity, diabetes and suicide. Although inequalities in health by ethnicity—including Roma—were included in the criteria for inclusion, very few comparative papers were identified that examined the impact of ethnicity. This suggests a strong need for more comparative longitudinal research across the EU in this area.

The report examines some of the factors causing health inequalities. The analysis supports the findings of the WHO CSDH that social inequalities in health arise because of inequalities in the conditions of daily life and the fundamental drivers that give rise to them. This review found many examples of associations between risk factors for health, including tobacco use and obesity, and socioeconomic

circumstances. This reflects the influence that lack of control, stress and reduced capabilities—all strongly associated with social disadvantage—have on both health and health-related behaviours.

At a national level, the report identified that Member States with lower levels of social protection tended also to have higher rates of self-reported bad or very bad health. This is supported by recent research showing that the association is greatest among those with lower levels of education. A number of other key socioeconomic determinants also vary across the EU, such as income distribution and unemployment levels, which help to explain inequalities between Member States. Of particular concern for health is the variation in long-term unemployment, the proportion with education levels at lower secondary level or below and those suffering material deprivation. Variability between Member States was also identified in lifestyles and behaviours, such as the proportion of people smoking or who are overweight or obese. Current inequalities in mortality between regions—based on net disposable income per inhabitant—are largely explained by inequalities in non-communicable diseases (NCDs) for both men and women. The most pronounced gradients in the relationship between health and average income at a regional level are for circulatory diseases, in particular those for cerebrovascular disease.

There is very strong evidence that inequalities in health follow a social gradient, with the lowest socioeconomic groups experiencing the worst health.

This is an important dynamic in understanding how best to address health inequalities, as it implies that high-quality pilot projects alone cannot tackle health inequalities. Instead, they require sustained interventions that are included in the mainstream of core service delivery. Furthermore, focusing solely on the most disadvantaged will not reduce health inequalities sufficiently. To reduce the steepness of the social gradient in health, actions must be universal, but with a scale and intensity that is proportionate to the level of disadvantage. The practical implications of this approach, known as "proportional universalism", are particularly complex where small pockets of deprivation exist surrounded by more prosperous areas and where many individuals and families experiencing deprivation live outside such pockets. There is strong evidence that economic crises lead to a deterioration in health and well-being for many people because they increase unemployment and poverty.

This review concluded that it is not possible to reduce inequities in health without addressing inequities in the causes of ill health—social divisions, unequal exposure to harm and differential levels of resilience. Countries can utilise "health equity in all policies" as a key commitment to inform further action to reduce health inequality and address the social determinants of health, but new systems of governance and delivery are also required. These need to operate at all levels of governance, involving both the whole of society and the whole of government. In all countries in Europe, it recommended that reduction of health inequities should become one of the principal criteria used to assess health-system performance and the performance of government as a whole.

3.3 The 2008 Recession in Europe and Its Consequences on Health

The 2008 economic crisis led to rising unemployment, homelessness and poverty—all important determinants of health. Government debt increased, as public money was used to prevent the collapse of the financial system, and many governments then cut public services to reduce this debt. But what has been the effect of all of this on health? [6].

In a linked systematic review in *The BMJ*, Parmar and colleagues find that most studies investigating the 2008 recession in Europe show it was associated with adverse health outcomes. These findings were strongest for suicides and mental health problems [7].

The Lancet has dedicated a paper to the 2008 recession [8] that starts like this: "The financial crisis in Europe has posed major threats and opportunities to health. We trace the origins of the economic crisis in Europe and the responses of governments, examine the effect on health systems, and review the effects of previous economic downturns on health to predict the likely consequences for the present." It also reads: "Some countries decreased the extent of coverage by instituting or increasing user charges for some health services in response to the crisis. In most countries, the scarcity of data and potential lagged effects mean that assessment of the effects of these reforms on access to care and health outcomes is not yet possible. However, evidence from the wider medical literature suggests probable consequences. Rises in user charges are a particular cause of concern, because they increase the financial burden on households and probably reduce the use of high-value and low-value care equally, especially by people with low incomes and high users of health care, even when user charges are low. Introduction or increases of user charges in primary or ambulatory specialist care might worsen health outcomes and lead to increased use of free but resource-intensive services— eg emergency care. Thus, cost savings and enhanced efficiency are scarce. (…) The most vulnerable people are those in countries facing the largest cuts to public budgets and increasing unemployment. Both job loss and fear of job loss have adverse effects on mental health, and income reduction, growing health-care costs, and cuts in services prevent patients from accessing care in time. (…) Further insights can be gained from individual-level research, which shows that unemployment adversely affects health. For example, the prevalence of psycho- logical problems in unemployed people (34%) is more than twice that in employed people (16%), and the negative effects of unemployment on mental health were less in countries with strong employment protection systems than in those with poor employment protection. Poor health in unemployed groups is partly a result of reduced financial resources, because loss of income can lead to poor nutrition and potentially to barriers in accessing health care. Martikainen and Valkonen showed that, when demographic and socioeconomic factors are controlled for, unemployed people have higher mortality than do employed counter- parts. Morris and colleagues reported that duration of unemployment correlates with increased risk of mortality. Unemployment is

associated with increased unhealthy behaviours and affects mental health, leading to increased psychological and behavioural disorders and increased risk of psychosomatic diseases and suicides".

The paper concludes with a clear complaint against the European health authorities: "Public health voices have been largely absent from the debate about how to respond. Many health ministries have been silent. The Directorate-General for Health and Consumer Protection of the European Commission, despite its legal obligation to assess the health effects of EU policies, has not assessed the effects of the troika's drive for austerity, and has instead limited EU commentary to advice about how health ministries can cut their budgets. A small source of European civil society organisations, including professional bodies, have spoken out about the adverse health effects of cuts to health and social spending. The question is whether anyone will listen".

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Part II

Ethnic Disparities in Cardiovascular Disease

Ethnic Disparities in Stroke

4

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4.1 Ethnic Disparities in Stroke

Stroke is the second most common cause of mortality and the third most common cause of disability globally [1]. Stroke is the acute neurologic injury that occurs as results of a sudden death of some cells in the brain caused by lack of oxygen when the blood flow to the brain is lost by blockage (ischemic stroke) or rupture (hemorrhagic stroke) of an artery to the brain. About 80% of strokes are due to ischemic cerebral infarction and 20% are due to brain hemorrhage. While the incidence of stroke is falling in high-income countries, the incidence is increasing in low- and middle-income countries [2–5]. The global estimate in 2013 shows that there were 6.5 million deaths due to stroke, 113 million disability-adjusted life years (DALYs) lost because of stroke, and 10.3 million new cases of strokes [6]. The majority of the stroke burden, about 75% of all stroke-related mortality and 81.0% of the associated DALYs lost, occurred in low- and middle-income countries. In addition, stroke occurs 15 years earlier in people living in low- and middle-income countries than people living in high-income countries [7]. Although the global estimates of stroke morbidity and mortality favor high-income countries than their low- and middle-income counterparts, there are clear ethnic disparities in stroke mortality, morbidity, and survival across ethnic groups in high-income countries. This chapter discusses ethnic disparities in stroke in high-income countries with major focus in Europe.

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4.2 Ethnic Disparities in Stroke Mortality

Early observations on ethnic differences in stroke relied on hospital admissions in Birmingham, UK [8, 9], showing more frequent hospitalization for stroke in West Indians when compared to the native European population. Mortality data from cerebrovascular disease for England and Wales for 1970–1972 and 1979–1983, classified by country of birth and centering on the 1971 and 1981 census, respectively, then showed distinct ethnic differences in mortality from cerebrovascular disease [10]. More precisely, in both the periods, death rates from cerebrovascular disease were highest for men and women born in Caribbean countries followed by subjects born in Africa and the Indian subcontinent. These data were repeatedly confirmed [11] and the association with a different distribution in risk factors was considered [12]. In the following years, ethnic differences in stroke mortality were observed by comparing European descent populations with people originating from West Africa, the Caribbean, and South Asia living both in the UK and in other European countries [13–18]. Interpretation of such differences required longitudinal studies of a broader range of ethnic groups.

4.3 Ethnic Disparities in Stroke Incidence

Although several studies have shown ethnic differences in stroke mortality in Europe, data on ethnic differences in stroke incidence are limited. The limited data on stroke incidence show variation between ethnic groups depending on ethnicity and country. A retrospective cohort study of 4.65 million people was created in Scotland linking ethnicity from the census and stroke incidence and mortality from NHS databases and self-reported ethnicity was used as indicator of ethnic group [19]. Differently from what observed using mortality data by country of birth in England and Wales, ethnic variations were found to be modest in Scotland, probably reflecting the high rates of cardiovascular disease in the White Scottish population [19]. Important ethnic differences in the incidence of stroke were reported using data from the south London stroke register [20] where the incidence rate ratio adjusted for age and sex in African compared with European patients was 2.21 [20].

Ethnic differences in the incidence of overall stroke and stroke subtypes (ischemic, intracerebral hemorrhage, and subarachnoid hemorrhage) in the Netherlands were investigated in the Dutch nationwide register-based cohort study ($n = 7{,}423{,}174$) conducted between 1998 and 2010 [21]. Compared with ethnic Dutch, Surinamese men and women had higher incidence rates of all stroke subtypes combined (adjusted hazard ratios 1.43 and 1.35, respectively), followed by Indonesian (1.04 and 1.07, respectively), whereas Moroccan had a lower incidence than ethnic Dutch (HR 0.42 and 0.37, respectively). Men of all ethnic groups (except for Moroccans) had higher risk than ethnic Dutch for intracerebral hemorrhage (HR ranging from 1.48 in Turkish to 2.29 in Chinese with 0.61 in Moroccans).

Only recently data from the South of Europe (i.e., Italy) were made available [22]. These data also showed that sub-Saharan Africans had the highest risk of

hospitalization for stroke vs. native Italian population (3.1 for both genders), followed by subjects coming from South Asia (males 1.68; females 1.55) and other Asian countries (1.92 and 1.88, respectively). The main limitation of these observations was the lack of data on risk factors such as hypertension, diabetes mellitus, smoking, alcohol, and diet, which made it impossible to assess the direct contribution of the various risk factors to the observed ethnic differences. Prevalence of modifiable risk factors, such as hypertension and diabetes, may explain how a rapid transition from subsistence living to a "Westernized lifestyle" may provide exposure needed for activation of inherent ethnic traits culminating in stroke. Also differences in the control of modifiable risk factor might play a role.

4.4 Ethnic Disparities in Risk Factor Control

In African descent populations, the higher risk of stroke was consistent with the higher rates of hypertension [23] and higher blood pressure levels when compared with European populations [24]. Interactions between trends in stroke incidence and before stroke risk factors were investigated with the South London Stroke Register, a population-based register covering a multiethnic population of 357,308 inhabitants [25]. Total stroke incidence decreased by 39.5% during this 16-year period, from 247 to 149.5 per 100,000 per year ($P < 0.0001$). A similar decline in stroke incidence was observed in men from 277.3 to 158 ($P < 0.0001$) and in women from 217.3 to 138.6 ($P < 0.0001$). However, there were differences in the incidence trends between ethnic groups and between age groups. During the study period, a 41.3% reduction in stroke incidence was observed in the European group from 233.4 to 137.1 ($P < 0.0001$), whereas no significant changes in incidence rates were seen in the black group (from 310.1 to 267.5, not significant, with $P = 0.3633$), and a constantly higher incidence was observed in the black group compared with the white group. A higher prevalence of hypertension and diabetes mellitus in African descent patients compared with the European descent patients was observed in each of the four time periods in all age groups. South Asians experience a 1.5- to 2-fold higher stroke risk than Europeans [26]. A significantly higher 30-day ischemic stroke mortality in the South Asians compared with white European and African-Caribbean groups in the UK was also reported [27]. In addition, South Asians with diabetes were also demonstrated to have higher long-term stroke mortality [28]. Differences in hypertension prevalence between South Asians and Europeans do not explain the greater stroke risk in South Asian groups [24]. Among South Asians mean blood pressure levels [24], the use of antihypertensive therapy, and secular trends in blood pressure appeared to be comparable with white European counterparts. In this ethnic subgroup, the high prevalence of diabetes [24, 29] may however explain poorer stroke survival [27, 28], a greater incidence of CVD outcomes among patients with hypertension, and an excess risk of developing small vessel disease [30]. Furthermore, a high relative risk of stroke associated with high blood pressure was recently observed in the UK because blood pressure was found to be more strongly associated with stroke in South Asians than Europeans [31]. The study was

performed on 1375 European and 1074 South Asian men of Indian origin, mostly Punjabi Sikhs, residing in the UK. Over a median of 20-year follow-up, incident stroke was higher in South Asians (10%) than in Europeans (8%). All measures of blood pressure (SBP, DBP, MAP, and PP) were strongly positively associated with incident stroke in South Asians, even on multivariable adjustment. In contrast, with the exception of PP, associations were either weaker (SBP) or absent for Europeans. The combination of high blood pressure and glycemia as dichotomized variables appeared more deleterious for South Asians than Europeans [31]. No ethnic differences in achieving blood pressure control were observed among subjects who attended the follow-up clinic. Ethnic inequalities in stroke incidence were reported to reduce with age [32]. However, short- and long-term mortality were found to be enhanced among ethnic minorities after stroke either in US and in Europe independently from acute stroke care [32, 33]. A consistent impact on stroke survival among minority ethnic patients was conversely attributable to socioeconomic deprivation [33]. Rather than representing elimination of social disadvantages driving high stroke incidence in young blacks, age attenuation of ethnic inequalities in stroke incidence was thus considered to be an artefact of selected survival [34].

The relative risk of CVD associated with the risk factors is an important component of risk assessment models [35]. The use of risk assessment models developed using data from Western populations may underestimate the risk of stroke in South Asians. To better quantify this risk and develop more effective guidelines, we need to improve risk assessment and use risk scores validated for ethnic minorities [36]. As in African patients, South Asians also develop hypertension at an earlier age, with more end-organ damage, but there are no known differences in the blood pressure-lowering response to antihypertensive drugs, and despite the greater mortality, there are no trials in South Asians with morbidity and mortality outcomes. Also, we need data on whether lower thresholds to start treatment and lower therapeutic goal blood pressures need to be applied [37].

Studies in many high-income countries demonstrate that individuals with low socioeconomic status whether measured by income, occupational group, or by level of educational attainment have an elevated risk of dying from cardiovascular diseases, including stroke. The mechanisms through which low socioeconomic status affects stroke risk and outcomes are unclear, but some studies suggest that the comparatively high prevalence of predisposing risk factors among poorer people could account for some of the variation. The importance of socioeconomic inequalities in stroke incidence among major first-generation ethnic minority groups was specifically investigated in the Nationwide register-based cohort study (n = 2,397,446) in the Netherlands [38]. Data were obtained from the Dutch national registers (population register, hospital discharge register, cause of death register, and regional income survey) in the Netherlands between January 1, 1998, and December 31, 2010. Among ethnic Dutch, the incidence of stroke was found to be higher in the low-income group than in the high-income group (adjusted HR, 1.18). Similar socioeconomic inequalities in stroke incidence were found among Surinamese (1.36), Indonesians (1.15), Moroccans (1.54), Turkish (1.19), and Antilleans (1.24). When compared with ethnic Dutch, the incidence of stroke was lower in Moroccans, similar in Turkish, but higher in Surinamese among all income groups. The incidence of

stroke was higher in Indonesian low- and high-income groups than in their ethnic Dutch counterparts. Among Antilleans, the risk of stroke was higher than ethnic Dutch but only in the low-income group. Within each income group, the incidence of stroke was higher in most migrant groups than in ethnic Dutch. Reduction of socioeconomic inequalities in stroke incidence among all ethnic groups may lead to a public health improvement for all. Policy measures tackling socioeconomic inequalities should take the increased risk of stroke among ethnic minority populations into account [38].

4.5 Ethnic Differences in Stroke Subtype

Ischemic stroke is usually classified on the basis of the presumed mechanism of the focal brain injury and the type and localization of the vascular lesion according to the TOAST classification [39] in (1) large artery atherosclerosis (LAAS), which may be extracranial or intracranial; (2) cardioembolic infarct (CEI) (embolism from a cardiac source); (3) lacunar infarct (LAC) (small vessel disease); (4) stroke of other determined etiology (ODE) (such as dissection, hypercoagulable states, or sickle cell disease); and (5) stroke of undetermined etiology (UDE). The certainty of the classification of the ischemic stroke mechanism is far from ideal and reflects the inadequacy of the diagnostic workup in some cases to visualize the occluded artery or localize the source of the embolism.

Clear differences in the distribution of stroke subtypes between European and African descent stroke patients were observed in the South London Ethnicity and Stroke Study [40, 41] where small vessel stroke was 2.6 times more common in African descent patients, after controlling for risk factors and deprivation. The study, conducted between 1999 and 2010, prospectively recruited 1200 African and 1200 European descent stroke patients from a contiguous geographical area in South London, UK [40, 41]. All patients had brain imaging and 96% had either carotid duplex or magnetic resonance angiography to image the extracranial vessels. Intracranial computed tomography angiography or magnetic resonance angiography was performed to determine the presence of intracranial stenosis in 25.8 and 40.5% of European and African descent stroke patients. On brain imaging, leukoaraiosis, which is a radiological marker of small vessel disease, was also increased in African descent patients. Hypertension and diabetes, two major risk factors for small vessel disease stroke, were both more common in the African descent stroke patients, but the increase in small vessel disease persisted after controlling for these risk factors although it is also possible that increased severity of hypertension in the African descent patients could contribute to the increased risk of small vessel disease. Stroke due to extracranial large artery stenosis was 2.6 times more common among Europeans, on fully adjusted analysis. Cardioembolic stroke was also more common in European stroke patients. In contrast, stroke secondary to intracranial stenosis appeared to be more common in African descent stroke patients than in European descent stroke patients.

A high frequency of lacunar strokes is also a familiar pattern among South Asians, which suggests a greater prevalence of small vessel disease in South Asians

[42]. A trend toward more lacunar infarcts and less total anterior circulation infarcts in South Asians was early reported among all admissions to the St Mary's Hospital stroke unit [43]. In comparison with Europeans, higher rates of age-adjusted stroke (1.5-fold), lacunar infarction (threefold), and ischemic infarction due to large artery disease (twofold) were found in Pakistanis enrolled in a prospective 12-month study consisting of 273,327 adults (≥18 years) residents in Bradford (UK) [44]. Two South Asian studies which also classified their stroke population according to the TOAST taxonomy found a higher prevalence of lacunar strokes (42.7 and 68%) compared with large vessel infarctions (26 and 10%) [30, 45]. Predominance of intracranial disease over extracranial disease was reported among stroke patients of South Asian population [46].

The proportions and relative importance of stroke subtypes thus differ with ethnicity. The prevalence of small vessel disease was reported to be higher in South Asians than in Europeans [47]. In addition, intracranial atherosclerosis causes 30–50% of strokes in South Asian [48], whereas it is the cause of only 8–10% of strokes in Europeans [49, 50] although the causes for these ethnic differences remain unknown. Intracranial atherosclerotic stroke can be caused by branch occlusive disease as well as artery-to-artery embolism or hemodynamic impairment. Patients with branch occlusive disease often also show a mild degree of stenosis. Due to the relatively low frequency of intracranial atherosclerosis in Western countries, the option of intracranial atherosclerotic stroke in South Asian patients could be not adequately considered in Europe, and South Asian patients with intracranial atherosclerosis are likely to be classified as having other cryptogenic causes.

4.6 Ethnic Differences in Stroke Mechanisms and Implications for Treatment

While cardioembolism is now considered as the most common (25–30%) cause of ischemic stroke in Western countries, atherosclerotic stroke accounts for up to 25–65% of strokes in Asian countries [47]. Guidelines for stroke prevention emphasize the use of antiplatelet agents and statins for atherosclerotic strokes and anticoagulants for patients with atrial fibrillation (AF) based on the results of large clinical trials. However, from a therapeutic point of view, AF might be more complicated in Asian patients with ischemic stroke. While the use of anticoagulants is the standard treatment applied to prevent stroke in patients with AF, AF may not always be the cause of stroke in AF patients. In fact, one-sixth of strokes in AF patients were reported to be unrelated to AF and showed clinical and echocardiographic characteristics distinct from those with AF-related stroke [51]. Because the prevalence of micro- and macroangiopathy is higher in South Asians than in Europeans, more South Asian patients with AF are classified as having undetermined etiology with two or more causes, and differentiation of AF-related vs. AF-unrelated stroke may be more important in South Asians than in Europeans.

The pathogenic mechanisms of lacunar stroke are similar to those of hypertensive intracranial hemorrhage, and patients with lacunar stroke often experience

hemorrhagic stroke [52]. The two subclinical subtypes of lacunar stroke are cerebral deep microbleeds and leukoaraiosis [53]. Cerebral microbleeds are more common in Asians than in Europeans and are associated with intracranial hemorrhage as well as ischemic stroke [54], while leukoaraiosis may be caused by silent, acute lacunar infarcts [55]. The optimal treatment strategies may differ between the two conditions because the risk of subsequent intracranial bleeding was found to increase in the presence of cerebral microbleeds and the high risk and mortality of intracranial bleeding outweighed the modest benefit of antithrombotic agents in patients with at least five cerebral microbleeds [55]. Finally, specific stroke etiologies should be considered in certain stroke populations due to the presence of genetic differences between populations. For example, sickle cell disease can cause stenosis in cerebral vessels and can result in stroke in African populations but is very rare in Asian populations. In contrast, the prevalence of moyamoya disease is higher in Asians than in Europeans.

Conclusions

Although the global estimates of stroke morbidity and mortality favor high-income countries than their low- and middle-income counterparts, there are clear ethnic disparities in stroke mortality, morbidity, and survival across ethnic groups in high-income countries. Consideration of the above characteristics leads to the conclusion that the optimal treatment strategies may differ among patients with the same stroke subtype, with special regards to ethnic minority groups. Owing to the paucity of evidence, current guidelines do not provide detailed treatment strategies according to the subclassification of stroke subtype in ethnic minorities. Future studies should investigate different treatment strategies for the various subclassifications, such the optimal dose of statins for intracranial vs. extracranial atherosclerosis, the use of antithrombotics for white vs. red phenotypes of lacunar stroke, and the addition of antiplatelet agents to anticoagulation for AF-related vs. AF-unrelated stroke. The continuing advances in technology mean that more diagnostic tests will become available, but this does not mean that it will be possible to apply these advanced techniques in routine clinical practice. Continuous efforts are needed to refine the approach applied for the workup of patients with ischemic stroke belonging to ethnic minorities.

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Intracranial Atherosclerosis in Asian Populations

5

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5.1 Ethnicity and Distribution of Atherosclerosis Lesions

Different mechanisms play a role in the pathogenesis of ischemic stroke and other forms of ischemic brain injury. Small vessel, large-artery atherosclerosis, and cardioembolic stroke are the most common subtypes encountered in clinical practice. However, ethnic differences in the distribution of lesions in the cerebrovascular district have long been a subject of interest [1–3]. Caucasians have been reported to have a higher incidence rate of extracranial atherosclerosis, whereas among African-Americans and Asians, a higher rate of intracranial atherosclerosis was observed. Carotid stenosis was extensively studied in terms of epidemiology, pathophysiology, and treatment. Unfortunately, relatively little is known about intracranial atherosclerosis until recently when modern neuroimaging methods allowed noninvasive screening of susceptible patients. Stroke has become the leading cause of death in the People's Republic of China since 2005, causing about one fifth of all deaths annually (≈1.6 million deaths) [4]. Furthermore, it is estimated that there are ≈7.5 million survivors of stroke in China, with ≈2.5 million new stroke cases per year [5]. Improved stroke education and awareness of stroke in the past 30 years have helped in reducing stroke mortality. Many major risk factors for stroke were actually not well controlled in China during the study period, and the prevalence of hypertension (the most important risk factor for stroke) in China has increased rapidly in adult population since 1991 [5]. However, a different distribution of

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cerebrovascular atherosclerosis in Asian populations might also play a role. In China, intracranial atherosclerosis was reported to account for about 46–56% of stroke [6–11]. In Thailand, intracranial atherosclerosis was found in 47% of stroke patients. In Koreans, 56.3% of stroke patients had intracranial atherosclerosis although the authors used 30% stenosis as cutoff. In Singapore, significant intracranial stenosis was found in 47.9% of stroke patients [12]. The risk of stroke was reported to be higher for intracranial than for extracranial atherosclerosis. As the majority of the world's populations are Asians, it is reasonable to conclude that intracranial atherosclerosis is the most common vascular lesion in stroke patients worldwide. This point is now of interest to Europe because the observed ethnic variance in the distribution of cerebral atherosclerosis [1–3] might require a different approach to screening of high-risk patients belonging to ethnic minorities.

5.2 Anatomy of Main Intracranial Arteries

Intracranial arteries of major clinical interest are internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA). The ICA is the terminal branch of the common carotid artery, together with the external carotid artery. It starts at C3 and C5 vertebral level, and it is divided into seven segments (named from C1 to C7). The ICA gives rise to two terminal branches: MCA and ACA. MCA originates from the ICA and runs into the lateral sulcus where it then branches and gives blood to many parts of the lateral cerebral cortex. It can be subdivided into four parts: the horizontal segment (sphenoidal segment, M1), insular segment (M2), opercular segments (M3), and cortical segments (M4). The ACA is smaller than MCA and, at the level of corpus callosum, is divided into pericallosal and callosomarginal branches. The PCA represents the terminal branches of the basilar artery (BA) and irrigates the occipital lobes and posteromedial temporal lobes.

5.3 Stroke Mechanisms and Intracranial Stenosis

Ischemic stroke is usually classified on the basis of the presumed mechanism of the focal brain injury and the type and localization of the vascular lesion according to the TOAST classification [13] in (1) large-artery atherosclerosis (LAAS), which may be extracranial or intracranial; (2) cardioembolic infarct (CEI) (embolism from a cardiac source); (3) lacunar infarct (LAC) (small vessel disease); (4) stroke of other determined etiology (ODE) (such as dissection, hypercoagulable states, or sickle cell disease); and (5) stroke of undetermined etiology (UDE).

The certainty of the classification of the ischemic stroke mechanism is far from ideal and reflects the inadequacy of the diagnostic workup in some cases to visualize the occluded artery or localize the source of the embolism. As regards

intracranial stenosis (ICS), patterns of ischemic stroke are (a) border zone infarctions as a result of hypoperfusion due to a highly stenotic artery, (b) territorial infarctions as a result of artery-to-artery embolism, and (c) lacunar infarction due to plaque extension over small penetrating artery ostia (also known as branch occlusive disease).

It might be beneficial to divide the atherosclerotic subtype into isolated intracranial and extracranial (with or without intracranial) atherosclerosis subtypes. Differences in clinical and neuroimaging features and risk factors have been reported between extracranial (e.g., cervical carotid) and intracranial atherosclerosis [14, 15]. Previous studies have found atherosclerosis to be frequently localized to either the intracranial or the extracranial arterial system, rather than occurring in both systems [14, 15]. More importantly, intracranial stenosis can be caused by diverse conditions, including moyamoya disease, dissection, vasculitis, and reversible cerebral vasoconstriction syndrome. In contrast, atherosclerosis is the main cause of cervical carotid stenosis, with only rare exceptions of carotid dissection, fibromuscular dysplasia, Takayasu arteritis, and radiation arteritis being differentiated clinically. In addition, intracranial atherosclerotic stroke can be caused by branch occlusive disease as well as artery-to-artery embolism or hemodynamic impairment. Patients with branch occlusive disease often show a mild degree of stenosis and are misclassified as having lacunar stroke or other cryptogenic stroke.

In a large prospective study, different stroke mechanisms were studied in acute stroke patients with ICS (>50%) as evaluated by MRI DWI (diffusion-weighted imaging) and MRA, CTA, or DSA [16]. The following prevalence of stroke mechanisms was reported in intracranial atherosclerosis: artery-to-artery embolism (46%), perforator branch occlusion (21%), in situ thrombo-occlusion (19%), hemodynamic impairment (1%), and mixed (13%) [17]. In another study of more than 130 symptomatic ICS patients, similar results were shown: artery-to-artery embolism caused approximately 50% of strokes, perforator occlusion about 25%, hypoperfusion in <10%, and mixed in 16% [18]. With regard to localization, intracranial atherosclerosis in the anterior circulation was more often associated with artery-to-artery embolism (52% vs. 34%) and less often with perforator branch occlusion (12% vs. 40%) than intracranial atherosclerosis in the posterior circulation [16]. Studies with microembolic signal monitoring by transcranial Doppler indicate that a combined embolism-hypoperfusion mechanism could be common in symptomatic MCA stenosis. In a prospective study of 30 patients with symptomatic MCA stenosis, TCD monitoring showed microembolic signals in 8 out of 16 patients with border zone infarcts [17]. Hemodynamic compromise in conjunction with multiple small artery-to-artery emboli may result in border zone infarctions because of failure to clear emboli in a poorly perfused brain area [17].

The risk factors, vessel wall pathology, and treatment strategies may differ between these two subtypes of intracranial atherosclerotic stroke. Patients with branch occlusive disease often show a mild degree of stenosis and are misclassified

as having lacunar stroke or other cryptogenic stroke. However, high-resolution MRI studies have demonstrated intracranial plaques occluding perforating arteries, which suggests that statin plays a role in these patients [19].

5.4 Diagnosis, Quantification, and Characterization of Intracranial Stenosis

In general, timely diagnosis is important in ICS because time is a predictor of stroke recurrence, that is, a higher recurrent stroke risk in patients within 2.5 weeks after the first ischemic event than later (hazard ratio, 1.7; 95% CI 1.1–2.7) [20]. Raised mean blood flow velocities on TCD or luminal narrowing and absence of flow, or both, on MRI, CT, and catheter angiography are used to identify and quantify the severity of intracranial atherosclerosis. The application of advanced diagnostic technologies may reduce the proportion of patients diagnosed with cryptogenic stroke. These techniques could also play a role in diagnosing patients with known vascular and cardiac abnormalities.

5.4.1 Digital Subtraction Angiography (DSA)

DSA is considered the gold standard for the quantification of stenosis and collateral flow assessment [21]. DSA has been widely used to evaluate ICAS because the high spatial resolution allows a high image quality to be achieved. However, disadvantages include high costs, limited availability, and the small risk (<1%) of severe periprocedural complications.

5.4.2 Transcranial Doppler Ultrasound

Transcranial Doppler ultrasound (TCD) is safe, inexpensive, and easily applied in clinical practice. Transcranial Doppler provides flow information in real time, can detect microembolic signals, and can provide information on brain self-regulation.

In clinical practice, the most frequently used transducer is a pulsed Doppler sectorial probe with a 2.0–3.5 MHz emission frequency (Fig. 5.1). The probe can be fixed to the scalp with a headband so that the same angle of insonation for continuous flow velocity recordings is maintained throughout the examination. TCD is conducted using either transcranial color-coded duplex sonography, in which it is displayed in a two-dimensional color-coded image, or, once the desired blood vessel is insonated, blood flow velocities may be measured using pulsed-wave (PW) Doppler (Fig. 5.2). The TCD with combined colorflow and power Doppler allows direct imaging of the intracranial arteries, their anatomic course, diameter, and relationships with the adjacent structures [22, 23]. Because of its high negative predictive values, TCD is a good screening test, but might be inadequate to measure the severity of disease in some circumstances. TCD is highly operator dependent and time consuming, and clinical use can be limited by the

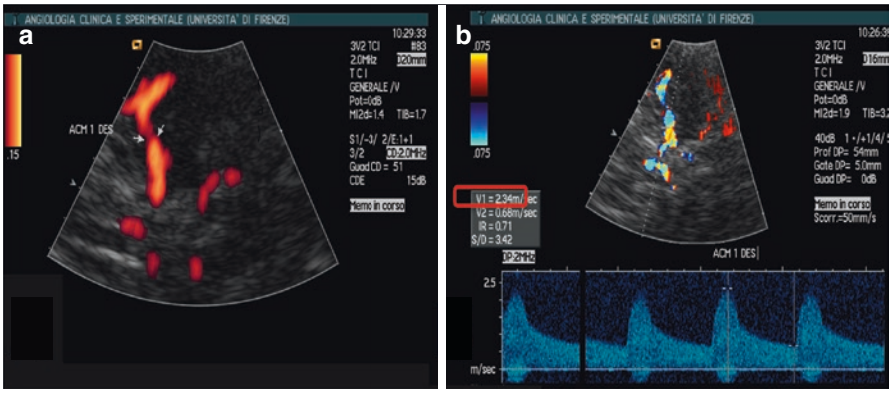

Fig. 5.1 Power Doppler provides a direct visualization of focal middle cerebral artery (MCA) lumen reduction (**a**). Spectral Doppler analysis confirms the presence and allows to grade the severity of MCA stenosis (**b**)

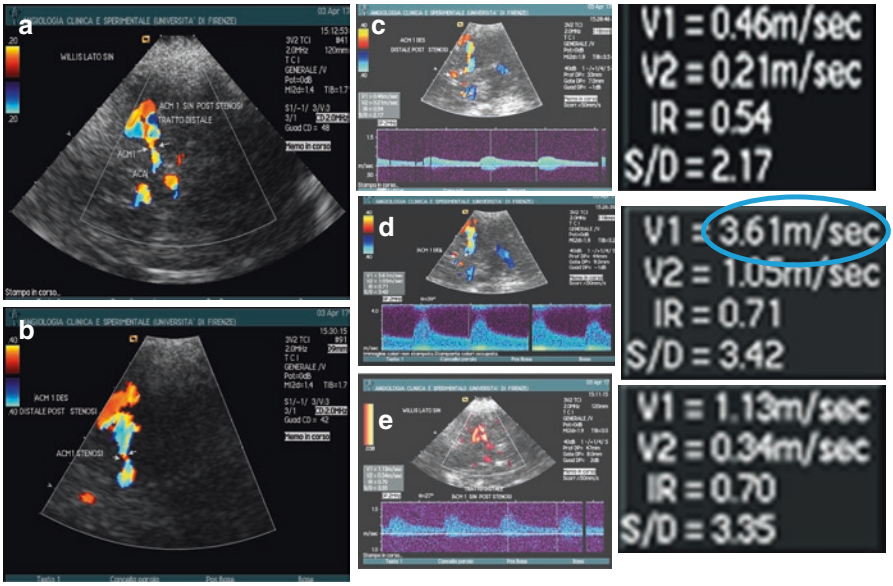

Fig. 5.2 Color flow mapping allows to detect the site and extension of a lumen reduction and the presence of a focal turbulent flow (panels **a** and **b**). The sequential interrogation of contiguous arterial segments (**c**, **d**, and **e**) can provide the evidence of a focal increase in peak systolic velocity in the middle part of MCA (PSV = 361 cm/s), consistent with a >50% lumen reduction

possible absence of suitable temporal bone acoustic window (absent up to 20% of patients). Stenosis of intracranial carotid artery (any degree of stenosis) can be diagnosed when the peak flow velocity at TCD was ≥120 cm/s for ACA, ≥155 cm/s for MCA, ≥100 cm/s for PCA and BA, and ≥ 90 cm/s for intracranial vertebral arteries (VA) (Fig. 5.2).

5.4.3 Computer Tomography Angiography (CTA)

CTA is a useful screening tool because it is only minimally invasive, fast, and more widely available in clinical practice than MRA and DSA. CTA has a high interoperator reliability when assessing stenosis grade, and it is less susceptible to motion artifacts compared with MRI techniques. Disadvantages are the exposure to radiation and the necessity of iodinated contrast material use. CTA is not suitable for depiction of vessels with a diameter smaller than 0.7 mm, due to limited spatial resolution. Also, dense and extensive mural calcifications may reduce the accuracy of measuring the degree of stenosis with CTA. Overall, studies show that CTA is useful as a screening tool for identification of ICAS and intracranial occlusion. It may therefore be used to exclude cases of ICAS, replacing the use of DSA in many cases.

5.4.4 Magnetic Resonance Angiography (MRA)

Time-of-flight (TOF)-MRA is a noninvasive technique that does not use any radiation nor contrast material to visualize arteries (Fig. 5.3). The main disadvantage is the high susceptibility of TOF-MRA to flow-related artifacts. Complete absence of MR signal in an artery can occur even though the vessel is not entirely occluded. Severe stenosis not only causes these flow-related artifacts in most cases but also in <70% stenosis these artifacts are reported, which influences the reported sensitivity and specificity values of MRA compared with DSA. Studies comparing TOF-MRA and CTA for its ability to identify intracranial stenosis and occlusion compared with DSA conclude that CTA is superior to TOF-MRA; CTA had higher sensitivity than MRA (98% compared with 70%) and a higher PPV than MRA (93% compared with 65%) [24]. Studies do not indicate that MRA can replace the gold standard DSA

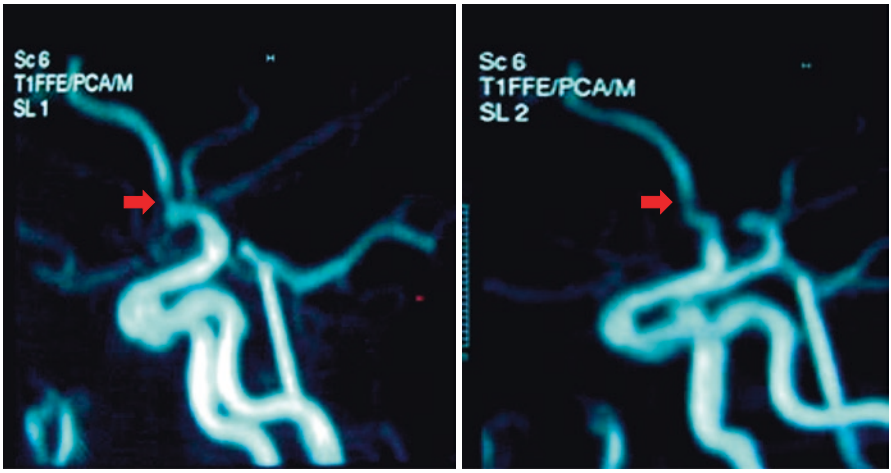

Fig. 5.3 MRA representation of a proximal MCA (M1) >50% stenosis

with respect to the degree of vessel stenosis in the intracranial vasculature. High-resolution (HR) MRI can already be accomplished at a field strength of 1.5-Tesla (T). Studies with higher magnetic field strengths (3 or 7 T) report the ability to detect smaller intracranial arteries, the vessel wall, and atherosclerotic plaques. The stenosis grade for the HR MRI has a good agreement with the DSA stenosis grade. An important advantage of HR MRI is that various components from the plaque can be identified, in which the presence of lipid core and intraplaque hemorrhage has been associated with vulnerability of atherosclerotic plaques.

As regards the characterization of ICS, luminal imaging techniques traditionally used for the assessment of vasculopathy do not adequately assess vessel wall pathology and can be of limited value in differentiating non-atherosclerotic causes of stenosis of intracranial vessels. While anatomic diagnosis of arterial narrowing is made with reasonable accuracy, ascribing the etiology for the stenosis remains challenging in clinical practice. Radiologic mimics of ICAS are often encountered such as vasculitis, moyamoya disease, fibromuscular dysplasia, or vasospasm and may require multimodal imaging to be able to distinguish between them. Luminal imaging techniques traditionally used for the assessment of vasculopathy do not adequately assess vessel wall pathology and can be of limited value in differentiating between causes of intracranial vasculopathies. ICAS generally reveals eccentric thickening with variable enhancement, whereas vasculitis shows smooth, intense, and homogeneous enhancement.

5.5 Epidemiology of Intracranial Stenosis

Most of the available data were obtained in patients after acute stroke, although few studies were also performed in patients at risk for stroke and in the general population.

5.5.1 Stroke Patients

In an angiographic comparison between two groups of stroke patients, one Japanese, another American [25], the atherosclerotic occlusive vascular disease in the white population was more commonly demonstrated in the extracerebral vessels than in the Japanese population, while atherosclerotic plaques were more frequent in the small intracranial vessels among the Japanese [25]. Very high rates of middle cerebral artery stenosis (up to 61% of total stenosis) and middle cerebral artery occlusion (up to 62% of occlusions) were found in an angiographic study of cerebrovascular disease in Japan [26].

Among patients with ischemic stroke, intracranial stenosis was considered the etiology for stroke in 9% of whites, 17% of African-Americans, and 15% of Hispanics in the Northern Manhattan Stroke Study in the 1993–1997 period [27]. In a recent prospective, multicenter, hospital-based, transcranial ultrasound study performed in Italy, ICAS was identified as a cause of ischemic stroke in almost 8.7% of first-ever

Table 5.1 Prevalence of intracranial stenosis (ICS) in Oriental (China, Thailand, Korea) populations

Author	Year	Ref	Population	Ethnicity	Total (*n*=)	ICS (*n*=)	ICS %
Huang HW	2006	[31]	General population	Chinese	1068	63	5.9%
Wong KS	2007	[32]	General population	Chinese	590	41	6.9%
Wong KS	2007	[35]	High-risk patients	Chinese	3057	385	12.6%*
Modesti PA	2017	[34]	High-risk patients	Chinese	96	17	18%
Huang YN	1997	[6]	Stroke or TIA	Chinese	96	49	51.0%
Wong KS	2000	[7]	Stroke or TIA	Chinese	705	329	47.0%
Suwanwela NC	2003	[9]	Stroke or TIA	Thailandese	108	51	47.0%
Lee SJ	2003	[8]	Stroke or TIA	Koreans	142	80	56.0%
De Silva DA	2007	[10]	Stroke or TIA	South Asians	200	102	54.0%
Wang Y	2014	[11]	Stroke or TIA	Chinese	2864	1335	46.6%

* = only stenosis of the middle cerebral artery were assessed

stroke patients [28]. Patients consecutively admitted for their first-ever acute ischemic stroke were assessed prospectively over a 24-month period either with transcranial color-coded Doppler sonography (TCCS) or transcranial Doppler (TCD). ICAS was diagnosed when there was an evidence of a cerebral infarction in the territory of a ≥50% stenosis detected by TCCS/TCD and confirmed by magnetic resonance angiography or computed tomography angiography [28]. The prevalence of intracranial stenosis in Oriental (China, Thailand, Korea) patients admitted with ischemic strokes was conversely very high ranging between 46 and 56% (Table 5.1) [6–11].

Using noninvasive Doppler methods, a prospective study showed a 51% prevalence of intracranial arterial lesions among Chinese patients referred for the investigation of TIA [6]. The rate of intracranial disease was approximately three times that of extracranial disease [6]. In a prospective study [10] enrolling 200 consecutive ethnic South Asian patients with acute ischemic stroke in Singapore, intracranial large-artery disease at transcranial color-coded Doppler was prevalent among 54% of all stroke subtypes and was independently associated with hypertension and higher serum erythrocyte sedimentation rate. Comparable rates (46.6%) were found using magnetic resonance angiography in 2864 consecutive patients who experienced an acute cerebral ischemia <7 days after symptom onset in 22 Chinese hospitals [11]. ICAS was defined as ≥50% diameter reduction on magnetic resonance angiography.

It has been observed that extracranial atherosclerosis is increasingly common among Asian populations. Among 705 consecutive Chinese stroke patients, 258 patients (37%) had intracranial lesions only, 71 (10%) had both extracranial and intracranial lesions, and 16 (2.3%) had extracranial lesions only [7]. Some investigators postulate that the changed lifestyle, particularly the eating habit, might determine the alteration of the site of vascular pathology. In a retrospective study [9] considering patients with ischemic stroke in the carotid territory, among the patients with extracranial stenosis, 98% had associated intracranial disease, whereas none of those with intracranial stenosis had more than 50% of extracranial carotid stenosis. Liu et al. [29] reported that, in Taiwan Chinese, 19 (42.2%) of 45 patients with steno-occlusive extracranial carotid artery disease had combined intracranial lesions on magnetic resonance angiography. Among 142 consecutive patients who had atherosclerotic

steno-occlusive lesions (defined as ≥30% narrowing of the luminal diameter or occlusion) of an extracranial carotid artery confirmed by conventional angiography, intracranial atherosclerotic disease was observed in 53% of the patients [8].

Patients with intracranial large-artery disease had more severe stroke, stayed longer in the hospital, and had higher risk of recurrent stroke [11]. Importantly, the degree of stenosis assessed with magnetic resonance angiography was not the only independent predictor for recurrent stroke. Other factors such as diastolic blood pressure, no use of antithrombotic drug, complete circle of Willis, and history of cerebral ischemia or heart disease and family history of stroke were also independent predictors [11].

5.5.2 High-Risk Patients

In a cohort of patients recruited in Hong Kong with at least one vascular risk factor (age > 65 years, hypertension, diabetes mellitus, ischemic heart disease, hyperlipidemia) without history of stroke or TIA (mean age 56 years), the overall prevalence of MCA stenosis was 12.6% [30]. In the same study, the prevalence of MCA stenosis increased from 7.2 to 29.6% according to the number of associated risk factors [30], elderly, hypertension, diabetes, and hyperlipidemia being associated factors. A strong association between ICS and T2DM (OR 2.9–5.9) was also consistently observed in different studies [31–33]. These figures fit well with recent data obtained in Chinese migrants in Europe [34]. In Europe vascular screening is commonly limited to extracranial vessels. Therefore, Chinese patients with newly diagnosed T2DM underwent the screening of cerebral vascular lesions. Minor plaques of carotid artery were identified in 48 patients (50%). No patient had carotid stenosis of any degree. Four (4.2%) of the 96 investigated patients had at least one cerebral artery that was unable to be insonated. Seventeen out of the 96 patients had at least one ICS of any degree with a per person prevalence of 18.2%. Among all vessels included in the analysis, ICS was most prevalent in middle cerebral artery (n = 13, 13.6%) and posterior cerebral artery (n = 12, 12.5%). Nine patients out of the 17 participants with any ICS (52%) had >1 intracranial lesions. More precisely eight patients had lesions in one vessel, five patients had lesions in two vessels, and four patients had lesions in three vessels [34]. The present findings may lead to greater attention to intracranial vessels in Chinese outpatients with T2DM.

Transcranial Doppler does not provide information regarding the pathological nature of the stenosis. In addition to atherosclerosis, other conditions may lead to increase in blood flow velocity in the cerebral arteries.

5.5.3 General Population

There are limited data on the prevalence of asymptomatic intracranial stenosis in the general population. Wong et al. [32] studied intracranial stenosis in a population-based study using TCD and reported intracranial stenosis in 6.9% of Chinese

population aged ≥40 years. Huang et al. [31] studied middle cerebral artery (MCA) stenosis using TCD in 1068 Chinese subjects with adequate acoustic windows aged ≥50 years with no history of stroke or TIA and reported MCA stenosis in 5.9%.

5.6 Treatment Options for Atherosclerotic Intracranial Stenosis

The present treatment of patients with ischemic events attributable to intracranial atherosclerotic stenosis is based on a combination of antiplatelet drugs and optimization of blood pressure and LDL cholesterol values through lifestyle modification and drug treatment [21, 36, 37]. Intracranial atherosclerosis is one of the most common causes of stroke worldwide and is associated with a particularly high risk of recurrent stroke. Despite this, there have only been a few large, multicenter randomized trials evaluating stroke preventive therapies for this disease.

In the large, double-blind, randomized controlled trial called Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) [38], 569 patients with stroke or TIA attributable to 50% to 99% intracranial stenoses of the MCA, intracranial ICA, intracranial vertebral artery, or basilar artery were randomized to aspirin 1300 mg or warfarin (target international normalized ratio [INR], 2–3). This double-blind trial was stopped early because of higher rates of death and major hemorrhage in the warfarin arm (aspirin group, 3.2%; warfarin group, 8.3%; HR 0.39; 95% confidence interval [CI] 0.18–0.84; $P = 0.01$). The mortality rate was lower in the aspirin group (aspirin group, 2.4%/year; warfarin group; 5.2%/year; HR 0.46; 95% CI 0.23–0.90; $P = 0.02$). Based on these results, oral anticoagulation is now rarely used in patients with ICAS. NOACs have yet to be tried in patients with non-cardiogenic stroke. Although patients in the WASID trial were given aspirin 1300 mg/day, on the basis of data for general safety and efficacy, daily aspirin doses of 50–325 mg are recommended [39]. However, in WASID trial, the 1- and 2-year rates of recurrent ischemic stroke in the territory of the stenotic artery were high (12% and 15% in the aspirin arm and 11% and 13% in the warfarin arm, respectively) [20]. In recent years, two strategies were proposed for the treatment of high-risk patients: aggressive medical therapy (combination antiplatelet therapy and intensive management of risk factors) and percutaneous transluminal angioplasty and stenting (PTAS). Three trials have compared different antiplatelet therapies in patients with intracranial arterial stenosis, but the primary end points in all these trials were related to imaging or transcranial Doppler ultrasound findings [40–42]. There have been no randomized trials to evaluate the effectiveness of clopidogrel alone or the combination of aspirin and dipyridamole for prevention of recurrent stroke in patients with intracranial arterial stenosis. In the recent CHANCE substudy on 481 patients with ICAS [43], there was no statistically significant trend for more favorable outcomes (recurrent strokes at 90 days) in the clopidogrel plus aspirin group than in the aspirin monotherapy group (11.3% vs. 13.6%).

In the Stenting and Aggressive Medical Therapy for Intracranial Stenosis (SAMMPRIS) trial [36], aggressive medical management using aspirin plus

clopidogrel was compared with angioplasty/stenting. Aggressive medical therapy in both arms consisted of aspirin 325 mg/d, clopidogrel 75 mg/d for 90 days after enrollment, intensive risk factor management that primarily targeted SBP <140 mmHg (<130 mmHg in patients with DM) and LDL-C < 70 mg/dL, and a lifestyle modification program [36]. Symptomatic patients with ICAS of 70–99% of the diameter of a major intracranial artery were enrolled. The primary end point was stroke or death within 30 days after enrollment or stroke in the territory of the qualifying artery beyond 30 days. Enrollment in SAMMPRIS was stopped after 451 patients had been randomized primarily because the 30-day rate of stroke and death was significantly higher in the stenting arm. By 30 days, 33 (14.7%) of 224 patients in the stenting group and 13 (5.8%) of 227 patients in the medical group had died or had a stroke (percentages are product limit estimates). The early benefit of aggressive medical management over stenting with the Wingspan stent for high-risk patients with intracranial stenosis persists over extended follow-up [37].

In the VISSIT (the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) trial, worse outcomes after stenting were also shown with a different (i.e., balloon expanding) stent in comparison with medical therapy in symptomatic intracranial atherosclerotic stenosis (24% vs. 9% at 30 days, 36% vs. 15% at 12 months follow-up) [44].

Therefore, current guidelines recommend aspirin 325 mg/d for patients with a stroke or TIA caused by 50–99% stenosis of a major intracranial artery, the addition of clopidogrel 75 mg/d being reasonable for 90 days in patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70–99%) of a major intracranial artery [39]. This point is crucial for Oriental patients with atrial fibrillation where cerebral atherosclerosis was found to be more common with higher CHADS2 scores [45]. These patients may require additional measures for prevention of ischemic stroke, because of concomitant cerebral atherosclerosis, with possible combined use of an antiplatelet drug and oral anticoagulants. Asian patients are vulnerable to intracranial hemorrhage, and new studies with NOAC are needed.

Hypertension, diabetes, dyslipidemia, and cigarette smoking are risk factors associated with cerebral artery atherosclerosis including ICAS. Differences in risk factors between ICAS and extracranial atherosclerosis (ECAS) have been reported; dyslipidemia seems to be more closely associated with ECAS, while advanced hypertension, metabolic syndrome, or diabetes may be more closely associated with ICAS [16]. The presence of risk factors may also be linked to the severity of ICAS [46]. These risk factors should be aggressively managed for the primary and secondary prevention of stroke in patients with ICAS. Given the poor prognoses in patients with ICS [47], aggressive control of vascular risk factors as well as lifestyle modification is to be pursued to prevent ICS-related ischemic stroke. Maintenance of SBP below 140 mmHg and high-intensity statin therapy are recommended [39]. However, the intensity of blood pressure reduction for the secondary prevention of stroke remains unclear in ICAS patients. Although strict blood pressure control is generally recommended, the risk of hypoperfusion is to be considered [48]. Current guidelines emphasize lipid-lowering (statin) therapy to reduce the risk of atherosclerotic strokes. A single-center, randomized, single-blind clinical trial [49]

enrolled 120 Chinese patients with symptomatic ICAS identified by computed tomography angiography (CTA) and CT perfusion. Patients were randomly divided into the low-dose (10 mg/day), standard-dose (20 mg/day), and intensive-dose atorvastatin therapy (40 mg/day) groups in a 1:1:1 ratio. After 52 weeks of treatment, improvement in serum lipid profiles, degree of stenosis, and perfusion-related parameters was significantly better in the intensive-dose group. In addition, the cumulative probability of cerebrovascular events was significantly lower in the intensive group than in the low-dose group. These results suggest that high-intensity statin treatment may be safe and effective in Asian ICAS patients.

5.7 Non-atherosclerotic ICS: Moyamoya Disease

Moyamoya disease (MMD) is a chronic occlusive cerebrovascular disease with unknown etiology characterized by steno-occlusive changes at the terminal portion of the internal carotid artery (ICA). This occlusion results in the formation of a fine vascular network (the moyamoya vessels) at the base of the brain. The appearance of this vascular network on an angiogram looks like a puff of cigarette smoke drifting in the air. The disorder was called "moyamoya disease," because "moyamoya" means "puff of smoke" in Japanese [50]. In 2015 the Research Committee of MMD of the Japanese Ministry of Health, Labour, and Welfare revised the diagnostic criteria for definitive MMD to include patients with both bilateral and unilateral presentations of terminal ICA stenosis with an abnormal vascular network at the base of the brain. The current diagnostic criteria also state that a definitive diagnosis of MMD requires catheter angiography in unilateral cases, while bilateral cases can be promptly diagnosed using catheter angiography, magnetic resonance imaging (MRI), or magnetic resonance angiography (MRA).

The incidence of moyamoya disease is high in East Asia, and familial forms account for about 15% of patients with this disease. The prevalence of MMD is relatively high in East Asian countries being 6.03 per 100,000 in 2003 in Japan [51], whereas studies involving non-Asian populations are rare. Because both MMD and intracranial atherosclerotic stenosis (ICAS) are more prevalent in Asians than in Westerners, the increased prevalence of ICAS may in part be caused by adult-onset MMD that is misclassified as ICAS. In adult patients with intracranial occlusive disease, diagnostic criteria based on molecular or mechanistic classification rather than angiographic findings may be needed [52]. The female to male ratio was shown to be 1.8, and the distribution of age at onset has been suggested to have two peaks: one at 5 years of age and one lower peak at about 40 years of age [50]. The main pathological changes induced by MMD in the stenotic segment are fibrocellular thickening of the intima, irregular undulation of the internal elastic laminae, medial thinness (weakening of the media), and a decrease in the outer diameter [50].

Although uncommon, MMD is an important cause of non-atherosclerotic intracranial arterial disease, especially in East Asian countries. MMD is the most important cause of stroke and transient ischemic attack (TIA) in children in this region. The

clinical presentations of MMD include TIA, ischemic stroke, hemorrhagic stroke, seizures, headache, and cognitive impairment. The incidence of each symptom varies with the age of the patients. Ischemic symptoms, especially TIAs, predominate in children, and intellectual decline, seizures, and involuntary movements are also common in this age group. On the other hand, adult patients present with intracranial hemorrhages more often than pediatric patients do. Approximately 30% of MMD patients presented with intracerebral hemorrhage. Significant brain hypoperfusion may lead to cognitive impairment or intellectual disability (intellectual developmental disorder). Since most stroke episodes are related to hemodynamic insufficiency, ischemic strokes caused by MMD are rarely catastrophic. The mortality rates during the acute stage have been reported to be 2.4 and 16.4% in ischemic and hemorrhagic stroke types, respectively [53]. Although there have been few long-term follow-up studies of patients with MMD, reportedly 75–80% of patients follow a benign course without a significant compromise in their daily activities [54].

There are no effective medical therapies for moyamoya disease. Through the provision of collateral pathways, surgical revascularization is the most successful therapy to improve cerebral hemodynamics and to reduce the risk of subsequent stroke [50].

5.8 Conclusions: Which Options for Screening?

According to the current guideline recommendations, at a minimum, all acute stroke patients should have brain imaging with computed tomography or magnetic resonance imaging (MRI) to distinguish between ischemic and hemorrhagic events [39]. Intracranial vascular study is recommended when either intra-arterial fibrinolysis or mechanical thrombectomy (endovascular treatment) is contemplated for management [55], occlusion of middle cerebral being reported as the most frequent site of lesion in registry (46.9%) [56].

In the approach to patients with previous stroke or transient ischemic attack, high-risk modifiable conditions such as carotid stenosis or AF as the cause of ischemic symptoms are usually searched, and imaging of the intracranial arteries is considered in the diagnostic workup of cryptogenic stroke [57]. The search for major-risk cardioembolic source of embolism, such as atrial fibrillation, currently receives major attention in the Western countries, a position which could be justified by the low prevalence of intracranial stenosis in these populations. When facing different ethnic populations, this position can be misleading and the high prevalence of ICS in ethnic minorities should be considered.

Population-based studies have shown correlations between the severity of atherosclerosis in one arterial territory and the involvement of other arteries. Therefore, early detection of arterial disease in apparently healthy individuals has focused on peripheral arteries and in particular on the carotid arteries [58]. A specific approach for ethnic groups different from North American and European patients is not covered in current guidelines for stroke prevention [39, 59].

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Coronary Heart Disease Among Non-Western Immigrants in Europe

6

Pietro Amedeo Modesti and Ugo Fedeli

6.1 Coronary Artery Disease at a Global Level

According to the Global Burden of Disease 2016 Study (GBD 2016), a comprehensive assessment of cause-specific mortality, cardiovascular diseases remain the main cause of death globally [1]. Most importantly, between 2006 and 2016, total deaths from coronary artery disease (CAD) rose by 19.0%, increasing from 7.96 million deaths in 2006 to 9.48 million deaths in 2016. The world is not equally affected by the dynamics of this epidemic. Differently from what a young medical student may expect, the global rise of CAD can be entirely attributed to the sharp increase of coronary events experienced by low- and middle-income countries in the last decades, whereas the affluent part of the world experiences an opposite trend. This pattern is clear when the world is categorised according to quintiles of socio-demographic index (SDI), a summary indicator derived from measures of average income per capita, educational attainment, and total fertility [1]. So in 2016, middle-SDI and low-middle-SDI were the main contributors to ischaemic heart disease, whereas high-SDI (including countries in North America and Western Europe) and also high-middle-SDI world areas (with countries such as Argentina and Brazil) continued to witness a reduction of ischaemic heart disease [1]. The importance of prevention is currently recognised. Funding priorities, international programmes, attention to social determinants of health and behaviours, as well as the crucial role of access and quality of both primary and secondary healthcare in preventing deaths from non-communicable diseases are marking the differences in high-income

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countries. On the other hand, most deprived world areas are facing ageing, growth of the population, and most importantly a progressive reduction of neonatal mortality. However, probably we are not fully aware that the importance of socioeconomic inequalities in health is now evident also within most affluent countries of Western Europe [2].

6.2 Ethnic Disparities of CAD in Europe

6.2.1 Prevalence and Incidence

The early and most commonly adopted data source to describe chronic disease risk among populations is represented by mortality or admission to hospital registries at a national or local level.

Early studies, consisting in *cross-sectional* analysis of mortality statistics or surveys, were performed in the UK in the 1970s and 1980s. An investigation on the causes of deaths in immigrants to England and Wales highlighted that mortality due to ischaemic heart disease was high in subjects originating from the Indian subcontinent [3]. Immigrants from South Asia living in the UK were then confirmed as a population at highly raised risk for acute myocardial infarction [4]. The following analyses noted that rate ratios for coronary mortality were higher for both men and women born in South Asia [5]. The burden of cardiovascular disease (CVD) in the UK was reported to vary between ethnic groups and type of CVD diagnosis [6]. Many migrant SA populations show higher coronary heart disease (CAD) prevalence and mortality rates compared with native populations, a phenomenon demonstrated in several countries including Canada [7] and South Africa [8]. Further, CAD presents at a younger mean age in migrant SA populations compared with indigenous populations [9].

Incidence of CAD was then investigated in retrospective study or prospective follow-up of cross-sectional surveys (turning them into *cohort studies*). High incidence of AMI among South Asians was observed in different countries of Northern Europe such as Scotland [10], Sweden [11], Denmark [12], Norway [13], the Netherlands [14], and Italy [15].

In an early record-linked, retrospective cohort study of 4.6 million people that linked individual ethnic groups from the 2001 census to Scottish hospital discharge and mortality data from 2001 to 2003 [10], the *incidence of acute myocardial infarction* (fatal combined with non-fatal) was found to be higher in South Asian compared to non-South Asian both in men and in women [16].The following analyses of the same study with the combined endpoint of hospitalisation or community death, incidence of *chest pain and angina* [17], myocardial infarction, and heart failure [18] were observed to be higher in South Asian than in Europeans.

Using data on 3207 European (n = 1787) and South Asian (n = 1420) men from the Southall [3, 5] and Brent [19] population-based studies, which were conducted with identical protocols between 1988 and 1991 in west London and followed since

then for deaths and causes of death, incidence of coronary death was found to be higher in South Asian than in Europeans [20]. Over an 18-year follow-up of London healthy civil servants in the Whitehall II study, South Asians had higher frequencies of *typical angina* (17.0% vs. 11.3%, $p < 0.001$) compared with European individuals [19]. In contrast, African descents have been found to be at similar or lower risk of heart diseases compared to UK descent residents [21–23]. Compared to UK descent, people of South Asia (SA) (countries of the Indian subcontinent, India, Pakistan, Sri Lanka, Bangladesh, and Nepal) have also been found to be at increased risk of angina [17, 19], myocardial infarction [22], and coronary heart disease [23, 24]. Such finding has been confirmed in other European countries and North America [25].

High incidence of myocardial infarction in South Asians was recently observed also in the South of Europe [15]. During the 1990s and 2000s, the northeastern area of Italy has been a destination area for economic migrants mainly from Eastern Europe, Africa, and Asia, and this adult immigrant population is now mostly represented by first-generation immigrants. When considering the period 2008–2013 (analysis limited to the 20–59 age band), the standardised hospitalisation ratio for myocardial infarction (computed as the ratio between admissions observed for ethnic group and those expected according to age- and gender-specific rates registered among Italian citizens) of South Asians was 4.18 and 2.51 for men and women, respectively [15].

More recently, data obtained from primary care medical records were made available, giving the opportunity to perform comparisons across a broad range of outcomes and a full range of cardiovascular disease presentations. First lifetime cardiovascular disease diagnosis is indeed a turning point in a patient's experience, marking the end of the possibility of primary prevention and the beginning of the need to consider secondary prevention. In this large population-based cohort of over one million patients, with a median of 5.7 observation years and more than 95,000 events, strong evidence of heterogeneity in both size and direction of associations between ethnic group and 12 different CVD presentations were confirmed [26]. The study considered 1,068,318 patients (study cohort comprised of 971,283 UK descent, 38,292 South Asian descent, 30,896 African descents, and 27,847 mixed/other patients) registered between January 1997 and March 2010 from 225 general practices across England submitting data to Clinical Practice Research Database (CPRD). At study entry, patients were aged >30 years and free of diagnosed CVD and had been followed up for at least 1 year [26]. An overwhelming predominance of CAD diagnoses as the first lifetime expression of CVD in South Asian patients was observed. The hazard ratios (HRs) of South Asian compared to UK descent patients were 1.67 (1.52–1.84), 1.82 (1.56–2.13), and 1.67 (1.49–1.87) for initial lifetime diagnosis of stable angina, unstable angina, and myocardial infarction, respectively. Conversely, African descents were significantly less likely than UK descent to be diagnosed with one of the coronary heart disease diagnoses as a first CVD diagnosis. In African descents, increased hazards of ischaemic (1.29; 1.03–1.62) and haemorrhagic stroke (1.44; 0.97–2.12) were consistent with previous

studies. The associations were generally robust to adjustment for cardiovascular risk factors and medication use [26]. Screening for cardiovascular disease should thus be prioritised in South Asian patients, especially in the under 60s, compared to other ethnic groups.

6.2.2 Prognosis

The outcome after presentation with coronary disease seems to be not worse in South Asians in spite of their high prevalence of diabetes. In the retrospective cohort study of 4.6 million people [10], prognosis following myocardial infarction was investigated. After adjustment for age, sex, and any previous admission for diabetes, the hazard ratio for death at 2 years was 0.59 (95% CI 0.43 to 0.81), indicating a better survival among South Asians [27].

High CAD mortality in SA patients in the UK does not appear to be related to increased case fatality after AMI. In a retrospective cohort study of 4111 (17.8% of SA ethnicity) consecutive patients hospitalised for AMI between 1 October 2002 and 30 September 2008, primary end point being all-cause mortality, adjusted short-term (0–30 days) and long-term (>30 days—end of follow-up) survival was similar for SA patients and European patients [28]. This was consistent in subgroups of patients with STEMI and NSTEMI [28]. Rates of coronary reperfusion and revascularisation therapies during the index admission and prescription of secondary prevention treatments at discharge were similar between the ethnic groups. A North American study reported that South Asians have improved survival after AMI compared with Caucasians [29]. Therefore, although South Asian ethnicity is associated with a higher incidence of CAD, there appears to be a lower mortality once the CAD presents compared with Caucasian patients [29–31]. In the Netherlands, similar long-term (5-year) mortality rates after AMI among Indonesian subjects compared with the ethnic Dutch population were reported [32, 33]. Mortality at 5 years was conversely higher among Surinamese, Antilleans, and Chinese compared with the ethnic Dutch population [33].

The influence of ethnicity on the prognosis of patients undergoing percutaneous coronary intervention (PCI) was investigated in a retrospective analysis of 279,256 patients undergoing PCI from 2004 to 2011 from the British Cardiovascular Intervention Society national database, of whom 259,318 (92.9%) were Caucasian and 19,938 (7.1%) were South Asian. The main outcome measures were in-hospital major adverse cardiac and cerebrovascular events and all-cause mortality during a median follow-up of 2.8 years (interquartile range, 1.5–4.5 years) [34]. Despite being on average 5 years younger, the South Asians had more extensive disease, more complex cardiac histories, and a high rate of diabetes mellitus (42% vs. 15% for Caucasians). After correcting for these differences, in-hospital and medium-term mortality of South Asians was no worse than that of Caucasians. This suggests that in South Asians, the high prevalence of diabetes exerts an adverse influence on mortality, but ethnicity itself is not an independent predictor of outcome [34]. In this

cohort, STEMI was a more common presentation among South Asians, and consequently South Asians were more likely to undergo primary percutaneous coronary intervention than Caucasians.

On this basis, the proposed strategy to reduce persisting ethnic disparities in coronary mortality was to concentrate on reducing ethnic inequalities in disease incidence (i.e. primary prevention) [27]. The combination of higher incidence and equitable or even better prognosis in South Asian compared to white populations of coronary disease, coupled with the general ageing of the whole UK population, will lead to an increase in the size of the prevalent pool of South Asian people with coronary disease.

6.3 Risk Factors for Incident Coronary Artery Disease

6.3.1 Coronary Size

Asian-Indians have a much higher rate of CAD than Caucasians and at a younger age, with approximately 50% having their first CAD-related event at <55 years old, and 25% of those occur at <40 years old. Asian-Indians also have more severe cases of CAD [35, 36]. Research has suggested smaller coronary artery size to be one of the biggest causes for increased CAD in this population [35, 37–39]. However, currently, there is a lack of consensus regarding the contribution of coronary artery size in South Asian patients. Nonetheless, the South Asian population still has a higher prevalence of both severe diffuse and three-vessel CAD. Although studies are usually performed on a limited number of subjects, difference in the mean diameter size might have implications for more challenging performance of procedures such as coronary artery bypass grafting, stent implantation, or atherectomy.

6.3.2 Diabetes and Conventional Risk Factors

Compared with white people of European descent, South Asians living in high-income countries have an age standardised rate of type 2 diabetes of about two to four times higher, with these risks being highest in Bangladeshis (roughly four times) and lowest in Indians (about two times). A high risk of diabetes was observed also in subjects from other Asian countries, such as in Filipinos [40], Chinese [41], and African-Caribbeans [42–44]. However, although the presence of DM is associated with a significant increase in the overall death rate, its impact on CAD events and the related morbidity and mortality indeed may differ based on ethnicity because the risk of CAD is known to be higher for South Asians than African-Caribbeans. In a tri-ethnic community-based cohort study from northwest London, 4196 middle-aged subjects (mean age, 52 years) enrolled originally for assessment for DM and other cardiometabolic risk factors in the SABRE study were evaluated after a mean of 20 years for mortality and incident CVD, and survivors were invited for

follow-up evaluation [23]. Compared with Europeans, the incidence of CAD events was higher in South Asians but lower in African-Caribbean subjects [23]. More precisely the risk of coronary heart disease for diabetes was elevated in South Asians compared with their European counterparts (subhazard ratio 1.55; 95% CI 1.38–1.75) being reduced in African-Caribbeans (0.60; 0.49–0.75). There was a higher prevalence (almost threefold) of DM in South Asians and African-Caribbeans compared with Europeans. In Italy, South Asian ethnicity is at very high risk of diabetes, dyslipidaemia, and ischemic heart disease; immigrants from sub-Saharan Africa are affected by high rates of hypertension, cerebrovascular diseases, and heart failure, with a more pronounced unfavourable profile among females [45]. However, South Asians had more central obesity and atherogenic dyslipidaemia than the African-Caribbeans [23]. It is conceivable that a higher prevalence of insulin resistance [46] may account for a higher incidence of CAD events in South Asians when compared with both European and African-Caribbean cohorts [47]. Migrant South Asians seem to be more insulin resistant than white Europeans across the life course and potentially experience β-cell exhaustion at a younger age [46]. South Asians might experience transition through the high-risk prediabetes phase more rapidly than white Europeans. Thus, early intervention for diabetes prevention might be particularly important in this ethnic group [46].

Although the higher risks of cardiovascular complications in South Asians with diabetes relative to their European counterparts were confirmed in different cohort studies, taken together, these studies broadly reveal that risk differences, at least in Northern Europe, are appreciably lower than those seen a few decades ago [48, 49]. In clinical terms, cardiovascular risks have attenuated over time in South Asians with diabetes although retinopathy and renal complication risks remain high probably because of the high levels of glycaemia and rapid glycaemic deterioration noted in this population [46].

The early onset of diabetes in South Asians may have implication for the process of care, more precisely linked to a possible delay in the diagnosis. South Asians typically develop diabetes 5–10 years earlier than white Europeans and are therefore likely to benefit from earlier and more prolonged exposure to these agents, for example, statins and ACE inhibitors [50]. In Norway, general practitioners were found to deliver comparable quality of diabetes care to all ethnic patient groups with respect to process measures. However, the early onset of diabetes and the poor glycaemic control of relatively young ethnic minority patients represent a major concern because the diagnosis can be delayed [51].

Whilst glycaemia levels tend to still be somewhat worse in South Asians with diabetes relative to Europeans, such differences are likely to have markedly reduced over the last few decades [52]. Interestingly, over the last three to four decades, a reduction in the relative risk of mortality in South Asians with diabetes versus Europeans was observed [48]. A recent retrospective cohort study examines the relationship between ethnicity, life expectancy, and cause-specific mortality in the UK [49]. The years of life lost in association with diabetes relative to non-diabetes were fewer in South Asians compared with white Europeans [49].

Overall, cardiovascular disease risk associated with type 2 diabetes in migrant South Asians seems to have declined over time. This pattern would be consistent with improvement in risk factor management in South Asians with type 2 diabetes, particularly in lipids and blood pressure and to earlier diabetes diagnosis [46, 48]. Ethnically specific trials assessing benefit of blood pressure and diabetes treatment targets are now needed.

6.3.3 Healthcare Access

The importance of understanding and tackling healthcare inequities between ethnic groups, a significant factor in poor health outcomes, is increasingly recognised globally [53] and is a continuous matter of debate in the USA [54–58]. As regards the UK, there is little evidence of ethnic inequities in healthcare access and provision for cardiovascular health in the country. Small and narrowing ethnic health disparities were reported for cardiovascular diseases in primary [59] or secondary care settings [24]. Likewise in populations already selected for coronary angiography, South Asians have been shown not to be inequitably managed in terms of prescription medication [60].

However, evidence from the Whitehall II study suggests that suboptimal prescribing of lipid-lowering drugs is an issue for South Asians and that poor risk awareness is likely to impact patients' ability to participate in self-management of chronic disease [61]. Significant variations in adherence to prescribed medicines between the major ethnic groups were also observed by using aggregated prescribing data of 76 general practice surgeries in the Heart of Birmingham teaching Primary Care Trust [62]. In some minority ethnic groups, delaying or refusing medical treatment may indeed increase the risk of preventable morbidity and mortality in conditions such as cardiac disease [63], as also observed in the Netherlands among Surinamese, Antilleans, and Chinese population [33]. This is probably highly dependent on differences in receiving and adhering to secondary preventive measures. Previous literature showed a lower use of cardiac rehabilitation among ethnic minorities and difficulties in adhering to lifestyle changes and medication therapy [64]. Among Surinamese in the Netherlands, for example, poor blood pressure control has been reported [65]. In Italy, a distinct pattern of cardiovascular risk could be identified among South Asians, with high rates of diabetes, dyslipidaemia, ischemic heart disease, and chronic kidney disease [45]. Immigrants with diabetes were also reported to have a lower probability to undergo annual controls for glycated haemoglobin and renal function [66, 67], to be treated with glucose-lowering drugs [68], and to have poorer glycaemic control with respect to the native population [69].

Low compliance among migrant groups may be caused by several factors, such as linguistic and cultural barriers, low health literacy, and differences in health beliefs. Difficulties in reaching mutual understanding between the migrant patient and the physician may also contribute to non-compliance to lifestyle modifications and drug use.

6.3.4 Behavioural Factors

Despite conventional and novel risk factors, it has been shown that the beliefs and attitudes of South Asian patients have a direct result on their health outcomes. The lack of knowledge of CAD was found to be influenced by the country of birth [70]. This lack of knowledge of CAD is linked to poor dietary habits, low levels of physical activity, and social support. Despite healthy-eating campaigns, there was a definite lack of information among the South Asian community regarding dietary intake and its correlation with CAD. Most South Asians believe in a healthy diet, yet few adhere to dietary constraints. The usual diet for South Asian countries, which traditionally consisted of high carbohydrates and low fat, has been replaced with a decline in complex carbohydrates and a high intake of dietary fat. This deficit in dietary knowledge, along with urbanisation, has translated to poor dietary habits for Indians immigrating to Europe, leading to central obesity and a predisposition to accelerated atherosclerotic disease [71]. In general, South Asians do believe physical activity is important, yet it seems only younger men actually engage in regular physical activity. Women and children believe daily activity is sufficient, whereas elderly South Asians believe physical activity over a certain age would be detrimental to their health [72]. As a result, South Asians with CAD exhibit poor health-related quality of life when compared with Europeans with CAD [70].

6.3.5 Physical Activity and Fitness

The issue of physical activity has special implication in South Asians. Although lower physical activity levels are likely to contribute to the higher level of insulin resistance and diabetes risk, South Asians are still more insulin resistant than are white Europeans after adjustment for differences in physical activity level [73]. Increasing evidence suggests that South Asians have lower levels of cardiorespiratory fitness than do white Europeans, which cannot be accounted for differences in physical activity [73, 74]. Adjustments for differences in fitness between South Asian and white European men attenuated the excess HOMA-estimated insulin resistance noted in South Asian people [73]. As increases in fitness can only be brought about by physical activity or losing weight (as maximum oxygen uptake is generally expressed per kg of body weight), South Asians need to engage in greater levels of physical activity or have a lower body weight to achieve similar levels of fitness. In line with this, recent guidelines [75, 76] are suggesting higher levels of physical activity for South Asians for diabetes and cardiovascular disease prevention than the classical recommendation of 150 min of moderate intensity physical activity per week [77]. Irrespective of future mechanistic discoveries, South Asians need to be encouraged and helped, by various culturally appropriate methods, to maintain a high physical activity level and low body weight across the life course to prevent diabetes and cardiovascular diseases.

Conclusion

With the exception of variations by gender and age, no other epidemiological variable is as powerful as ethnicity in accounting for population-level differences in coronary artery diseases [78]. However, only few countries specifically consider ethnic minorities in their national health plans for metabolic and cardiovascular prevention. Furthermore, the main scientific societies in Europe still give limited attention to specific risk profiles in immigrant populations [2]. The effects of this between country and discrepancy are now becoming evident because the recently reported reduction in cardiovascular disease risk of some ethnic groups is not equally observed in Europe. Of utmost importance, public health professionals, healthcare workers, and policymakers are often unaware of a rapidly changing scenario.

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Hypertension and the Heart in Africa

7

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7.1 Introduction

Cardiovascular disease (CVD) constitutes a major public health problem both in the developed and developing countries. Africa is characterized by a lack of good registries on incidence and mortality of non-communicable diseases (NCDs). Nevertheless, the Global Burden of Disease group [1], with the data available, showed recently that among the estimated 422 million cases of existing cardiovascular disease in the world in 2015, the age-adjusted highest prevalence of cases were from western and eastern Africa. Specifically, hypertensive heart disease was more prevalent in Africa, and this was accompanied by a higher mortality rate of this condition in this continent compared with other parts of the world.

Another important issue is the relative weight of CVD mortality related to the more important infectious diseases in Africa [2]. Of the 58 million deaths from all causes worldwide in 2005, an estimated 17.5 million were due to CVD, three times more deaths than those caused by infectious diseases including HIV/AIDS, tuberculosis and malaria combined.

LMIC are faced with a dual burden of communicable and chronic diseases, which require tertiary care, and a consequent diversion of the limited resources available. In conjunction with the loss of productive years of life, the consequences

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lead to economic constraints with an impact on both the private and the public sectors.

Sub-Saharan African (SSA) countries are currently experiencing one of the most rapid epidemiological transitions characterized by increasing urbanization and changing lifestyle factors [3], which in turn have raised the incidence of NCDs and CVD including hypertension [4].

The pattern of increasing risk factors with higher rates of urbanization is likely to affect most of SSA [5]. As "civilization" spreads, so does CVD, becoming an increasing health burden that requires skilful and cost-effective management [6].

7.2 The Epidemiology of Hypertension in Africa

Hypertension is the main risk factor for general morbidity and mortality in the world. With a worldwide distribution, its presence in SSA is relatively recent. A paper published in the 1930s [7] reported that among 1800 patients screened for 2 years, not a single case of high blood pressure was found in a rural community of Kenya. Since then, a great change has occurred. A recent review by Ogah et al. [8] revealed the prevalence of hypertension in the two national studies from SSA was about 31% (35.7% and 37% in men and 37% and 29% in women in Mozambique and Malawi, respectively). They also found that, in rural areas, the prevalence ranged from 16% in rural Rwanda to as high as 46.4% in a rural community in Eastern Nigeria. The values for urban studies ranged from 15.2% in the Democratic Republic of Congo to as high as 47.5% in Cameroon. During the last 40 years while in most of the developed world mean systolic and diastolic blood pressure are decreasing, in SSA, the situation is inverse with a significant increase of both in both sexes [9]. The evolution of the prevalence of hypertension and the mean systolic and diastolic blood pressure shows a constant increase in SSA making this continent the one with the highest prevalence rates of hypertension in the world. Added to this high prevalence, a second major issue is related to its extremely low levels of awareness. In most of these countries the levels of awareness are below 30%. Women and urban populations have a higher level of awareness compared with man and rural populations. Nevertheless in several countries, less than 10% of all hypertensive patients have their blood pressure controlled. In a recent review comparing the levels of awareness, treatment and control in different parts of the world between 2000 and 2010 [10], SSA countries were among the regions with the lowest levels of awareness, treatment and control, which allied with the high prevalence rates are likely to result in an enormous burden of target organ damage mainly stroke and heart failure. The rising incidence of hypertension, its high general prevalence and poor control, as well as the premature mortality, calls for more research into the details of hypertension on the continent.

7.3 From Hypertension to Hypertrophy to Heart Failure

Left ventricular (LV) hypertrophy (LVH) is defined as an increase in LV mass (LVM) either with or without LV geometric changes. As the current gold standard measurement for LV mass and LV geometric changes is echocardiography, we will primarily focus on the current literature pertaining to echocardiographic data. However, as Africa largely consists of poorly resourced communities with limited access to echocardiography, a section on electrocardiographic (ECG) determined LVH has also been included.

Currently various thresholds and indexations are used to define the presence of an increased echocardiographic LVM and hence LVH. These indexations and thresholds are discussed in detail below. The LV geometric changes depend upon the presence or absence of LV wall thickening. In this regard, concentricity is defined as an LV relative wall thickness (RWT, the ratio of the thickness of the LV wall to the diameter of the LV chamber diameter) of $\geq$0.42. Concentric LV remodelling refers to those patients in whom there is no LVH, but the RWT is $\geq$0.42, whereas in concentric LVH, there are both an increased LVM and RWT. Patients in whom LVH is present but the RWT is <0.42 are classified as having eccentric LVH.

The classification of patients according to the presence or absence of LVH and LV geometric changes is important as both have prognostic implications. In this regard, LVH is an independent predictor of cardiovascular mortality and morbidity [11]. In addition, LV geometric changes are associated with an increased risk of mortality and morbidity [12], with concentric LVH having the highest risk followed by eccentric LVH and then concentric remodelling [12, 13]. As there is a higher prevalence of concentric LVH in African American Blacks compared to Whites [14–16], the question arises whether such ethnic differences have been documented in Africa. Currently, no direct Black versus White comparisons are available in Africa; however, a high prevalence of concentricity similar to that in African American Blacks is reported in South African Blacks.

Although the prognostic implications of LVH and geometric remodelling in Africans living in Africa are currently unknown, longitudinal studies in African Americans suggest that LVH contributes more to the risk of cardiovascular mortality in Blacks than it does in Whites [17, 18]. Moreover, in African Americans, for every 100 deaths, 37% were attributable to LVH which is far greater than the percentages attributable to single-vessel disease (1%), LV systolic dysfunction (9%) and multi-vessel disease (22%) [17]. Bearing in mind the higher prevalence of LVH, especially concentric LVH, in Black Africans, and the higher mortality associated with LVH in Black African Americans [19], early detection of and intervention for LVH are paramount in Africa.

7.4 Indexations of LVM to Define LVH

To define LVH, various indexes of LVM have been used. The indexation of LVM to body surface area (BSA) is largely designed to eliminate the effects of body size, whereas the indexation to allometric signals of body height (e.g. 1.7 and 2.7) eliminates the impact of growth but not obesity on LVM. Consequently, indexation of LVM to allometric signals of height has been recommended in guidelines for the management of hypertension and for the assessment of LVH in the overweight and obese [20]. Indeed, in a large (n = 5004) multiethnic (White, Black, Hispanic and Chinese) community-based study in the USA, when using LVM indexed to BSA, the prevalence of LVH did not differ (p = 0.19) between normal weight (9.1%), overweight (7.5%) and obese (8.5%) participants [21, 22]. However, when using LVM indexed to height$^{1.7}$, the prevalence of LVH in overweight (17.6%) and obese (40.4%) was markedly higher compared to when using LVM indexed to BSA and indeed differed substantially from the prevalence in normal weight participants (9.2%, $p < 0.0001$) [21, 22]. Similar differences have been observed when assessing the prevalence of LVH in African populations. Data from a community-based study (n = 793 Blacks) in South Africa showed that the prevalence of LVH in overweight (28.1%) and obese participants (43.2%) when using LVM indexed to height$^{1.7}$ was higher ($p < 0.0001$) than that in normal weight participants (10.3%). Similarly, the prevalence of LVH in overweight (25.5%) and obese participants (41.8%) when using LVM indexed to height$^{2.7}$ was higher ($p < 0.0001$) than that in normal weight participants (10.3%). However, when using LVM indexed to BSA (overweight = 19.3%; obese = 18.9%), the prevalence of LVH was no different (p = 0.18) from that in normal weight participants (13.9%) [22–24].

7.4.1 Thresholds for Echocardiographic LVH

Thresholds for echocardiographic LVH have largely been derived from White populations. There is limited data from other ethnic groups and particularly from Black Africans. As ethnic groups differ in anthropometric variables which impact on heart size [25], ethnic-specific thresholds may be required. Indeed, the EchoNoRMAL study (see data provided for Europeans, Africans and African Americans in Table 7.1) showed substantial differences in the thresholds between ethnic groups. Nevertheless, to date, only two studies have defined thresholds for echocardiographic LVH in healthy, non-hypertensive, nondiabetic, nonobese Black Africans (Table 7.1) [26, 27]. Data from Woodiwiss and Norton (unpublished) are preliminary reported here [28]. The EchoNoRMAL study included 227 females from seven studies in Africa and 190 males from five studies in Africa. The countries from

Table 7.1 Thresholds for echocardiographic LVH in African compared to other ethnic groups (community studies)

Ethnic group	Population (*n*)	Gender (*n*)	LVM/BSA (g/m^2)	LVM/height$^{2.7}$ ($g/m^{2.7}$)	LVM/height$^{1.7}$ ($g/m^{1.7}$)	Reference
White/black (AA)	(265/65)[a]	Female (214)	≥83	≥51	≥60	[21]
White/black (AA)	(265/65)[a]	Male (116)	≥111	≥51	≥80 or 81	[21]
European	(3463 from 19 studies)[a]	Female (3463)	≥107[b]	≥50[b]	–	[26]
European	(3038 from 20 studies)[a]	Male (3038)	≥130[b]	≥57[b]	–	[26]
Black (African)	(227 from 7 studies)[a]	Female (227)	≥110[b]	≥59[b]	–	[26]
Black (African)	(190 from 5 studies)[a]	Male (190)	≥113[b]	≥51[b]	–	[26]
Black (AA)	(851 from 1 study)[a]	Female (851)	≥102[c]	≥51[c]	–	[26]
Black (AA)	(717 from 1 study)[a]	Male (717)	≥119[c]	≥52[c]	–	[26]
Black (SA)	(205 from 1044)[a]	Female (133)	≥97.7	≥47.8	≥72.6	[27, 28]
Black (SA)	(205 from 1044)[a]	Male (72)	≥119.0	≥50.6	≥83.4	[27, 28]
Black (SA)	(205/1044)[a]	Both (205)	≥109.2	≥49.7	≥78.6	[27, 28]
Black (SA)	(808) 43.6% with HT[d]	Female (525)	≥95	≥47	≥73.6	[23, 24]
Black (SA)	(808) 43.6% with HT[d]	Male (283)	≥115	≥50	≥83.2	[23, 24]
Black (SA)	(808) 43.6% with HT[d]	Both (808)	≥125	≥51	–	[23, 24]
Black (AA)	(108)[a]	Both (108)	–	≥52.9	–	[29]
Black (AA)	(1616) 57% with HT[d]	Both (1616)	≥105	≥50 to 51	–	[29]
Black (AA)	(1046) 57% with HT[d]	Female (1046)	–	≥47	–	[29]
Black (AA)	(570) 57% with HT[d]	Male (570)	–	≥50	–	[29]

HT hypertension; *AA* African American; *SA* South African; – data not provided

[a]Upper 95% CI derived in participants without clinically significant disease and normal clinical blood parameters who were normotensive and nondiabetic and had a BMI <30 kg/m^2 (or 18–25 kg/m^2 for [21])

[b]Values for age = 50 years

[c]Values for age = 30 years (only age for which values reported)

[d]Participants with prevalent cardiovascular disease excluded but participants with BMI > 30 kg/m^2 included

which these African participants were recruited were not listed. Thresholds were defined for LVM indexed to height$^{1.7}$ and height$^{2.7}$, but not BSA. It is clear that within the EchoNoRMAL study, the thresholds for African participants differed from those for Europeans as well as to some degree from those for African Americans. Similarly, the thresholds defined in the South African study [27] differed from those obtained in Europeans/Whites and African Americans, especially when LVM was indexed to height$^{1.7}$ or BSA. Indeed, the thresholds for LVM indexed to height$^{2.7}$ appear to show more uniformity across ethnic groups than thresholds for either LVM indexed to height$^{1.7}$ or BSA. These differences highlight the need to define thresholds specific to Black African populations. In addition, as within ethnic groups thresholds also differed according to gender, gender-specific thresholds are recommended (Table 7.1).

7.4.2 Prevalence of LVH and LV Geometric Patterns

Large cohort studies have provided evidence that LV mass indexed to height$^{2.7}$ [14, 15, 30] and the prevalence of LVH [14, 15] is higher in African Americans than in Whites. A higher LVMI (g/m$^{2.7}$) was evident in a longitudinal study of young adults (the Coronary Artery Disease Risk Development in Young Adults, CARDIA, study) (566 African Americans and 792 Whites) at both baseline [31] and after 5 years of follow-up [30] in both women and men, despite a low prevalence of LVH (<5%). Similarly, in the Hypertension Genetic Epidemiology Network (HyperGEN) study (1060 African Americans and 580 Whites), in multivariate analyses, the African Americans had a 1.8-fold higher prevalence of LVH (defined by indexation to height$^{2.7}$) and a 2.5-fold higher prevalence of LVH (defined by indexation to BSA) compared to the Whites [15]. In the Dallas Heart Study (1335 African Americans and 858 Whites) (age = 30–65 years), the prevalence of LVH (indexed to height$^{2.7}$ or BSA) was 2–3 times greater in African Americans compared to Whites [14]. The higher LVM observed in African Americans persisted after adjustments for fat mass, fat-free mass, SBP, age, gender and socioeconomic status [14]. Nevertheless, for a given level of SBP, a higher prevalence of LVH was observed in African Americans compared to Whites [14]. In addition, a greater degree of LV concentricity has been reported among African Americans compared to Whites [14–16]. Moreover, after adjusting for covariates, African Americans had a 2.3-fold higher prevalence of concentric geometry (defined by RWT $\geq$0.43) [15]. It has therefore been suggested that the greater LVM and LV remodelling in African Americans is driven by a greater pressure overload.

There are currently no direct evaluations of the prevalence of LVH and/or LV geometric patterns in Blacks versus Whites living in Africa. Data are therefore provided from a large cross-sectional community-based study in Blacks living in South Africa [28], for informal comparisons with data from the literature in Whites and African Americans (Table 7.2). It is clearly evident from this table that the prevalence of LVH is strongly influenced by the type of indexation of LVM. When LVM is indexed to BSA, the prevalence is much lower than when LVM is indexed to

Table 7.2 Prevalence of LVH and LV geometric patterns in African communities compared to other ethnic communities

Ethnic group	HT %	ECHO or ECG threshold	Gender (*n*)	LVH (%)	Normal (%)	Concentric remodelling (%)	Concentric LVH (%)	Eccentric LVH (%)	Reference
White	32%	LVMI (g/m^2) ≥112	Male (422)	6.0	–	–	–	–	[14]
Black (AA)	43%	LVMI (g/m^2) ≥112	Male (574)	14.0	–	–	–	–	[14]
White	27%	LVMI (g/m^2) ≥89	Female (436)	3.4	–	–	–	–	[14]
Black (AA)	48%	LVMI (g/m^2) ≥89	Female (760)	14.0	–	–	–	–	[14]
White	32%	LVMI ($g/m^{2.7}$) ≥48	Male (422)	8.7	–	–	–	–	[14]
Black (AA)	43%	LVMI ($g/m^{2.7}$) ≥48	Male (574)	25.0	–	–	–	–	[14]
White	27%	LVMI ($g/m^{2.7}$) ≥39	Female (436)	22.0	–	–	–	–	[14]
Black (AA)	48%	LVMI ($g/m^{2.7}$) ≥39	Female (760)	47.0	–	–	–	–	[14]
White	36.4%	MRI –	Both (1959)	5.0	86.0	9.0	1.0	4.0	[16]
Black (AA)	56.9%	MRI –	Both (1286)	12.0	76.0	12.0	6.0	6.0	[16]
White	36.4%	LVMI (g/m^2) –	Both (1959)	8.0	–	–	–	–	[16]
Black (AA)	56.9%	LVMI (g/m^2) –	Both (1286)	16.0	–	–	–	–	[16]
Black (AA)	60.2%	LVMI (g/m^2) ≥96 (female) ≥116 (male)	Both (4721)	8.2	80.0	11.8	3.9	4.3	[32]
Multiethnic (12.3% AA)	80%	LVMI (g/m^2) ≥95	Female (2670)	11.1	50.6	38.3	6.4	4.7	[33]
Multiethnic (12.3% AA)	80%	LVMI (g/m^2) ≥115	Male (1642)	5.4	54.3	40.3	3.4	2.0	[33]
Black (AA)	57%	LVMI ($g/m^{2.7}$) ≥47	Female (1046)	49.5	22.0	34.3	31.2	12.5	[29]
Black (AA)	57%	LVMI ($g/m^{2.7}$) ≥50	Male (570)	36.1	23.9	35.8	28.3	12.1	[29]
Black (SA)	43.6%	LVMI (g/m^2) ≥95	Female (525)	18.0	60.7	21.3	6.9	11.1	[24]

(continued)

Table 7.2 (continued)

Ethnic group	HT %	ECHO or ECG threshold	Gender (*n*)	LVH (%)	Normal (%)	Concentric remodelling (%)	Concentric LVH (%)	Eccentric LVH (%)	Reference
Black (SA)	43.6%	LVMI (g/m^2) ≥115	Male (283)	15.9	69.3	14.8	7.4	8.5	[24]
Black (SA)	48.2%	LVMI ($g/m^{1.7}$) ≥73	Female (698)	30.4	53.7	15.9	9.3	21.1	[28]
Black (SA)	48.2%	LVMI ($g/m^{1.7}$) ≥83	Male (346)	19.6	67.9	12.4	7.8	11.8	[28]
Black (SA)	48.2%	LVMI ($g/m^{1.7}$) ≥60	Female (698)	57.0	34.4	8.6	16.6	40.4	[28]
Black (SA)	48.2%	LVMI ($g/m^{1.7}$) ≥80	Male (346)	22.6	65.3	12.1	8.1	14.5	[28]
Black (SA)	48.2%	LVMI ($g/m^{2.7}$) ≥48	Female (698)	27.2	55.9	16.9	8.3	18.9	[28]
Black (SA)	48.2%	LVMI ($g/m^{2.7}$) ≥51	Male (346)	17.1	68.5	14.4	5.8	11.3	[28]
Black (SA)	48.2%	LVMI ($g/m^{2.7}$) ≥47	Female (698)	29.6	54.7	15.8	9.5	20.1	[28]
Black (SA)	48.2%	LVMI ($g/m^{2.7}$) ≥50	Male (346)	19.1	67.0	13.9	6.4	12.7	[28]
Black (SA)	48.2%	LVMI (g/m^2) ≥98	Female (698)	13.3	66.5	20.2	5.0	8.3	[28]
Black (SA)	48.2%	LVMI (g/m^2) ≥119	Male (346)	12.4	72.6	15.0	5.2	7.2	[28]
Black (SA)	48.2%	LVMI (g/m^2) ≥95	Female (698)	16.3	64.1	19.6	5.6	10.7	[28]
Black (SA)	48.2%	LVMI (g/m^2) ≥115	Male (346)	14.5	71.4	14.1	6.1	8.4	[28]
Black (AA)	57%	LVMI ($g/m^{2.7}$) ≥47	Female (1046)	49.5	22.0	34.3	31.2	12.5	[29]
Black (AA)	57%	LVMI ($g/m^{2.7}$) ≥50	Male (570)	36.1	23.9	35.8	28.3	12.1	[29]

HT hypertension; *LVH* left ventricular hypertrophy; *LVMI* left ventricular mass index; *AA* African American; *SA* South African; *MRI* magnetic resonance imaging; *ECHO* echocardiography; *ECG* electrocardiography; – data not provided

height$^{2.7}$. This is largely because indexation to BSA eliminates the effects of obesity on LVM. With respect to ethnic differences, the prevalence of LVH in Black South Africans more closely represents that in African Americans, with both being higher than in Whites. Similarly, as reported for African Americans versus Whites, there is a higher frequency of concentricity in the Black South Africans.

7.4.3 Detection of LVH: Electrocardiography (ECG) Versus Echocardiography and Challenges with Accuracy of ECG

Although the current gold standard for the detection of LVH is echocardiography, access to echocardiography proves to be problematic in Africa with vast areas of the continent being largely underdeveloped. Hence, in many settings, the detection of LVH relies on electrocardiography (ECG) as a more accessible and cost-effective option. However, it is well recognized that ECG criteria have a poor sensitivity in detecting LVH in comparison to imaging techniques [34]. In addition to comparisons between modalities used to detect LVH, ethnic differences in the ability of ECG to detect LVH have been reported [11]. Indeed, ECG criteria for LVH have been shown to be less well correlated with echocardiographic LV mass index in African Americans as compared to Caucasians [35]. These poor correlations may be attributed to increased ECG amplitudes in groups of African descent [36, 37], possibly produced by alterations in skin conductivity [38], or a diminished thoracic diameter reducing the distance from the skin surface to the heart [39]. In addition, an excess adiposity attenuates the utility of all ECG voltage criteria for LVH detection [40]. Consequently, the sensitivity of some ECG criteria may be particularly low for the detection of LVH in groups of Black African ancestry [40–42]. Hence, the value of ECG criteria for the detection of LVH in individuals of Black African ancestry has been questioned [41, 43]. Moreover, none of the current ECG voltage criteria can be recommended for the use in obese people of Black African ancestry [40]. However, as universal screening for LVH using echocardiography carries a high cost [44], solutions to reducing these costs are required. Moreover, bearing in mind the limited access to alternative measures, especially in Africa, various options to try and improve on the accuracy of ECG in detecting LVH have therefore been proposed.

A composite of Cornell product with Sokolow voltage or Sokolow product increases the diagnostic ability of ECG [45]. In addition, the composite of these voltages was associated with increased LVM index and a greater prevalence of echocardiographic LVH than either criterion alone. Moreover, in the LIFE study (only 5.8% Blacks), a combination of Cornell product and Sokolow-Lyon voltage was associated with a higher rate of myocardial infarction, stroke, cardiovascular death and all-cause mortality (4.8 year follow-up in hypertensive patients) in comparison to either criterion alone or neither [46]. These data from predominantly non-African communities suggest that in resource-limited settings (such as in Africa), ECG is still a useful tool especially when combined with other clinical criteria and when ECG criteria are combined in preference to being used alone.

However, are there data in African communities indicating possibilities for improving the accuracy of ECG criteria in detecting LVH?

In a study of 182 Cameroonian patients (69% with echocardiographic LVH), adjusting Sokolow-Lyon voltage to BSA or body mass index (BMI) improved the sensitivity from 26.5% to 55.8% and 58.4%, respectively [47]. However, these improved sensitivities were associated with reductions in specificity from 84.1% (unadjusted) to 46.4% (BSA adjusted) and 40.6% (BMI adjusted). Hence there was limited improvement in accuracy (unadjusted = 48.4%, BSA adjusted = 52.2%, BMI adjusted = 51.7%). Adjustments of Cornell voltage to BSA or BMI proved more promising with improvements in sensitivity from 37.2% to 68.1% and 69.0%, respectively, associated with increases in accuracy from 56.0% to 62.1% and 61.5%, respectively [47].

In 621 participants of African ancestry (South African), the accuracy of a combination of ECG criteria with readily available clinical variables [age, BMI, systolic blood pressure (SBP) or estimated glomerular filtration rate (eGFR)] was compared to the accuracy of ECG criteria alone [48]. Compared with ECG criteria alone, the combination of individual ECG criteria with age, BMI and SBP showed an improved level of performance [area under the receiver operator characteristic (ROC) curve, AUC] for all ECG criteria for LVH detection (ECG alone = 0.65–0.71; ECG plus age, BMI, SBP = 0.78–0.79, $p < 0.005$; ECG plus age, BMI, eGFR = 0.78, $p < 0.005$). In addition, the sensitivity at 85% specificity was increased (ECG alone = 32.6%–37.2%; ECG plus age, BMI, SBP = 46.5%–52.7%, $p < 0.005$; ECG plus age, BMI, eGFR = 42.6%–48.8%, $p < 0.005$). However, the use of both SBP and eGFR in combination with age, BMI and ECG criteria did not further enhance the performance of ECG criteria. Another approach to improve the ability of ECG criteria to detect LVH in a group of African descent (South African) was to correct ECG QRS voltages for the attenuating effect of BMI [27]. In 661 randomly selected participants (43.0% obese) of Black African ancestry in South Africa, correcting RaVL and Lewis voltages by the difference in the slope of BMI-voltage relations in those with BMI < 29 kg/m^2 versus those with BMI ≥ 29 kg/m^2 showed the greatest performance (AUC) for LVH detection (uncorrected RaVL = 0.69, corrected RaVL = 0.73, $p < 0.0001$) and also increased the sensitivity (uncorrected RaVL = 30.6%, corrected RaVL = 42.4%, $p < 0.0005$) with no change in specificity (uncorrected RaVL = 86.3%, corrected RaVL = 83.0%; $p = 0.28$). These novel approaches [27, 48] offer practically useful alternatives to improve the performance and sensitivity for LVH detection in individuals of African ancestry.

7.4.4 Factors That Contribute Towards Ethnic Differences in the Prevalence of LVH and Concentric Geometry

Various factors have been shown to impact upon the development of LVH and LV geometric changes. Importantly, increased LVM and LV remodelling among different ethnic groups could be influenced by socioeconomic factors, as well as dietary and lifestyle risk factors for cardiovascular disease. However, to date, the most

consistent explanation for an increased prevalence of LVH and LV geometric remodelling in African populations is a higher pressure load. A recent ECG study comparing Black Nigerians to White Flemish reported a threefold steeper relationship between SBP and ECG voltages in the Blacks versus the Whites [49]. The higher prevalence of ECG LVH in the Blacks (54.4%) versus the Whites (36.0%) was in part attributed to this steeper relationship. These data confirm previous reports of a steeper relationship between BP and LVM in African American Blacks compared to Whites [14, 30, 50]. Moreover, in a cross-sectional study of 430 hypertensive Black South Africans, blood pressure was the strongest determinant of ECG-LVH, independent of age, BMI, antihypertensive use and markers of a poor lifestyle (smoking drinking, cholesterol, diabetes) [51]. Similarly, in a study of stroke patients in Ghana and Nigeria, blood pressure was the major modifiable risk factor which independently predicted LVH [52]. In a cross-sectional community-based study of Blacks in South Africa, pulse pressure (the difference between SBP and DBP) was associated with an increased LVM index as well as LVH [33]. In addition, aortic stiffness (pulse wave velocity) was associated with an increased LVM index as well as LVH, independent of pulse pressure [33]. Although augmentation index (a marker of aortic function) is increased in Blacks in South Africa compared to Whites [53], whether the ethnic differences in aortic stiffness contribute towards ethnic differences in LVM and LVH is not known.

Obesity is also an important determinant of LVH and LV geometric changes. Independent of age and blood pressure, BMI was a strong predictor of LVM [54, 55] and RWT [55]. Even among healthy young adults, BMI is associated with increases in LVM and changes in LV geometry (increased RWT) [30]. The relationship between BMI and LVM was stronger in African Americans than Whites [30]. In Blacks in South Africa, an interactive effect between blood pressure and obesity has been noted for LVM [56], whereby adiposity-induced increases in LVM reflect an enhanced effect of blood pressure on LV growth. As consequence of this interactive effect (which may be mediated by leptin), increased blood pressure (never treated hypertension) impacts on LVM in centrally obese but not lean people of African descent in South Africa [56]. In addition, in a population sample of Blacks in South Africa with a high prevalence of obesity, excess adiposity promoted concentric rather than eccentric LV geometric changes. These effects of obesity on LV geometric changes were independent of conventional, central artery and 24-hour blood pressures [57]. Indeed, the greater clustering of insulin resistance and obesity with high blood pressure in African Americans compared to Whites may play a role in ethnic differences [58]. In addition, in the MESA study acculturation due to the adoption of poor lifestyle behaviours (such as poor diet, smoking and drinking) may explain ethnic differences in the prevalence of LVH [59]. However, formal comparative studies are required to determine whether these factors account for the high prevalence of LVH and concentric remodelling in Blacks in Africa versus other ethnic groups.

Similarly, although genetic factors play a role in the development of LVM and LV geometric changes, whether genetic factors explain ethnic differences is unknown. In a large family-based study (181 nuclear families) of Blacks in South Africa, both

LVM (independent of confounders including blood pressure) and LV geometric remodelling (independent of confounders including blood pressure and LVM) showed significant intrafamilial aggregation and heritability [60]. However, familial clustering of LVH and LV concentricity (independent of confounders including blood pressure) was also shown in a large family-based study of Whites [61]. Whether inheritance of these traits is stronger in Black Africans than Whites (and hence explains the higher prevalence of LVH and LV concentricity in Blacks than Whites) is not known.

7.4.5 Consequences of LVH and Geometric Changes

Bearing in mind the high prevalence of LVH, LV geometric changes and hypertension (one of the main determinants of LVH and LV geometric changes) in African communities, it is relevant to discuss the consequence of LVH and geometric changes. As LVH is associated with the development of decreased LV ejection fraction [62], heart failure [63] and mortality [11], it is speculated that the higher prevalence of LVH in African Americans would translate into a higher burden of systolic dysfunction and heart failure. However, to date there is no convincing data showing that LV dysfunction is more common in African Americans than it is in Whites. Indeed, in the CARDIA study, LV ejection fraction was comparable between African American and Whites [64]. Although, in multivariate analysis in the HyperGEN study, African Americans had a lower LV ejection fraction than in Whites, this did not translate into a higher prevalence of a decreased ejection fraction [65]. It is also unclear whether heart failure is more prevalent in African Americans than in Whites. Data from NHANES indicate that this is the case [66]; however, data from the National Health Interview Survey indicated a similar prevalence of heart failure in these two ethnic groups [67]. Importantly, in most studies, Black race was no longer a predictor of new heart failure after adjusting for potential risk factors [68, 69]. Nevertheless, in African American patients with hypertension, the risk of incident heart failure (4.7-year follow-up) was greater than in White patients with hypertension. Although this increased risk was independent of ECG LVH, in a cohort with echocardiographic LVH, increased LVM and RWT in African Americans compared to Whites were associated with decreases in systolic function (LV midwall shortening) [19].

As LV concentricity is more closely associated with heart failure with a preserved ejection fraction than heart failure with a reduced ejection fraction, it could be speculated that African populations are more prone to the development of heart failure with a reduced ejection fraction. Although there are currently limited data, one study failed to show a high proportion of African Americans among patients with heart failure with preserved ejection fraction [70]. However, in the Anglo-Scandinavian Cardiac Outcomes Trial, African-Caribbean hypertensive patients had greater diastolic dysfunction than Whites after adjusting for confounders including LVM [71]. There are currently no outcome data in Africans compared to other race groups; however, blood pressure [72], obesity [73], insulin resistance and concentric remodelling [74] are all independent determinants of diastolic dysfunction in a community study of Black South Africans. Whether increases in LVM and

concentricity in Africans translate into an increased prevalence of heart failure independent of other cardiovascular risk factors remains unclear. Future studies are clearly required in order to address these issues in Black Africans.

7.5 Heart Failure in Africa and the Contribution of Hypertension

7.5.1 Epidemiology

Heart failure (HF), the end stage of all diseases of the heart, is one of the most important causes of morbidity and mortality both in the developed and the developing nations. It was estimated that there were 37.7 million cases of prevalent heart failure recorded globally in 2010, leading to 4.2 years lived with disability (YDLs). Heart failure was distributed across a number of causes. More than two-thirds (68.7%) of heart failure globally was attributable to four underlying causes: hypertensive heart disease, rheumatic heart disease, cardiomyopathies and ischaemic heart disease [75].

HF has been shown to have a significant impact on health-related quality of life [76] and appears to impose a huge economic burden to all nations [77]. It is associated with shorter life expectancy, greater morbidity and impaired quality of life than most common diseases. About 30% of people die within 3 months of HF diagnosis. Those with severe HF have an annual mortality of >50% [78, 79].

The sub-Saharan African survey on heart failure (THESUS-HF) [80] revealed that there are major differences in the epidemiology of acute heart failure (AHF) in sub-Saharan Africa, compared to North America, Europe and Asia. Table 7.3 compares the characteristic from patients with AHF from the USA, Europe, Asia and sub-Saharan Africa [81].

Table 7.3 Features of patients with acute decompensated heart failure in registries in the ADHERE (United States), EHFS II (Europe), ATTEND (Asia) and THESUS-HF (sub-Saharan Africa) registries (modified from [75])

	ADHERE[a] registry (n = 105,388)	ADHERE—AP[b] (n = 10,171)	EHFS II[c] registry (n = 3580)	ATTEND[d] registry (n = 4842)	THESUS-HF[e] registry (n = 1006)
Male, %	48	57	61	58	49
Mean age, years	72	66	70	73	52
Hypertension,%	73	64	63	69	45
Ischaemic heart disease, %	57	50	54	31	7
Diabetes, %	44	45	33	34	11
Atrial fibrillation, %	31	24	39	36	18
Anaemia, %	NA	NA	15	NA	15
Renal insufficiency, %	30	NA	17	69	8

[a]*ADHERE* Acute Decompensated Heart Failure National Registry
[b]*ADHERE-AP* ADHERE Asia Pacific
[c]*EHFS II* EuroHeart Failure Survey II
[d]*ATTEND* acute decompensated heart failure syndromes registry
[e]*THESUS-HF* the Sub-Saharan Africa Survey of Heart Failure

In sub-Saharan Africa, AHF affects relatively younger people (mean age 52 years). In Western countries, acute decompensated heart failure is a disease of the elderly with a mean age of 70–72 years [82, 83]. AHF therefore strikes the generation of breadwinners and caregivers in African patients, thereby having major economic implications. The younger African patients with AHF also have a lower frequency of ischaemic heart disease, diabetes mellitus, atrial fibrillation and renal insufficiency, compared to elderly heart failure sufferers in developed countries.

Compared to a summary of the causes of heart failure in sub-Saharan Africa, based on the case series published between 1957 and 2005 [84], THESUS-HF shows a changing trend in the epidemiology of acute heart failure in sub-Saharan Africa [80]. There was a rise in the contribution of hypertension as a cause of heart failure (from 23 to 45%), a reduction in the role of rheumatic heart disease (from 22 to 14%) and an apparent increase in recognition of ischaemic heart disease as a cause of heart failure (from 2% to nearly 8%). The high prevalence of hypertension and relatively low rate of coronary artery disease have also been observed in other single-centre studies, such as the Heart of Soweto study, where <10% of cases of heart failure were attributed to coronary artery disease [85].

Ojji and colleagues [86] compared 1515 consecutive HF patients with 4626 patients from the Heart of Soweto project [87]. They showed that hypertension contributed 60% of all cases presented with HF in Abuja versus 33% in Soweto. On an age- and sex-adjusted basis, compared with the Soweto cohort, the Abuja cohort were more likely to present with a primary diagnosis of hypertension (adjusted OR 2.10, 95% CI 1.85–2.42) or hypertension heart disease/hypertension heart failure (HHD/HHF) (OR 2.48, 95% CI 2.18–2.83); $P < 0.001$ for both. In the Heart of Soweto study, HHF (682/1196–57%, mean age 60 ± 14 years) was the most common manifestation of HHD among African women with diagnosis of hypertension [88].

In the Abeokuta HF registry, over 90% of the patients were known hypertensives. Most patients present in the fourth decade of life with severe heart failure and secondary functional valvular dysfunction and significant in-hospital mortality [89]. In a study of 52 Gambians and 55 Nigerians between ages 16 and 69 years with hypertensive heart failure, the mean duration of diagnosis of systemic hypertension among the previously known hypertensives was 4.3 years [90]. The overall 1-year survival rate was 71%, although it was unclear whether this was largely systolic or diastolic heart failure and whether the cases were primarily essential hypertension or included large numbers with secondary hypertension. The prognosis of hypertensive heart failure among this population is poor, with the first 3 months from onset of heart failure being critical for survival [90]. In a Nigerian study, acute left ventricular failure from hypertensive heart disease was the commonest cause of sudden cardiac death, while acute myocardial infarction was rare [91].

There are few reports on heart failure with preserved systolic function from SSA. This is commonly seen due to hypertensive heart disease either alone or in addition to systolic heart failure [92]. This needs to be addressed in future studies as it is likely that the profile of heart failure will also change in those regions due to shifts in population demographics, prevalence of specific risk factors, and influenced by the evolution and access to therapeutic options.

7.5.2 Pathophysiology

Hypertensive heart disease (HHD) is the cardiac damage related to chronic systemic arterial hypertension. It has been documented that some genes are implicated in the development of the cardiomyocyte hypertrophy in patients with hypertension which affect intracellular signalling, degradation of normal extracellular collagens and contractile dysfunction among other functions ultimately leading to left ventricular hypertrophy and HF [93]. There is also the possibility that these genes interact with environment as seen in Black Americans whereby weight gain, high salt intake and psychosocial factors may facilitate the rapid development of hypertension and hypertensive heart disease in susceptible individuals [94]. The presence of LVH adversely affects the prognosis of patients with arterial hypertension. In the Framingham Study, cardiovascular mortality among patients with arterial hypertension and increased left ventricular mass measured by echocardiography was double in comparison with patients with normal mass [11].

The role of biomarkers in diagnosing hypertensive HF is still being defined and does not yet impact treatment decisions [95]. However, it has recently been shown that the novel serum biomarker soluble ST2 differentiates hypertensive patients without LVH from those with LVH and those from hypertensive patients with heart failure [96]. The same author showed that in hypertensive patients with heart failure, there was a strong correlation between the levels of soluble ST2 and right ventricular diameters, right ventricle systolic pressure and right atrium area evaluated by echocardiography [96]. This suggests that serum soluble ST2 may have the potential of predicting who develops HF among hypertensive patients. It is therefore important to note that although markers for early detection remain a challenge, efforts should be made to explore combinations of genotypic, biochemical and physiological approaches to define and stratify the population at risk.

Conclusions

Hypertension is an increasing health problem in Africa. Although some research on left ventricular function on hypertensive patients have recently been developed, most of the data are still extrapolated from studies done in the USA with African Americans. Several studies, coming mainly from HHF in Africans, occur among individuals in their productive age group with attendant high economic loss and disability-adjusted life-years. The disease is often severe as a result of late presentation. Efforts should be made at the community level to ensure primordial prevention, early detection, treatment and control of hypertension on the continent. There is currently an unmet critical need in HHF research in Africa. It is essential that cohort studies of hypertensive patients are established to better understand this heterogeneous patient population, inform public policy decisions and guide basic, translational and clinical research. This kind of studies should capture comprehensive and longitudinal data including hospital course and post-discharge outcomes over long period of time. Future studies should also incorporate quality improvement initiatives focusing on continuity of care from initial presentation to the early post-discharge vulnerable period. In addition to

traditional endpoints (i.e. hospitalization and mortality), patient-centred outcomes should be designed that comprehensively and longitudinally capture the burden of worsening HF (i.e. quality of life impairments and functional limitations).

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Ethnicity and Hypertension-Related Target Organ Damage

8

Stefano Perlini

The global burden of hypertension cannot be underestimated, since this condition represents a major cardiovascular epidemic condition in both the developed and developing world, which remains asymptomatic until its later stages [1, 2]. Indeed, arterial hypertension affects about 40% of the industrialized populations, and its prevalence is increasing in particular for high-risk patients [3, 4], being affected by age, gender, and ethnicity as well as by many other factors [5]. As to the ethnic/racial differences, a higher prevalence of hypertension and an excessive amount of target organ damage in Blacks have been recognized in the past [6], possibly related to a very complex interplay between genetic, environmental, and socioeconomic factors. Hypertensive patients of African or South Asian ethnicity may require ethnic-specific approaches, since they tend to have higher blood pressure values at an earlier age, associated with higher occurrence of diabetes, more extensive target organ damage, as well as earlier cardiovascular mortality [7]. On a worldwide base, hypertension is recognized as the main cause of approximately 54% of cerebrovascular events, 47% of coronary events, and 30% of end-stage renal disease [8, 9], being responsible for 9.4 million deaths per year (13.5% of total) as well as for 7.0 million global disability-adjusted life years (DALYs) [8]. It has to be underscored that, as recently pointed out by the noncommunicable disease (NCD) Risk Factor Collaboration (NCD-RisC), the highest worldwide blood pressure levels have shifted from high-income countries to low-income countries in sub-Saharan Africa and South Asia during the past decades [5]. Attention to the importance of raising our understanding of the importance of cardiovascular risk assessment in low-resource settings has been underscored by a consensus document of the European Society of Hypertension Working Group [10].

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In arterial hypertension, chronic exposure to increased blood pressure levels induces several changes in the structure and function of tissues and organ systems that clinicians collectively recognize as target organ damage (TOD). Since these alterations are responsible for hypertension-related morbidity and mortality, the presence of target organ damage should be actively searched in any hypertensive patient. Moreover, it is very important to recognize the presence of asymptomatic TOD before it becomes clinically evident as a cardiovascular event or as irreversible damage. Given its profound impact on prognosis, the presence (and extent) of TOD should be identified and properly evaluated to assess the global cardiovascular risk profile and to choose and modulate the consequent therapeutic approach [1]. On the one hand, TOD assessment adds on conventional risk assessment in predicting the cardiovascular risk of hypertensive patients. On the other hand, regression of TOD has been addressed by several clinical trials as a surrogate treatment endpoint, since it may indirectly indicate that blood pressure is adequately controlled, although this issue is still debated [11].

In arterial hypertension, it is therefore important to identify what are the mechanisms that underlie the development and the progression of TOD, in order to have a better understanding of its clinical sequelae as well as of the need of an adequate and effective treatment. One obvious mechanism is dictated by the effect of the prevailing blood pressure level on the arterial wall and on the different tissues and organs. Indeed, the extent of blood pressure increase is one of the main determinants of the development and of the progression of target organ damage, as demonstrated by many clinical and experimental investigations. This has been proven for the absolute mean value of systolic, diastolic, and pulse pressure, when measured either noninvasively or invasively in the clinical setting, at home, or via 24-h monitoring devices, at the brachial or at the central aortic levels [12–23] (Fig. 8.1). Many studies also underscore the role of blood pressure variability, as recently reviewed by Kollias et al. [24]. Indeed, guidelines largely rely on the overwhelming amount of information directly relating blood pressure values to target organ damage and cardiovascular events [1, 2].

However, although the prevailing blood pressure level has to be recognized as one of the main determinants of the development and of the progression of target organ damage, several other factors play a key role in modulating the detrimental effects of increased arterial pressure. Among the many processes that are involved in the pathogenesis of TOD, endothelial dysfunction, platelet activation, increased thrombogenesis, changes in the renin aldosterone angiotensin system (RAAS), and collagen turnover should be included. Atherosclerotic plaque development is the result of the combination of several processes that are undoubtedly enhanced by the dreadful combination of diabetes, dyslipidemia, and smoking which potentiate the effects of hypertension on the arterial structure and function. In the same line, the development of left ventricular (LV) hypertrophy is clearly consequent to a prolonged cardiac exposure to increased afterload. Although this appears obvious from a mechanical (and mechanistic) standpoint, several other factors give an important contribution, and the relative weight of the factors that trigger the hypertrophic process still remains largely unclear [25]. Pressure overload interacts with volume overload (and with changes in sodium turnover) in stimulating cardiac hypertrophy, together with a

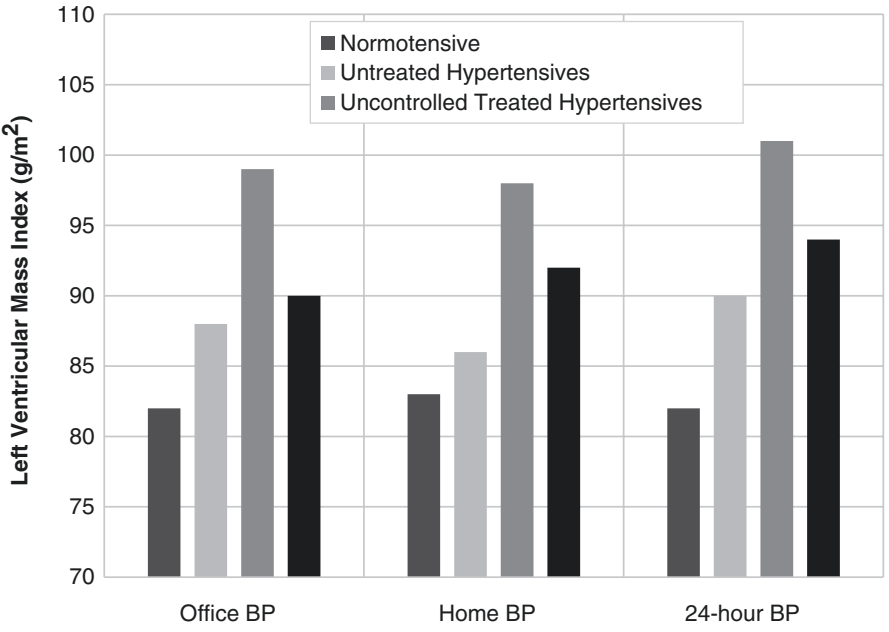

Fig. 8.1 Left ventricular mass index in normotensive subjects, hypertensive subjects with untreated hypertension, uncontrolled treated hypertensives, and treated hypertensives subjects with controlled blood pressure values, according to office, home, or 24-h blood pressure normality or elevation. Modified from Mancia et al. Hypertension. 2002;39:744–9 [19]

profound influence of sympathetic nerve overactivity and of the renin-angiotensin-aldosterone axis activation, both at the systemic and the tissue level. Indeed, catecholamines, angiotensin II, and aldosterone are able to trigger cardiomyocyte growth and extracellular matrix deposition (i.e., two key factors in the development of cardiac hypertrophy). This complex interplay is modulated by the genetic background, as demonstrated in several studies underscoring the role of ethnicity [26, 27] and heritability [28–31] in predicting the hypertrophic process. Moreover, environmental factors, such as diet, exercise, psychological stress, and social status (that are closely linked to genetic factors in a given family and in a well-defined ethnic group), also contribute to the effect of mechanical overload in triggering the development of LV hypertrophy. Also body size, obesity, diabetes, and other metabolic abnormalities influence this process [32], as well as gender, as shown both in humans [33–35] and in animal models of chronic pressure overload [36].

Therefore, hypertension-related damage at the arterial and at the cardiac levels represent two possible examples of how the effects of a chronic increase in blood pressure on target organs is profoundly influenced—among many other factors—by the genetic as well as the ethnic background. It has to be reminded that according to the Merriam-Webster dictionary "ethnic" relates to "large groups of people classed according to common racial, national, tribal, religious, linguistic, or cultural origin or background" [37]. Such a definition underscores the importance of taking into

account the many factors that are involved in the complex yet fascinating relationships between genes, race, and environment in determining the tissue, organ, and body system responses to a given stimulus. The epidemiological observation of ethnic-related differences in hypertension-related target organ damage is therefore a window from which we can try to better understand how to stratify cardiovascular risk and prognosis, in order to improve diagnosis and treatment.

One further example is related to ethnicity-related differences in the distribution of microalbuminuria, a well-known biomarker of endothelial dysfunction associated with increased cardiovascular, renal, and cerebrovascular morbidity and mortality, in the hypertensive population. An analysis of the National Health and Nutrition Examination Survey (NHANES) database suggests a complex and poorly understood relationship between race/ethnicity and the increased prevalence of microalbuminuria in the different blood pressure categories (normal, prehypertension, stage 1, and stage 2 hypertension) [38]. According to this report, in ethnic minorities, hypertension has a larger impact on microalbuminuria, suggesting greater target organ damage [38]. As detailed in Fig. 8.2, when comparing the magnitude of the differences in the prevalence of microalbuminuria between uncontrolled hypertensive patients and normotensive subjects, Mexican Americans presented a sixfold gradient, whereas non-Hispanic Whites and Blacks showed a four- and a fivefold difference, respectively [38].

When evaluating the cardiac response to hypertension, it has to be noted that the interplay between genetic background and ethnicity has an impact on baseline

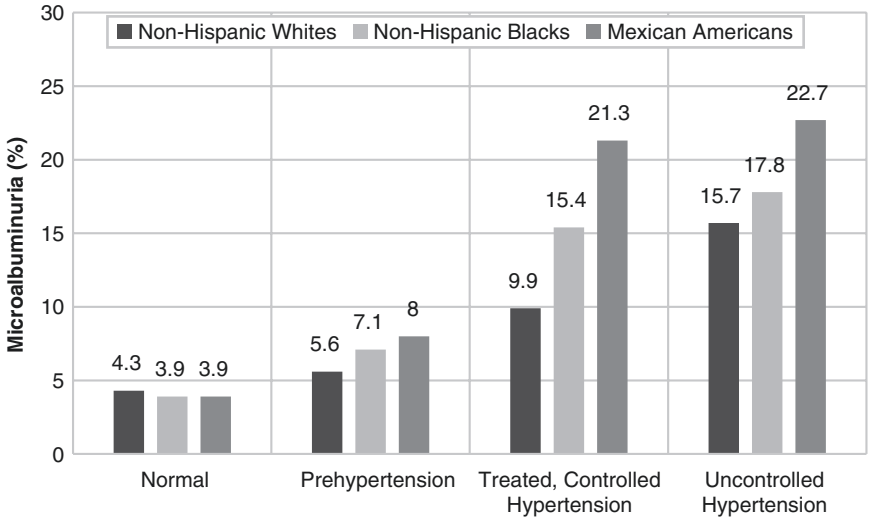

Fig. 8.2 Prevalence of microalbuminuria by race/ethnicity and selected blood pressure categories: normal (<120/<80 mmHg); prehypertension (systolic BP, 120–139 mmHg; diastolic BP, 80–89 mmHg); treated, controlled hypertension (systolic BP <140 mmHg and diastolic BP <90 mmHg, on treatment with antihypertensive medications); uncontrolled hypertension (systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, despite antihypertensive medications). Modified from Ogunniyi et al. Am J Hypertens. 2010;23:859–64 [38]

cardiac structure and function. Since "normality" parameters may differ between the different populations, the EchoNoRMAL (Echocardiographic Normal Ranges Meta-Analysis of the Left Heart) collaboration was recently started to develop contemporary normative reference ranges for standard echocardiographic measurements (www.echonormal.org) [39]. The aim of the project was to pool several population-based studies from different geographic areas in order to derive reference values in adults without clinically evident cardiovascular (CV) disease or risk factors. This led to derive age-, sex-, and ethnic-appropriate adult normative reference values for several left heart echocardiographic measures. Beyond confirming the known gender-related differences [33–36], the EchoNoRMAL collaboration underscored the importance of taking into account ethnic-based differences in LV dimensions and structure [39, 40] that are not corrected by simple indexation for body size [41–45].

To give one example, the Authors pointed out that the upper thresholds for left ventricular end-diastolic diameter of 5.8 cm for men and 5.2 cm for women as defined by the current ASE/EACVI recommendations [46], which are based on data from predominantly White European and American adults, are substantially higher than the reference values derived for East Asian, South Asian, and African men [40].

These ethnic-related differences in "normal" reference values that are obtained in normotensive populations cannot but have a profound impact on the effect of hypertension of cardiac structure and function, even assuming that the effect is exclusively due to the increased afterload per se. The issue is by far more complex, since the physiopathology of arterial hypertension may be different in the diverse populations and ethnicities, which present genotype, phenotype, as well as environmental differences. These differences also apply to the electrocardiographic assessment of left ventricular hypertrophy (ECG-LVH), as recently pointed out by a study that compared the association of ECG-LVH with office and home blood pressure in 225 Blacks Nigerians and 729 White Flemish [47]. By using any of the 12 different criteria, ECG-LVH was more prevalent among Black than White men (54.4% vs. 36.0%) without any ethnic difference among women (17.1%). Moreover, the relationship between ECG voltages and systolic blood pressure was threefold steeper in Blacks Nigerians than in White Flemish [47]. Further evidence on the effects of ethnicity on the diagnostic and prognostic performance of ECG is offered by an analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) database. In this study, Jain et al. concluded that 10 out of 13 traditional ECG-LVH criteria show superior sensitivity and diagnostic performance in African Americans as compared with Whites (P = 0.02–0.001) in detecting LVH as defined by magnetic resonance imaging, i.e., a gold standard for left ventricular mass measurement [48].

Beyond extending the observations that are derived from the morphological evaluation of the left ventricular structure and function, these studies underscore a very important practical aspect. Especially (albeit not exclusively) in low-resource settings [10], the combination of ECG and office and home blood pressure remains an essential instrument in risk stratification across the entire BP range. The potential of even simpler devices that may transmit the ECG tracings via smartphones is currently under active investigation [49].

Also arterial properties show ethnic variations, as shown by data derived from the Dallas Heart Study cohort (n = 2544) [50]. Compared with Whites, both Blacks and Hispanics presented higher levels of aortic arch pulse wave velocity and characteristic impedance, after adjustment for age, sex, body mass index, height, mean arterial blood pressure, antihypertensive treatment, heart rate, total cholesterol, diabetes mellitus, and smoking. Compared with Hispanics, Blacks had higher values of pulse wave velocity and characteristic impedance, independent of cardiac output and peripheral vascular resistance. The Authors suggest that these differences may contribute to the disproportionately higher risk for incident hypertension and target organ damage that is observed in the Black population [50]. Similarly, the Multi-Ethnic Study of Atherosclerosis (MESA) showed a relationship between arterial elasticity and race/ethnicity [51]. These data confirm previous observations in an urban population that showed higher carotid-femoral pulse wave velocity in African-Caribbeans (n = 99) when compared with Europeans (n = 103), a difference that persisted after adjustment for resting and ambulatory blood pressure [52]. Ethnic differences in arterial wave reflections, which markedly affect the central pressure profile, were assessed by Chirinos and coworkers in a healthy reference sample (n = 3497) [53]. Central (aortic) and radial augmentation index values were higher in African Blacks and Andean Hispanics than in British Whites and American Indians, after adjustment for age, body height, heart rate, and mean arterial pressure.

Indeed, the presence of marked ethnic differences in arterial wave properties may contribute to the observed differences in hypertensive target organ damage [50–53].

In conclusion, among the many factors that influence the development of hypertension-related target organ damage, genetic, racial, and ethnic differences play an important yet poorly understood role. Since target organ damage mediates the relationship between arterial hypertension and cardiovascular events, these differences may contribute to explain the worldwide variations in the impact of hypertension that are observed in the different populations. The awareness of these differences should be translated in a better profiling of the best diagnostic approach for any specific patient group. Obviously, this should also take into account the available resources, by choosing and implementing the cheaper diagnostic tools that are most cost-effective in any given setting.

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Chronic Kidney Disease: Global Burden and Perspectives for Africa

9

Faical Jarraya

The kidneys function as excretory, biosynthetic, and metabolic organs, is vital for maintaining normal physiology. Chronic kidney disease (CKD) and its terminal complication, end stage renal disease (ESRD), may progress, undetected, until later stage kidney failure develops. At this point in the disease process, few opportunities exist to prevent its adverse outcomes, such as its association with high cardiovascular mortality and morbidity. CKD is caused mainly by common diseases, such as diabetes, hypertension, and chronic infections, and so it has become a global public health problem. CKD is costly. Preventing its occurrence by early diagnosis and optimized treatment of related causes, and preventing its progression to ESRD may improve quality of life and benefit healthcare budgets. Such a strategy would be appropriate for developing countries, where CKD presents a significant challenge, which many of them, mainly in sub-Saharan Africa, are not equipped to handle.

9.1 Chronic Kidney Disease (CKD)

9.1.1 A Well Standardized CKD Definition and Grading Is Now Available

As introduced by the Kidney Disease Improving Global Outcomes KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [1], kidney disease is defined as an abnormality of kidney structure or function with implications for the health of an individual, which can occur abruptly, and either resolve or become chronic. CKD is a general term for the heterogeneous disorders that affect kidney structure and function with variable clinical presentation.

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Table 9.1 Criteria for CKD (any of the following present for >3 months) [1]

Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 h; ACR ≥30 mg/g (≥3 mg/mmol) Urine sediment abnormalities Electrolyte and other albuminuria abnormalities owing to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 mL/min/1.73 m^2 (GFR Categories G3a-G5)

CKD chronic kidney disease; *GFR* glomerular filtration rate; *AER* albumin excretion rate; *ACR* albumin creatinine ratio

To differentiate CKD from acute kidney diseases, including acute kidney injury, the above guideline arbitrarily defines a duration of renal disorders for at least 3 months as delineating CKD. There should be one or more pathological markers of kidney damage in regard to extent of albuminuria, urine sediment abnormalities, and electrolyte and other tubular disorder-related abnormalities. CKD can be evidenced by histological features, detected by renal biopsy, or structural abnormalities, shown by imaging. CKD can also be regarded as being present when there is a history of kidney transplantation without any renal abnormalities. A sustained decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73m^2 for more than 3 months, with or without other renal manifestations, is also considered to define CKD (Table 9.1).

Earlier stages of CKD are usually detected during the evaluation of comorbid conditions, such as hypertension, diabetes, obesity, and cardiovascular disease; however, because earlier stages of kidney disease are often asymptomatic, and the symptoms of CKD are usually owing to complications of decreased kidney function, these earlier stages are ignored by most physicians. Kidney failure is traditionally considered as the most serious outcome of CKD. However, until the past few decades, renal function was determined by simply measuring serum creatinine, which is not a suitable method for evaluating renal function; in fact, there is no linear relationship between GFR and serum creatinine [2]. The introduction of the estimation of creatinine clearance by the Cockroft and Gault formula [3], and then the estimation of glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) Study equation [2] or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [4] improved the detection of early stages of asymptomatic CKD. The MDRD and CKD-EPI equations are more precise methods of evaluating renal function, with the CKD-EPI equation having an advantage when the eGFR is above 60 mL/min/1.73m^2; however, this formula needs an enzymatic determination of creatinine, which makes the method more costly.

Most kidney diseases do not have symptoms or findings until later in their course. For this reason, they are usually underdiagnosed until they become chronic and they are mostly detected at an advanced stage of renal failure. Most physicians caring for patients with non-communicable diseases (NCDs), such as diabetologists, cardiologists, and familial and general practitioners, are

sensitized to the need for the early detection of CKD and the early referral of CKD patients to nephrology care.

Knowledge of the earlier stages of CKD is facilitated by the systematic reporting of eGFR on the biological report when creatinine is checked. In combination with the feature of urine albumin detection, the KDIGO [1] presented a prognostic table combining eGFR categories and albumin amount to help physicians to refer their patients to nephrologists, as CKD may be reversible and stabilized, and end stage renal disease (ESRD) may be delayed or avoided, especially when patients with CKD are referred to nephrology care early (Fig. 9.1).

Renal screening has to be considered in high-risk groups, with the highest priority being for patients with hypertension, diabetes mellitus, and cardiovascular disease. Renal screening should also be considered for older age groups, people with a family history of kidney disease, and in patients with other cardiovascular risk factors, as well as in patients who have been exposed to toxic drugs, and patients with certain chronic infections and cancers [5].

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severly increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90		Monitor	Refer*
	G2	Mildly decreased	60-89		Monitor	Refer*
	G3a	Mildly to moderately decreased	45-59	Monitor	Monitor	Refer
	G3b	Moderately to severely decreased	30-44	Monitor	Monitor	Refer
	G4	Severely decreased	15-29	Refer*	Refer*	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

*Referring clinicans may wish to discuss with their nephrology service depending on local arrangements regarding monitoring or referring. Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Fig. 9.1 Glomerular filtration rate (GFR) categorization and referral decision-making according to GFR and albuminuria [1]. *Referring clinicians may wish to discuss local arrangements regarding monitoring or referring with their nephrology service. *Green* low risk (if no other markers of kidney disease, no chronic kidney disease [CKD]); *yellow* moderately increased risk; *orange* high risk; *red* very high risk

9.1.2 Causes of CKD Across the World: The In-Between Developed and Developing Countries

The leading causes of CKD worldwide are diabetes mellitus and hypertension. Renal failure in type 2 diabetes is a medical catastrophe of world-wide dimensions, as declared in 1999 by the former president of the International Society of Nephrology [6]. Effectively, diabetic nephropathy is the leading cause of ESRD nowadays; it develops in one out of three diabetics worldwide [7]. Diabetic nephropathy is not only a characteristic of the developed world. A survey across 10 Asian countries showed that the most common cause of ESRD in 9 of the 10 countries was diabetic nephropathy. Its incidence increased from 1.2% of the overall population with ESRD in 1998 to 14.1% in 2000, and its prevalence increased from 4.2 to 17.3% for the same period [8]. India, with the highest incidences of diabetes and hypertension in the world, is likely to face a catastrophic CKD/ESRD burden, with 25–40% of its population at risk [9].

In Latin America, diabetes is also the leading cause of ESRD. The highest incidences are reported in Mexico (59%) and Paraguay (49.5%) and the lowest in Uruguay (23.9%) and Chile (17.8%) [10]. In Africa, most countries lack national renal disease registries [11]. In countries such as South Africa; Egypt, and Tunisia, where registries are available; diabetic renal disease is the leading cause of ESRD, accounting, respectively, for 51.5%, 34.7%, and 20.3% of the populations with ESRD [12–14]. In many developing countries, because of the non-availability of interventional cardiology treatment, the majority of diabetic patients with CKD often die of cardiovascular disease before developing ESRD [15].

Most developing countries are not equipped to handle widespread screening for CKD, and checking for CKD is often limited to high-risk populations [16]. Furthermore, there are many barriers to early detection, such as limited access to healthcare, lack of awareness, and the limited capacity of health workers in relation to CKD detection and prevention; further, those in the lowest socioeconomic population are often unaware of any risk factors for CKD, such as hypertension and diabetes. In Tunisia, for example, which is an upper-middle income African country, 60% of the population diagnosed with hypertension in a national survey were unaware of this condition of high blood pressure [17]. In Africa, hypertension is a major cause of CKD, because of the lack of awareness of blood pressure level and non-access to treatment, and so, as hypertension becomes more serious, qualified as malignant, acelerates progression of CKD to ESRD [18]. A recent systematic review showed that only 18% of the hypertensive adult African population was aware of their hypertension [19]. Moreover, in patients at high risk for hypertension who are already in contact with a healthcare system, it was found that 70% of HIV patients and 10.2% of diabetic patients were unaware of being hypertensive [20, 21]. In addition, genetic factors also contribute to the high burden of CKD in black populations. Variations in MYHA9 and APOL1 were recently reported to be associated with non-diabetic CKD in black individuals of African origin [22, 23].

Apart from diabetes and hypertension, infectious-related glomerulonephritis and other causes of CKD are more common in the countries of Asia and sub-Saharan

Table 9.2 Geographic distribution of the main causes of CKD across the world [25]

World region	Main causes of CKD
North America	DM, HT, GN
South America	GN
Europe	DM, HT
Central Asia	DM, GN, HT
Southeast Asia	GN, DM, MS, HT
Australia	DM, HT
North Africa-Middle East	DM, HT, GN, UD
Sub-Saharan Africa	GN, HT, DM, UD

DM diabetes mellitus; *HT* hypertension; *GN* glomerulonephritis; *MS* metabolic syndrome; *UD* urologic disease

Africa than in developed countries, and the lack of awareness of CKD leads to it being diagnosed at the terminal stage. Infectious diseases continue to be prevalent in low-income countries, secondary to poor sanitation, inadequate supplies of safe water, and high concentrations of disease-transmitting vectors [24]. Table 9.2 shows the geographic distribution of the main causes of CKD across the world, as reported by Nugent et al. [25].

9.2 Contribution of CKD to the Global Burden of Major Non-Communicable Diseases (NCDs)

9.2.1 Epidemiological Transition

Omran [26] has described three major successive stages of the epidemiological transition of mortality: (1) The Age of Pestilence and Famine, when mortality is high and fluctuating. The average life expectancy at birth is low and variable, ranging between 20 and 40 years. (2) The Age of Receding Pandemics, when mortality declines progressively. The average life expectancy at birth increases steadily from about 30 to about 50 years. (3) The Age of Degenerative and Man-Made Diseases, when mortality continues to decline and eventually approaches stability at a relatively low level. The average life expectancy at birth rises gradually until it exceeds 50 years.

9.2.2 Global Burden Shift of NCDs

During the epidemiological transition outlined above, a long-term shift occurs in mortality and disease patterns, whereby infection pandemics are gradually displaced by degenerative diseases. Lifestyle and nutritional changes occur in parallel with economic improvement and massive urbanization, and risk factors for NCDs become more prevalent in the worldwide population. A sedentary lifestyle, obesity, hypertension, smoking, alcohol abuse and drug use, and pollution become the leading risk factors for diabetes, cardiovascular diseases, cancers, chronic pulmonary diseases, and CKD. Moreover, owing to improvements in healthcare leading to survival until old age, NCDs, including coronary heart disease, stroke, chronic

obstructive pulmonary disease, cancer, type 2 diabetes mellitus, and CKD, are currently the leading causes of adult death and disability worldwide [27]. These new pandemic health problems are expected to become more prominent as a result of the increasing global older population. The worldwide elderly population above the age of 60 is expected to double between 2000 and 2050 [28]. This population is the most vulnerable to NCDs.

The Global Burden of Disease collaborations have assessed the metrics of disease burdens by measuring disability-adjusted life-years (DALYs), which are the sum of years of life lost (YLLs) and years lived with disability (YLDs). In recently available data from 2015, the fourth largest contributors to global DALYs among Level 3 risks were high systolic blood pressure (211.8 million global DALYs), smoking (148.6 million global DALYs), high fasting plasma glucose (143.1 million global DALYs), and high body mass index (120.1 million global DALYs) [27]. In Africa, infectious and parasitic diseases, child and maternal malnutrition, unsafe sanitation, and problems with safe water supply are still the major causes of death; as shown in Fig. 9.2, this is the case for the sub-Saharan region [29]. This situation is anticipated to change in the coming years. Standardized for age, mortality from NCDs in sub-Saharan Africa is projected to increase dramatically by 2030, as reported by the World Health Organization (WHO) [30]. This epidemiological transition in mortality has already occurred in many developing countries. Tunisia is an example of an African country that has managed its heath system—from the time of

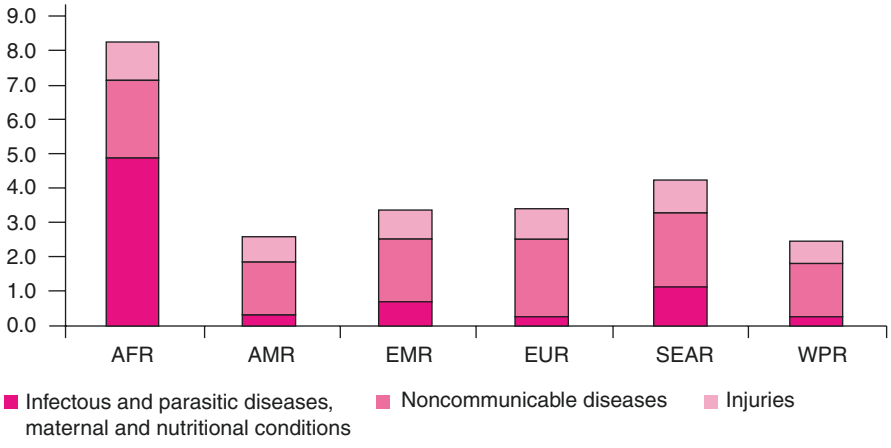

Fig. 9.2 Mortality rates of CKD, according to major causes, by World Health Organization (WHO) region, 2008 [29]. *AFR* African Region; *AMR* Region of Americas; *EMR* Eastern Mediterranean Region; *EUR* European Region; *SEAR* South-east Asia Region; *WPR* Western Pacific Region

its independence in 1956—to very quickly overcome its backwardness compared with industrialized countries. The development of a public health system with wide coverage of all rural regions, the establishment of national insurance for all workers with medical coverage, and the development of national programs to combat infectious diseases and carry out compulsory vaccination, sexual education, and family planning, has led to a decline in the birth rate from 45.1‰ in 1966 to 18.6‰ in 2010, and an extension of life expectancy from 51 years in 1966 to 74.7 years in 2010. An increase in the proportion of the elderly population, from 5.5% in 1966 to 9.9% in 2010, has been observed. The rate of urbanization has also increased, from 39.5% in 1966 to 66.1% in 2010 [17]. Against this background, cardiovascular diseases are already the top cause of death in the country, followed by cancers and chronic respiratory diseases [31].

9.2.3 CKD in the Global Burden of NCDs

Among NCDs, CKD is of particular significance and it participates profoundly in the NCDs paradigm. CKD is primarily induced by the risk factors described above; it can be a consequence of the disease per se, such as cardiovascular disease or diabetes, or a consequence of a treatment used, such as treatments for malignancies. The Global Burden of Disease collaborations assessed CKD according to low GFR, defined by the proportion of the population with a GFR of <60 mL/min/1.73 m^2, excluding those with ESRD. CKD does not belong to the top ten largest contributors to global DALYs; however, although low GFR is ranked in the top ten contributors to global DALYs in Latin America and Caribbean and high-income countries, low GFR is not in the top ten largest contributors to global DALYs in the other regions investigated by the Global Burden of Disease collaborations [27].

CKD, as defined by KDIGO, is frequently diagnosed when checked for systematically. CKD is an asymptomatic disease, particularly in stages 1–3, in the absence of nephrotic syndrome with leg edema, or in stage 4 in the absence of complications attributed to low GFR, such as overhydration with pulmonary edema or high potassium or phosphorus levels and anemia or metabolic acidosis. In the Global Burden of Disease Collaborations study, CKD assessed only by low GFR <60 mL/min/1.73 m^2 underestimated the burden of CKD. The prevalence of CKD was found to be 11% in the United States population [32], 12.1% in the Australian population [33], 13% in the Chinese population [34], and 13.2% in the Cameroonian population [35]; in a sub-Saharan Africa meta-analysis, the reported prevalence of CKD was found to be 13.9% [36]. The highest world prevalence of CKD, 19.1%, was reported in a survey of the adult population in Japan [37].

Diabetes, hypertension, dyslipidemia, and smoking are the leading risk factors for cardiovascular diseases [38]. The performance of interventional cardiology prolongs survival, and the use of this modality has led to the development of ischemic

hypertensive nephropathy, which has become a major cause of end stage renal failure in Western countries, whereas infectious-related glomerulonephritis and diabetic nephropathy are still the major causes of end stage renal failure in developing countries, except for sub-Saharan Africa, where severe, mostly insufficiently treated, hypertension is a major cause of end stage renal failure [39, 40]. The comprehensive development of interventional cardiology in developing countries will contribute to a worldwide pandemic of CKD. For example, predictions of ischemic heart disease and stroke mortality between 1990 and 2020 include more than 100% increases in Latin America, the Middle East, and sub-Saharan Africa [41].

The data from the Global Burden of Disease collaboration 2013 survey focusing on cardiovascular and renal outcomes of reduced GFR [42] reported 2.2 million deaths and nearly 52 million DALYs associated with reduced GFR. These figures represent, respectively, 3.9% of total global deaths and 2.1% of total global DALYs in 2013. When data since 1990 were analyzed at the global level, among all ages, GFR-attributable median DALYs counts had increased by 52.0%, whereas age-standardized rates of DALYs associated with reduced GFR had decreased by 8.1%.

In the above Global Burden of Disease collaboration 2013 survey [42], developed regions have shown lower GFR-attributable age-standardized rates of deaths and DALYs over time, and rates are decreasing, unlike the situation in developing regions, drawing attention to the alarming problem of CKD in these regions (Fig. 9.3). Indeed, reduced GFR ranked highest for inducing mortality in Latin America and the Caribbean in 2013 (fifth), with 7.0% of total attributed deaths, outranking the metabolic risk factor of high total cholesterol (seventh). Within the high income countries, reduced GFR ranked eighth in regard to deaths and was outranked by all metabolic risk factors except for low bone mineral density. However, reduced GFR ranked lowest in sub-Saharan Africa (sixteenth), arguing that CKD is not actually a major health problem in this region, although CKD still outranked high total cholesterol (twenty-fifth) with regard to deaths.

In 2013, globally, 1.2 and 18.7 million cardiovascular deaths and DALYs, respectively, were attributed to reduced GFR, with an age-standardized rate of 20.8 deaths and 304.2 DALYs per 100,000 population. Compared with the developed world, the developing world has had higher age-standardized death rates attributed to reduced GFR, as well as a smaller decrease in these rates since 1990. These rates have been declining in all regions since 1990, except in the Southeast Asian region and sub-Saharan Africa, where the rates have increased by 4.7% and 0.4%, respectively. In comparison, in North Africa and the Middle East region, age-standardized death rates attributed to reduced GFR have decreased by 29% since 1990 [42].

When ESRD deaths were considered, there were 956,246 deaths because of ESRD in 2013, with an age-standardized rate of 15.8 per 100,000. The age-standardized mortality rate in the developing region was almost twice that in the developed region, and this rate has increased by 44.7% since 1990, compared with a 9.8% increase in the developed region [42].

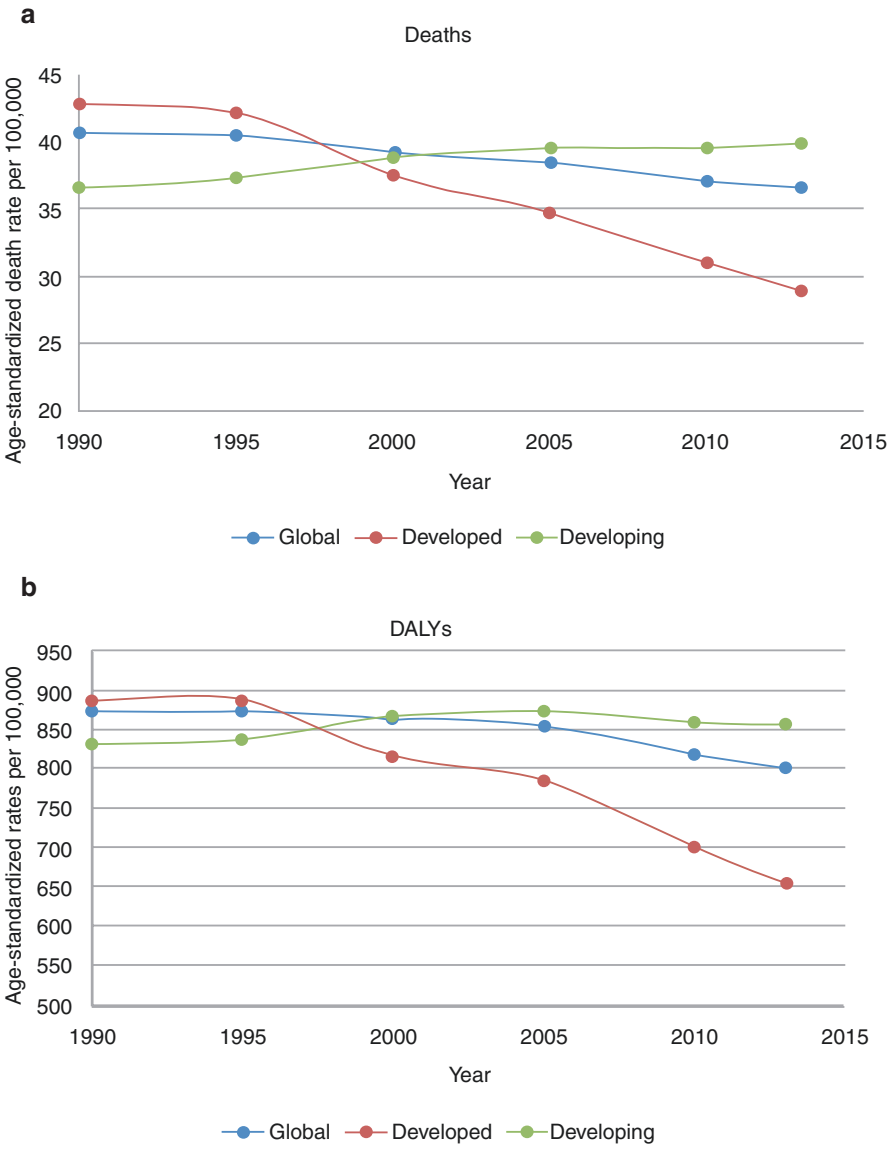

Fig. 9.3 The Developed World region has lower GFR-attributable age-standardized rates of deaths and disability-adjusted life-years (DALYs) over time. (**a**) Age-standardized mortality rate attributed to reduced GFR at the global, developed, and developing levels at six time points between1990 and 2013. (**b**) Age-standardized DALY rate attributable to reduced GFR at the global, developed, and developing levels at six time points between 1990 and 2013 [42]

9.3 Burden of Chronic Kidney Disease in Africa: Challenges

9.3.1 Problem of Screening and Non-Establishment of NCDs-CKD Programs

In most African countries, CKD prevention programs are non-existent. Most governmental interventions focus on cardiovascular disease, diabetes, and in some cases, cancers and chronic respiratory disorders [43]. CKD has not received the same kind of attention, despite its common modifiable risk factors, lack of clinical manifestations for most people with CKD, the relatively low cost of checking for CKD (serum creatinine and dipstick for albumin and blood checks in urine), and the possibility of an early diagnosis and referral to nephrologists to prevent or delay the progression of CKD to ESRD. As an example, Tunisia started by developing dialysis techniques and centers, offering treatment for the entire Tunisian population, with good coverage of dialysis centers throughout the country. Because there was a lack of nephrologists, general practitioners were trained for the delivery of dialysis treatment. However, a disequilibrium arose between the development of the very good dialysis coverage for the treatment of ESRD and the concomitant very slow increase in number of specialized doctors in nephrology and nephrology wards for early detection and treatment; this delayed progress led to the endemic situation of ESRD in the country, as shown in the 2015 ERA-EDTA registry report [44]. Similarly, there is a contrast between the fast development of dialysis availability and the slow progress made in the transplantation program, which has been available since 1986, even though today many centers, covering the country, perform transplantation [45]. Thus, the low primary prevention rate, high incidence of ESRD, low transplantation rate, increased patient survival on dialysis, and unrestricted access to dialysis contribute to the high prevalence of patients on dialysis treatment in Tunisia. The number of patients on dialysis treatment, and therefore the budget allocated to dialysis, are expected to continue to increase dramatically in the coming years [46].

Even if a national program for screening NCDs were to be developed in Tunisia, taking into account the prevalence of hypertension, diabetes, smoking, the frail elderly, and cancers, no such program would consider CKD. Although an African national ESRD registry has been available since the 1970s [11], no national epidemiological study has been performed in any African country to evaluate CKD from grade 1 to 5 in the general population. Indeed, no data are available to help government health departments in Africa to be aware of the epidemic situation of CKD (excluding ESRD) and to be aware of the need to establish programs to prevent, stop, or limit the progression of this current endemic CKD.

CKD is an increasing global public health issue, including in Africa, and it is considered that only one-third of people worldwide with CKD are diagnosed [47]; thus, is it acceptable and feasible to screen for CKD, and is this a cost-effective measure?

As discussed by George et al. [48], the Wilson and Jungner criteria for disease screening [49] appear to be a suitable model for explaining how easy, feasible,

Table 9.3 Wilson and Jungner criteria adapted for CKD screening [49]

Wilson and Jungner criteria for disease screening		The case for CKD screening
1	The condition sought should be an important health problem	CKD is recognized as a worldwide public health problem
2	There should be an accepted treatment for patients with recognized disease	Treatment is available, acceptable, and used to prevent or delay progression of CKD
3	Facilities for diagnosis and treatment should be available	Except for ESRD treatment, no specific facilities are needed to diagnose or treat CKD, treatment even possible with trained general practitioner at an early stage
4	There should be a latent or early symptomatic stage	CKD is a latent non-painful disease, usually diagnosed at an advanced phase in many developing countries
5	There should be a suitable test or examination	Simple tests are sufficient to diagnose CKD: urine albumin and blood, even by dipstick, and serum creatinine with calculated GFR estimation
6	The test should be acceptable to the population	Tests proposed are acceptable to the population. Invasive tests are not mandatory for the most common nephropathies
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood	The natural history of CKD is well known and well categorized, as proposed by the KDIGO guidelines. The prognostic profile is also well established
8	There should be an agreed policy on whom to treat as patients	ESRD is the tip of the iceberg. Even if facilities for ESRD treatment are not available, the treatment of CKD involves a higher number of patients, and treatment to prevent or delay ESRD is simple, available, and very effective
9	The cost of case finding (including diagnosis and treatment of the patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole	The CKD case-finding cost is not high when it is limited to the high-risk population. Checking for CKD is integrated in the follow-up of the common diseases noted below
10	Case finding should be a continuing process and not a 'once and for all' project	The treatment of CKD is a continuing process, which starts with the treatment of very common risk factors, such as infections, obesity, diabetes, and hypertension; continuing to the management of CKD progression and prevention of the development of ESRD, then continuing to the treatment of ESRD by dialysis and/or transplantation for some patients

ESRD end stage renal disease; *KDIGO* kidney disease improving global outcomes

non-costly, acceptable, and effective it is to screen for CKD, as shown in Table 9.3. This screening may be population-based or opportunistic, or it may be conducted in the context of healthcare and may be dependent on targets and healthcare budget allocations [50].

Questionnaires could be used as a first-line screening tool to select those who would benefit from biochemical tests. The cross-sectional population-based survey

SCreening for Occult REnal Disease (SCORED) is a suitable test that has been validated in mixed ethnic groups [51]. It appears to be suitable for CKD pre-screening in developing countries. However, this SCORED tool needs to determine the presence of type 2 diabetes and anemia [52]. In developing countries, it seems to be more cost-effective for CKD screening to test the population at high risk, since the major causes of ESRD are diabetes, hypertension, and cardiovascular diseases, as well as chronic infections such as malaria and HIV. Moreover, treatments routinely used to control these factors on their own can, in turn, prevent the onset of CKD (CKD primary prevention), and the presence of CKD can lead to the optimization or intensification of treatments of these risk factors to slow CKD progression (CKD secondary prevention). This is a personal point of view, since there are only limited data on the cost-effectiveness of CKD screening in developing countries at present. A systematic review [53] has shown that the cost-effectiveness ratios for GFR and proteinuria screening, as estimated by the cost/quality-adjusted life years (QALY) ratio, are lower in high-risk populations, such as diabetic and hypertensive populations, than in the general population. Crucially, in developing countries, a very large high-risk population remains undiagnosed, mainly because they do not have access to healthcare [54, 55].

9.3.2 The Physician Brain Drain Problem

Developed countries absorb immigrating physicians, many of whom come from developing countries. Although the recipient nations and the immigrating physicians themselves benefit from this migration, less developed countries lose their health resources, which are already weak, as a result of this loss of physicians. Medical training positions in developed nations, as well as opportunities for medical employment, have proven to be a strong draw for physicians from many nations. This medical emigration from less developed countries, often called the "brain drain," slows efforts to provide minimal medical coverage for developing countries.

Mullan studied the magnitude of medical doctor immigration to four nations (United States, United Kingdom, Canada, and Australia)—called recipient nations—using an emigration factor [56], computed as $[A \div (A + B)] - 100$, where A is the number of physicians from a source country practicing in the recipient countries and B is the total number of physicians practicing in the source country. The emigration factor is a more specific measure of the impact of emigration on a country than is the absolute number of emigrants. Mullan reported that India and the Indian subcontinent provided the largest absolute number of physicians to these recipient nations, but the relative draw on nations, as measured by the emigration factor, was greatest for sub-Saharan Africa, accounting for 13.9, versus 10.7 for the Indian subcontinent [56]. This study did not consider the brain drain of French-speaking African physicians to France and Belgium; this brain drain is very relevant in this context, but was not estimated. The migration of North African medical doctors to Saudi Arabia and other neighboring countries also has to be considered as a brain drain of physicians.

Nephrology resources in African countries are critically low. Most sub-Saharan African countries have fewer than ten nephrologists [57]. Apart from the problem of physician emigration, it is difficult to attract young doctors to the specialty of nephrology, as it is scientifically and clinically demanding and the remuneration is frequently lower than that for other specialties [58]. Moreover, the slow development of dialysis and transplantation in most sub-Saharan African countries contributes to the non-attractiveness of this specialty. Finally, as the results of dialysis per-se undertaken in sub-Saharan Africa are limited, this adds to the reluctance of young physicians to start nephrology training. Most patients in this setting are insufficiently treated, receiving two sessions a week, with many receiving only one session a week [59]. As reported by Halle et al., the rate of 12-month deaths in dialysis remained high, at up to 36.4%, in the period 2011–2012, despite the relatively young age (46.1 ± 14.5 years) of the patients [60]. Moreover, problems with dialysis equipment because of healthcare budget restrictions are also a cause of high mortality for dialysis in this setting [61]. Ulasi et al. reported that up to three-quarters of their hemodialysis patients discontinued treatment mainly for financial reasons [62]. All these conditions do not attract young nephrologists to study or practice in sub-Saharan Africa.

9.4 CKD and Perspectives for Africa

The burden of CKD in each country depends mainly on the level of development of that country's healthcare system. A well developed healthcare system will improve sanitation and provide safe water; will control, firstly, communicable diseases and chronic diseases related to these infectious diseases; will reduce maternal and child deaths; will improve child health; and will provide good vaccination coverage. Implementation of these factors will gradually improve life expectancy at birth. Thus, populations will live longer and more will be exposed to NCDs, leading to CKD later becoming a public health problem. Measures taken against sedentary lifestyles, obesity, diabetes, tobacco addiction, hypertension, and cardiovascular diseases, not only by primary prevention, but also by providing good medical coverage, treatment availability, and medical reimbursement, will reduce the occurrence of CKD. Thus, the incidence and causes of CKD can represent a barometer of the health status of a country and guide preventive measures that need to be undertaken in that country.

Healthcare in Africa differs widely, depending on the country and the region. People living in urban areas are more likely to receive better healthcare services than those in rural or remote regions. In sub-Saharan Africa, particularly in rural areas, many communities lack clean water and proper sanitation facilities. Diseases such as cholera and diarrhea, which are caused by poor hygiene, are common in some countries. Even if NCDs start to become a serious health problem in sub-Saharan Africa, communicable diseases are still the major problem in most of these countries. Excluding endemic HIV, malaria, per se, is widespread and kills one African child every 30 s. Malaria is still a leading cause of death among under-five-year-olds in many countries and so drives healthcare attention and budgets [29].

Africa is now facing two major healthcare problems: on one hand is the lack of mastery over devastating communicable diseases that show increasing endemicity, such as HIV and malaria; on the other hand is the continuous increase of cardiovascular and renal risk factors, with obesity, heavy alcoholism and tobacco addiction, a sedentary lifestyle, and the adoption of the Western fast food model, but with much higher salt intake and lower consumption of fruit; further, the consumption of vegetables is the lowest in the world [63]. In France, for example, sugared drinks are taxed according to their sugar content, tobacco taxes are increasing, and smoking in public areas is forbidden. In Tunisia, however, sugar is subsidized by the government and tobacco is not taxed, with so called "parallel markets"; in most African countries, there are no areas where smoking is restricted. Many efforts should be undertaken by governments in Africa to promote safer lifestyles and improve food intake.

Moreover, political instability, wars, and recurrent armed uprisings in Africa lead to recurrent famines and maternal malnutrition, factors that are responsible for unintended pregnancies, with delayed fetal growth, significant prematurity and maternal mortality, and insufficient child feeding. Maternal malnutrition leads to fetal underdevelopment, with reduced nephron numbers, which will be responsible for a reduced functional renal reserve in adulthood, with increased sensitivity to salt; water retention; and increased susceptibility to arterial hypertension, obesity, and metabolic syndrome, thus contributing to the burden of CKD [64].

Healthcare systems in Africa are disrupted so that priorities can be given to the programs developed to face the double endemicity of communicable diseases and NCDs. Much of the economic burden of the NCDs can be attributed to the direct medical expenditure associated with expensive and long-term treatment costs. In developing countries, public healthcare systems receive only 0.8–4% of the gross domestic product (GDP; used to face this double endemicity), as opposed to healthcare systems in developed countries receiving 10–15% of GDP [65]. At a 2001 African Union meeting in Abuja, Nigeria, African countries agreed to allocate 15% of their budgets to healthcare. To date, not only have few countries met this commitment, but even if the target is reached, 15% of a small budget is not sufficient to make major inroads into poor health. Allocating 15% of the country's budget in some sub-Saharan African countries means spending only US$ 14 per capita on health. Some of these countries invest as little as US$ 1–4 per capita.

For CKD management, developed countries dedicate more than 1% of their total healthcare budget to the approximately 0.1% of the population that has ESRD [7]. ESRD management in developing countries is unaffordable, and healthcare resources and budgets are unable to meet the burden of treatment. Moreover, most people in developing countries have no access to health insurance [66]. As an example, in Nigeria, a hemodialysis session costs US$ 100, an amount representing twice the minimum monthly wage paid to federal government workers [24]. In Tunisia, because the cost of hemodialysis is negotiated by the government and the national insurance, a hemodialysis session is cheaper, costing US$ 40; however, the minimum monthly salary in Tunisia is US$ 157.

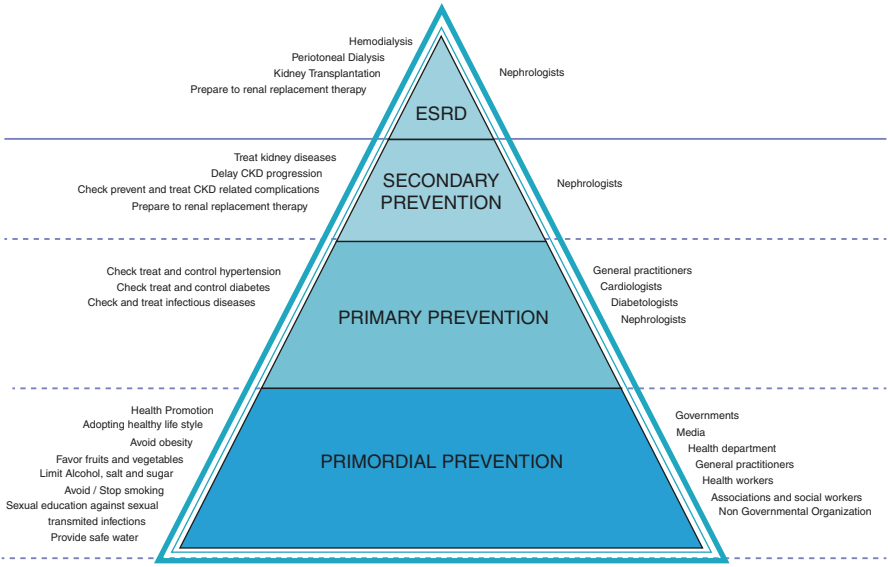

Fig. 9.4 Primordial, primary, and secondary prevention of CKD: interventions and actors

For these reasons, it is more reasonable to start by employing preventive measures with primordial and primary prevention (Fig. 9.4) than to focus on the development of dialysis treatment. Eradicating communicable diseases and optimizing medical coverage—starting by developing medical schools in African countries where they are not available—are important steps, along with communicating effective health advice against tobacco use, alcohol abuse, unhealthy lifestyles, and non-effective traditional medicine, favoring health. It is also important to develop a sustainable medical coverage system where contributions from governments will provide the most funds, awaiting the economic development, in terms of rate of GDP growth, that is expected for African countries.

Financial aid from most international donors is targeted to treatment for communicable diseases. It is known that most of the economic burden of NCDs can be attributed to the direct medical expenditure associated with excessive and long-term treatment costs. Thus, it is very important to attract some international funds to target advice and basic checks to diagnose and treat hypertension and diabetes and so prevent CKD. Pharmaceutical companies should contribute to this effort. For a developing country, it is also important to support medical education where needed and to build a sustainable healthcare system; the Tunisian healthcare strategy model is successful and can be taken as an example in Africa.

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Ethnicity and Atrial Fibrillation: A Counterintuitive Phenomenon

10

Andrea Colella and Pietro Amedeo Modesti

10.1 Atrial Fibrillation: A Global Perspective

According to the Global Burden of Disease Study (GBD) of 2010 [1], atrial fibrillation (AF), the arrhythmia most frequently encountered in clinical practice, has an age-standardized prevalence of 596 for 100,000 men and 373 for 100,000 women, corresponding to about 33 million people. In Australia, Europe, and the United States, the estimated prevalence of AF in adults is 1–4% [2–4] and rises to over 13% among people aged over 80 years [5–7]. Several prospective studies have documented the clinical consequences of atrial fibrillation especially stroke. Currently AF is detected in one third of all ischemic strokes [8]. AF also leads to increased healthcare resource utilization with a significant impact on global health budgets [9, 10]. AF prevalence increases with age so that in the next decades, AF is expected to become a crucial issue for countries recently experiencing epidemiological transition. In China, AF affects an estimated 3.9 million (2%) individuals aged ≥60 years [11]. By 2050, China will have 460 million individuals aged ≥60 years, of whom an estimated nine million will have AF [12]. Although accurate estimations are lacking, populations of elderly adults are indeed especially growing in low- and middle-income countries (LMICs, as defined by the World Bank), and AF is expected to become a major cause of morbidity in these world regions. However, at the moment AF burden has important regional variations, with high-income countries experiencing a higher prevalence, incidence,

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disability-adjusted life years (DALYs), and mortality associated with AF than LMIC [7]. In the 2010 Global Burden of Disease Study, where world areas were classified by using the Socio-demographic Index (SDI), a composite average of the rankings of the incomes per capita, average educational attainment, and fertility rates, 729 prevalent cases of AF per 100,000 (636–838), were estimated in high-middle SDI world areas and 344 (302–394) in low-middle SDI [13]. Likewise, estimation of DALYs attributable to AF was 94 (73–120) in high-middle SDI and 42 (32–54) in low-middle SDI [13]. The extent of these regional differences should be interpreted with caution for different reasons.

First, the lower rates of AF documented in developing countries may be related to underreporting, limited access to healthcare services, and geographical disparity in published data. The majority of epidemiological studies conducted outside Western Europe and North America have limitations, such as a cross-sectional design, the small number of individuals with AF, and the lack of inclusion of an adequate proportion of the population (people from remote or rural areas are often underrepresented in study cohorts). Most importantly, different risk factors for AF, such as an increased prevalence of rheumatic heart disease (RHD) in rural populations, are also not always considered [14, 15].

Second, AF could remain undiagnosed in surveys. However, this issue is intrinsic to AF and should be independent from the income of the country. A substantial proportion of AF cases are subclinical, limiting the ability to appropriately identify and detect AF without advanced medical technology. This point was evident in the last GBD report [16], which noticed an increased likelihood of reporting atrial fibrillation as the underlying cause of death certificates, resulting in an apparent noticeable increase in the mortality rate associated with AF, in the absence of a parallel increase in the same magnitude in reported rates of age-specific AF prevalence [16].

Third, the young age of population living in LMIC cannot explain the lower AF prevalence observed in surveys and estimated by GBD in LMIC when compared to wealthy nations because all data are standardized for age. Prevalence of hypertension, diabetes, and other risk factors as well as stroke incidence is following a different global pattern with growing rates in LMIC. The risk of AF in valvular heart disease (mainly mitral stenosis) is known to be high (Table 10.1) [17]. However, in LMIC a mild or moderate rheumatic mitral stenosis is not unfrequently discovered after stroke has occurred. Although, this condition may be discovered when echocardiography is performed, this relatively advanced technology is not often available in LMIC. There are some considerations arising out of this subject that deserve further notice.

Table 10.1 Cardiovascular and other conditions independently associated with atrial fibrillation [17]

Characteristics/comorbidity	Association with AF
Genetic predisposition (based on multiple common gene variants associated with AF)	HR range 0.4–3.2
Older age	HR
50–59 years	1.00 (reference)
60–69 years	4.98 (95% CI 3.49–7.10)
70–79 years	7.35 (95% CI 5.28–10.2)
80–89 years	9.33 (95% CI 6.68–13.0)
Hypertension (treated) vs none	HR 1.32 (95% CI 1.08–1.60)
Heart failure vs none	HR 1.43 (95% CI 0.85–2.40)
Valvular heart disease vs none	RR 2.42 (95% CI 1.62–3.60)
Myocardial infarction vs none	HR 1.46 (95% CI 1.07–1.98)
Thyroid dysfunction	(Reference euthyroid)
Hypothyroidism	HR 1.23 (95% CI 0.77–1.97)
Subclinical hyperthyroidism	RR 1.31 (95% CI 1.19–1.44)
Overt hyperthyroidism	RR 1.42 (95% CI 1.22–1.63)
Obesity	HR
None (BMI <25 kg/m^2)	1.00 (reference)
Overweight (BMI 25–30 kg/m^2)	1.13 (95% CI 0.87–1.46)
Obese (BMI ≥31 kg/m^2)	1.37 (95% CI 1.05–1.78)
Diabetes mellitus vs none	HR 1.25 (95% CI 0.98–1.60)
Chronic obstructive pulmonary disease	RR
FEV1 ≥80%	1.00 (reference)
FEV1 60–80%	1.28 (95% CI 0.79–2.06)
FEV1 <60%	2.53 (95% CI 1.45–4.42)
Obstructive sleep apnea vs none	HR 2.18 (95% CI 1.34–3.54)
Chronic kidney disease	OR
None	1.00 (reference)
Stage 1 or 2	2.67 (95% CI 2.04–3.48)
Stage 3	1.68 (95% CI 1.26–2.24)
Stage 4 or 5	3.52 (95% CI 1.73–7.15)
Smoking	HR
Never	1.00 (reference)
Former	1.32 (95% CI 1.10–1.57)
Current	2.05 (95% CI 1.71–2.47)
Alcohol consumption	RR
None	1.00 (reference)
1–6 drinks/week	1.01 (95% CI 0.94–1.09)
7–14 drinks/week	1.07 (95% CI 0.98–1.17)
15–21 drinks/week	1.14 (95% CI 1.01–1.28)
>21 drinks/week	1.39 (95% CI 1.22–1.58)
Habitual vigorous exercise	RR
Non-exercisers	1.00 (reference)
<1 day/week	0.90 (95% CI 0.68–1.20)
1–2 days/week	1.09 (95% CI 0.95–1.26)
3–4 days/week	1.04 (95% CI 0.91–1.19)
5–7 days/week	1.20 (95% CI 1.02–1.41)

10.2 Rheumatic Heart Disease

Valvular heart disease is a recognized condition independently associated with atrial fibrillation (RR 2.42; 95% CI 1.62–3.60) [17]. In a large study involving data from 26 countries [18], valvular heart disease was observed in 27% of participants with AF. In wealthy nations the etiology of valvular heart disease (VHD) has changed dramatically over the past few decades. Rheumatic heart disease (RHD) and associated mitral valve disease were a major cause of AF in the past [19], but the availability of early treatments for streptococcal infection has made RHD rare [17], so that VHD is now mostly degenerative [17, 20]. The latest studies do not often report RHD as a separate risk factor [18]. Conversely, in low middle SDI, RHD remains a major burden [21]. In Nepal RHD is the second most common cause of hospital admission (21%) [22]. In China, where the mortality rate from stroke is three times than that from coronary heart disease, one out of six cases of atrial fibrillation is due to RHD [23]. Studies from Africa, Asia, and the Middle East report a substantial prevalence of RHD in patients with AF [12, 24–26], reaching >60% in particular regions [24, 27]; even in high-income Middle Eastern countries, 15–29% of patients with AF also have RHD [24, 28].

The typical progression from episodes of acute rheumatic fever to subclinical rheumatic heart disease to clinical rheumatic heart disease and, in some cases, heart failure and death generally occurs over a span of at least 10 years. However, there is no clear relationship between the severity of RHD, limited valvular involvement, and many important complications [29]. Therefore also young patients with mild rheumatic heart disease that may not be clinically detectable are at increased risk for death and complications from heart-related causes [30]. Transient or sustained atrial fibrillation is sometimes observed in clinically asymptomatic patients with mild or moderate rheumatic mitral stenosis, which is often diagnosed on echocardiography after complications, such as stroke, have occurred [21, 31]. Since death from rheumatic heart disease is uncommon among children between 5 and 9 years of age, there may be a risk of serious underestimation of the endemic spread of rheumatic heart disease in several countries worldwide. In these countries the need to develop strategies for early diagnosis is deeply felt, and low-cost portable ultrasonographers are now available. However, physicians skilled in echocardiography or expert sonographers are rare in LMIC. Furthermore universal healthcare is often not available, and skilled personnel often work in the private sector. Therefore the possibility to develop different new, simple, low-cost diagnostic procedures for population screening might be relevant for low middle SDI world areas [32].

Anyway, geographical variations of AF prevalence are also supporting the view of Caucasian ethnicity as a possible risk factor for AF.

10.3 Atrial Fibrillation and Ethnicity: A Paradox

Notwithstanding reported limitations, all ethnicities, whether immigrant [33, 34] or indigenous [35, 36], in any parts of the world, have lower prevalence of AF than Caucasians.

In particular, despite the generally higher burden of most primary AF risk factors in ethnic minorities, epidemiology studies and clinical trials have consistently shown that individuals of non-European ancestry have a lower prevalence of AF. The discordance between the higher AF risk factor burden and the lower incidence and prevalence of AF was seen as a "paradoxical relationship" [37, 38].

In the United States, Caucasian ethnicity was found to be associated with significantly greater odds for atrial fibrillation compared to blacks, Asians, and Hispanics, after adjusting for comorbidities associated with the development of AF [39]. The cross-sectional study was performed in 2008 among the 430,317 members aged 60 years or older in a large California health maintenance organization where subjects with primary non-valvular atrial fibrillation were identified [39]. Among members with assigned race/ethnicity data, the prevalence among whites, blacks, Asians, and Hispanics was 8.0%, 3.8%, 3.9%, and 3.6%, respectively. The adjusted odds ratios (95% confidence intervals) of AF among blacks, Asians, and Hispanics with whites as referent were 0.49 (0.47–0.52), 0.68 (0.64–0.72), and 0.58 (0.55–0.61), respectively [39]. However, the study was cross-sectional, and race/ethnicity was classified on the basis of Asian/Hispanic surnames. Dewald et al. [40], using a large hospital-based retrospective cohort, also had similar findings; however, the study was hospital-based that is different from community-based surveys where the general population is assessed; secondly the study was a single-center study without the generalizability of a prospective, multicenter, community-based cohort. In the Northern Manhattan Study, AF prevalence was more common in whites (29%) than in either blacks (11%) or Hispanics (11%) [41].

There have been few studies examining AF risk in an Asian population in the United States. One study of male US veterans found the age-adjusted prevalence of AF to be 3.6% and 3.0% in Asian and Hispanics, respectively, compared with 5.7% in Caucasians [42]. Incidence rate of AF was investigated in the MESA multiethnic cohort, a population-based multicenter longitudinal cohort investigating prevalence, correlates, and progression of subclinical cardiovascular disease. Age- and sex-adjusted incidence rates of AF were significantly lower among Hispanics, blacks, and Chinese compared with whites. Among participants 65 years of age or greater, Hispanics, Chinese, and blacks had significantly lower AF incidence than whites, but incidence rates were similar among participants under age 65 years. The population attributable fractions for smoking were 27% among blacks but lower among other race/ethnic groups. Among whites, the age- and sex-adjusted population-attributable fractions for hypertension were 22.2%, but this was higher among blacks (33.1%), Chinese (46.3%), and Hispanics (43.9%). Overall, the incidence of hospitalized AF was significantly lower in Hispanics, blacks, and Chinese than in whites. A larger proportion of AF events appear to be attributable to hypertension among nonwhite populations compared with whites.

In Europe, most data rely on Asian patients. AF rates in the United Kingdom are lower among South Asians, despite a higher cardiovascular risk profile and stroke risk, than in the native British population. Data from the UK-based West Birmingham Atrial Fibrillation Project [43, 44] early reported a low prevalence of AF among Indo-Asian participants aged ≥50 years (0.6%), whereas the prevalence of AF was 2.4% in the general study population aged ≥50 years. A low

prevalence of atrial fibrillation was also observed among the South Asian and black African-Caribbean subjects enrolled in a community-based cross-sectional study performed from 2006 to 2009 in Birmingham, United Kingdom [45]. More recently, an observational study was designed to explore the relative differences between South Asians and whites in a well-defined, multiethnic population within Bradford Metropolitan District in the United Kingdom with careful consideration of traditional cardiovascular risk factors that are thought to contribute to the development of AF [34]. Data of 417,575 adults were obtained from primary care records. The South Asian sample has a mean age (39.4 years) approximately 10 years lower than that of the white population (48.8 years). However, after adjustment for age, sex, and established risk factors, the odds of AF in South Asians when compared with whites was 0.29 (with 95% CI 0.26–0.32). In both cohorts, hypertension, heart failure, ischemic heart disease, and aging significantly increased the likelihood of developing AF. However, diabetes did not increase the odds of AF in the SA sample (0.81, 95% CI, 0.63–1.05) but did so in whites (1.28, 95% CI, 1.19–1.38).

In Sweden the relationship between country of birth and the diagnosis of AF (ICD-10 code) was recently reviewed at national level using the Total Population Register and the National Patient Register [46]. A lower incidence of AF was observed in subjects originating from Asia, Africa, and South America when compared to the Swedish-born population [46].

The prevalence of AF in a cohort of young to middle-age Chinese first-generation migrants in Italy was recently assessed using single-lead ECG in a substudy of the CHIP survey [47]. At multivariate analysis only hypertension was associated with AF. The estimated prevalence of AF (0.75%) was low. However, subjects were younger than 60 years, the study was community-based rather than hospital-based, and paroxysmal AF was not specifically searched. Age-specific prevalence of AF in China rose from 0% in the 30–34 age group to 5.9% in the 80–84 age group [11]. When considering the same age group, in China AF was diagnosed in 61 out of 20,789 subjects (0.29%). Notwithstanding the low prevalence of AF, China is among the countries with the highest incidence of stroke [48], and Chinese ethnicity was proposed as a risk factor [49, 50]. The proposal to add one more "C" ("C" for Chinese) to CHA2DS2-VASc was recently advanced [50].

Morphological differences between the Caucasian and SA hearts have been reported. There is evidence to suggest that the SA left atrium is smaller than the atrium of Caucasians, and this appears to be associated with a smaller body surface, and a smaller LA might explain this discrepancy [51]. Secondly, part of the difference could be secondary to events at the ion channel level. There are reports of sodium channel variants in different ethnic groups, which could either be protective or make patients more vulnerable to heart rhythm disorders [52]. Finally, the extracellular matrix composition may also be different, or the response to fibrosis may be reduced in SAs [53, 54]. It is possible, therefore, that the difference in AF susceptibility is attributable to a different genetic makeup. Early onset of AF in populations with a lack of predisposing conditions for AF may also indicate a significant

underlying genetic etiology. Recently, a number of genes have been identified and ethnic associations made in genome-wide association studies.

10.4 Genome-Wide Association Studies

Genome-wide association studies (GWASs) conducted in mostly white patients of European ancestry have identified 14 AF susceptibility loci [55–60].

Ma et al. [61] reported that TBX5 gene gain-of-function mutations contribute to early-onset AF. The TBX5 was reported to reduce fibrosis and to improve cardiac function by reprogramming non-myocytes while increasing conduction heterogeneity by upregulating connexin-40 expression [61]. Similarly, HAND2, the closest gene to the novel AF variant (rs8180252) in the Korean early-onset AF population, was also reported as a cardiac transcription factor related to heart repair. HAND2 reprograms non-myocytes, and its overexpression can facilitate regenerative cardiomyocyte proliferation with reprogramming of cardiac fibroblasts into functional cardiac-like myocytes [62].

Lee et al. [63] recently reported the results of the latest GWAS from the Korean AF Network. The discovery cohort consisted of 672 Korean patients with early-onset AF (age <60 years) who had undergone radiofrequency catheter ablation for AF and a control group of 3700 patients without AF from a large community cohort. The replication cohort included 200 patients with AF and 1812 controls. The authors found that 5 of the 14 susceptibility loci previously identified by GWAS of patients of European ancestry were reproducibly associated with AF in this cohort of Korean patients with early-onset AF who underwent catheter ablation. Two novel risk loci at 1q32.1 (PPFIA4) and 4q34 (HAND2) specifically associated with early-onset AF in the Korean cohort were also identified [63].

When considering the possible clinical implication of genetic studies, some aspects have to be discussed. A major challenge when performing genome-wide association studies (GWASs) across racial/ethnic groups is the need to recruit tens of thousands of individuals with and without AF in order to meet pre-specified statistical significance. Secondly, despite recent advances in genetics, it is still challenging to investigate the mechanism through which these genetic variants influence AF risk. Although estimates of AF heritability have been reported as up to 60%, no genetic test is indicated for AF. This is because only a small portion of its mechanism has been defined and none of the known genes have been reported to account for >5% of AF pathogenesis. Furthermore, the study findings may not be generalized to other cohorts with different ethnicities and races. In addition, comparison of the Caucasian, African, Han Chinese, and Japanese data from the 1000 Genomes Project phase 3 revealed notable ethnic differences in allele frequencies in the risk allele. Especially, at chromosome 4, the major risk allele frequencies of six single nucleotide polymorphisms were much higher in a population of European ancestry than in an Asian population [63]. These substantial interethnic differences indicated different associations in individuals of different descents.

Therefore these findings support the concept of genetic heterogeneity in AF susceptibility loci across racial/ethnic groups. Such knowledge may contribute to elucidate the underlying molecular mechanisms of AF in diverse racial/ethnic groups.

10.5 Detection and Management of AF in Ethnic Minorities

Regional variation in burden of AF, and more precisely differences in AF burden among LMIC and high-income countries, should also be read with caution because patients with AF in LMIC are less likely to be managed according to recommended AF guidelines [25].

Great attention is now placed to AF in Europe. However, when knowledge and literacy about AF are lower in the community, fewer patients may receive diagnosis and treatment. This phenomenon should be kept in mind while considering the low prevalence of AF both in some world areas and within ethnic communities in Europe.

Investigators in studies of AF usually identify affected patients from single-occasion screening electrocardiograms, which are likely to reveal only permanent AF. Many patients with AF are asymptomatic, and some are identified only as a result of other investigations or interventions, such as after a stroke, during ambulatory electrocardiography, or implantation of a pacemaker device. The underestimation of AF prevalence is a worldwide problem and might explain some of the variability in prevalence reported worldwide. Consequently, upcoming studies using ambulatory and mobile electrocardiography might demonstrate an increased prevalence of AF, even in high-income countries. Warfarin use reduces risk of AF-associated thromboembolism by over 60% [64]. The estimated annual stroke risk without anticoagulation in the setting of AF is 4.5%. Racial differences in anticoagulation are evident: compared to whites blacks require higher, and Asians require lower warfarin dose [65]. Beyond increased dosage requirements, the time in therapeutic range (TTR), a measure of warfarin efficacy, has been found to be consistently lower in blacks compared to whites after multivariable adjustment [66]. In contrast, observed TTR in Asians and Hispanics was similar to whites [67]. In an AF Medicare cohort, the stroke rate in blacks was 10.6 per 100 patient-years of warfarin therapy compared to a rate of 5.2 in whites [68].

In the United States, racial differences in anticoagulation practice were reported to exist. Whites generally are more likely to receive anticoagulation than blacks and other racial and ethnic minorities. A retrospective study of a heart failure database showed that blacks were less likely to receive anticoagulation compared to whites after adjustment for multiple variables including age, sex, history of AF, liver disease, and alcohol use [69]. In a population-based study, the odds of blacks being treated with warfarin were only one fourth as great as whites (OR 0.28; 95% CI, 0.13–0.60) [70]. Similarly, Hispanics, Native Americans, and Asian/Pacific Islanders were less likely to receive warfarin in an analysis of hospital discharge records across five US states [71]. Data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation were recently reviewed to compare clinical

characteristics, quality of life (QoL), management strategies, and long-term outcomes associated with AF among various racial/ethnic groups [72]. The whole group of 9542 participants with AF (mean age 74 years) was composed by 43% women, 91% white, 5% black, and 4% Hispanic. Relative to white and Hispanic patients, black patients with AF had more symptoms, were less likely to receive rhythm control interventions, and had lower quality of warfarin management. More precisely, there were no significant racial/ethnic differences in CHA2DS2-VASc stroke or ATRIA bleeding risk scores, and rates of oral anticoagulation use were similar. However, racial and ethnic minority populations treated with warfarin spent a lower median time in therapeutic range of international normalized ratio (59% blacks vs 68% whites vs 62% Hispanics). Despite these differences, there was no difference in long-term outcomes associated with AF between the three groups at a median follow-up of 2.1 years [72].

In conclusion demographic factors contribute to racial disparities in healthcare. Socioeconomic and cultural factors may affect perception of illness and symptom reporting and result in underdiagnoses and suboptimal care in ethnic and racial minorities.

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Part III

Drivers Predisposing Ethnic Minorities to Cardiovascular Disease

Disparities in Hypertension in the Ethnic Minority Groups: Beneficial Aspects of Minority Ethnic Group Cultures

11

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11.1 Chronic Diseases in Ethnic Minorities in Europe

In a global perspective, increased systolic blood pressure (BP) remains the leading factor in the Global Burden of Disease (GBD) 2016 risk hierarchy [1]. Highly effective interventions exist to manage blood pressure at the primary care level, as do a range of public health interventions, so it is quite remarkable that global exposure to increased systolic BP (SBP) is increasing. Part of this increase might be tied to the global rise in high body mass index (BMI), but the increase in systolic blood pressure (SBP) represents significant missed opportunity for the world's health systems. Ethnicity is now an element of complexity in the prevention of cardiovascular

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disease in European Union (EU) [2]. During the last decades, increased prevalence of hypertension (HTN), inadequate blood pressure (BP) control, and limited access to diagnostic procedures and treatments have been observed among ethnic minorities living in Europe. Consistent with raised BP levels, an excess risk of stroke, renal, and myocardial diseases is being observed among populations originating from low- and middle-income countries now living in Europe. It is now clear that in this scenario, the health service must be able to shift attention from the traditional focus on infectious diseases to the problems that characterize a population that is permanently present, therefore more exposed to chronic health problems but also related to socioeconomic inequalities in health. Although the existence of barriers to care might be underestimated in countries where healthcare is universal, as in most EU countries, it is now evident that cultural elements can hinder access to health services or prevention by an ethnic minority. This point is crucial because evidence are showing that also in Europe, ethnic differences in cardiovascular (CV) events persist after adjusting for socioeconomic differences, suggesting that other variables might play a role [3]. Understanding the reasons behind the excess of CV risks in ethnic minorities is crucial for addressing inequalities in health also because the ageing of migrant populations carries the risk of overburdening the majority of the healthcare systems in the EU that offer free-of-charge access to emergency medical care [4]. Since the 1990s, Italian national health policies and laws allow non-Italian citizens the access to the National Health Service (NHS). Furthermore, the delivery of care is provided also to those who are temporarily irregular. Nevertheless the heterogeneity of health policies adopted by individual regions determines inequalities in the availability of services [5], which deserve more attention to integration policies. In this scenario, attention to prevention is crucial.

11.2 Absolute Blood Pressure Differences Among Ethnic Groups

11.2.1 Sub-Saharan African

As a major CV risk factor, high BP needs to be carefully considered. HTN was consistently reported to be highly prevalent among sub-Saharan African (SSA) descent populations living in high-income countries also in Europe [6, 7]. Consistent with raised BP levels, an excess risk of stroke and renal disease was observed for SSA both in Europe [8, 9] and in Italy [10]. A recent systematic review and meta-analysis analysed the absolute differences in BP between the population of EU origin and adult subjects belonging to SSA and South Asian (SA) ethnic groups [7]. The study included results of 23 observational studies conducted in Europe up to 2015 in nonselected adults. Sample size ranged from 115 to 59,952 participants (median, 1578), with a total of 9070 SSA (3894 men and 5176 women), 18,421 SA (10,021 men and 8400 women), and 130,380 EU (67,768 men and 65,612 women). Compared with EU, SSA had higher values of both SBP (3.38 mmHg) and DBP (3.29 mmHg). The term SSA was adopted to accommodate the population divisions

used in the papers analysed although it is to be acknowledged the heterogeneity of this SSA group in terms of language, diet, and religious practices [11, 12].

Whilst there may be genetic markers of predisposition to HTN in SSA populations [12–14], it is indeed now clear from international and migration studies that this higher burden of HTN is highly modifiable with adaptations to host environments [12, 15–17] and lifestyle changes. Special importance is played by salt intake [18–20]. A predominant role of the environment is suggested by studies that found a higher prevalence of HTN of West African migrants compared to people in their countries of origin [21]. Body weight and sodium intake increases were found to be the main determinants of BP increase in subjects who migrated to Israel and Italy from Ethiopia [22] and Somalia [23], respectively. More precisely 30% of normotensive migrants to Italy from Somalia were hypertensive after a 6-month stay in Florence [23]. In the same subjects, a reduced sensitivity of the afferent pathway of the cardiopulmonary reflex with resultant defective inhibitory afference to the sympathetic outflow was also shown [24]. Sodium sensitivity and the reduced response of the afferent pathway of the cardiopulmonary reflex [24] are in agreement with the better response of hypertensive blacks to calcium blockers and diuretics than to ACE inhibitors and β-adrenergic blockers [25]. High-sodium intake has effects on BP, all-cause mortality, CVD, stroke, and coronary heart disease which were recently quantified by the WHO Nutrition Guidance Expert Advisory Group Subgroup on Diet and Health [26–28]. When sodium intake was <2 g/day versus ≥2 g/day, systolic BP was reduced by 3.47 mmHg (0.76–6.18) and diastolic BP by 1.81 mmHg (0.54–3.08). Increased sodium intake was associated with an increased risk of stroke (risk ratio 1.24, 95% confidence interval 1.08–1.43), stroke mortality (1.63, 1.27–2.10), and coronary heart disease mortality (1.32, 1.13–1.53) [29]. The 2002 Joint World Health Organization/Food and Agriculture Organization of the United Nations expert consultation [30] and the 2007 WHO guideline [31] recommend the value of 2 g/day (equivalent to 5 g of salt daily). Estimation of the effects of low-sodium vs. high-sodium intake on BP showed larger increase in hypertensive and black populations than in normotensives and Caucasians, respectively [32]. This consideration encouraged public and healthcare systems to intervene in this group, and specific prevention strategies for HTN in SSA (mainly low-sodium diet) now exist [33]. A national strategy to reduce population levels of salt intake was also introduced in the UK in 2003 [34, 35]. Likewise UK physicians seemed to be aware of the higher burden of HTN in SSA subjects and more correctly recognize and diagnose HTN in SSA than in other ethnic groups [36]. However, the magnitude of the HTN burden among SSA descent populations varies across high-income countries [17]. Furthermore limitations of prevention strategies so far implemented in effectively reaching SSA minority subgroups and in modifying their CV risk profile seem to exist. When the potential interaction between time trends for differences in BP and other CV risk factors, body mass index, and diabetes was taken into account, the heterogeneity of the studies included in meta-analysis [7], carried out in Europe over a period of over 30 years (from 1977 to 2015), was not influenced by the year of survey. The difference of BP levels between SSA and EU was thus consistent over years thus suggesting that new specific intervention strategies for SSA subjects

are needed. The importance of careful BP measurement irrespective of ethnic group is to be specially considered because where this is not undertaken, erroneous difference may occur, which could have an impact on clinical decisions [37]. Accurate assessment of BP requires several measurements [38]. African Americans are more likely than whites to have abnormal autonomic function, abnormal baroreflex function, and altered sodium excretion [39–41]. These biological mechanisms are implicated not only in higher mean BP but also in increased BP variability and abnormal diurnal BP rhythm [42].

11.2.1.1 Peculiarities of Ambulatory Blood Pressure in African Descent Populations

Ambulatory BP monitoring (ABPM) is the most commonly recommended approach for out-of-office BP measurement [43, 44]. Ambulatory BP findings in SSA were consistent with resting BP data, with levels being generally higher for SSA when compared with Europeans [45]. In a meta-analysis investigating ethnic differences in nighttime BP, expressed using standardized mean differences, African Americans had higher mean nighttime SBP and DBP compared with whites [46]. Smaller nocturnal blood pressure falls, and a higher prevalence of non-dipping among black people was also observed in a more recent systematic review and meta-analysis [47], carried out for the years 1966–2003, including 11 studies from the USA, 1 from the USA and Canada, and 6 studies from the UK. Compared with whites, blacks had a significantly lower mean percentage nocturnal fall; the overall weighted mean difference in SBP was −3.07 (95% CI, −3.81 to −2.33; $P < 0.00001$) and in DBP was −2.98 (95% CI, −3.97 to −2.00; $P < 0.00001$). Two studies on South Asians showed a higher SBP but a similar mean DBP nocturnal fall compared with whites [47]. This makes it unlikely that ethnic differences in BP simply reflect different cardiovascular responses to BP measurement [48]. More precisely SSA was consistently reported to have high nighttime BP [23, 45, 46, 49] with a blunted nocturnal decline. Nighttime BP was higher in African-Caribbeans than in Europeans [45], and the percent fall in systolic BP from daytime to nighttime was higher in Europeans than in African-Caribbeans and remained significant when corrected for resting systolic BP [45, 50]. The finding of a smaller percentage nocturnal BP decline and a higher prevalence of non-dipping (<10% fall) in blacks may explain, at least in part, the comparatively high cardiovascular morbidity and mortality among these groups [10, 15, 51–53]. It is possible that a smaller nocturnal decline in ambulatory BP in SSA makes some additional contribution to the ethnic difference in risk of hypertensive end-organ damage so that ambulatory BP monitoring (ABPM) might be especially useful in this ethnic group [48, 54].

Data from the Jackson Heart Study (JHS), a population-based cohort comprised exclusively of African American adults, were recently reviewed to determine ambulatory daytime, 24-h, and nighttime BP and to define the diagnostic BP threshold, which is the threshold, if exceeded, to be associated with increased disease risk in this population subgroup [55]. Despite the relatively small differences in average 24-h ambulatory BP levels, the nocturnal decline in ambulatory BP was much smaller in the Jackson Heart Study (7.6/13.5%, systolic/diastolic) [55] than in the

IDACO study which included participants from general population from Denmark, Belgium, Sweden, and Japan (14.4/17.8%) [56]. However, the outcome-derived ambulatory BP thresholds identified for African American adults in the JHS [55] were found to be higher than those reported in the IDACO study [56, 57]. More precisely, the most important difference was the outcome-driven thresholds for nighttime BP, which was 129/133 mmHg in the Jackson Heart Study (for untreated/treated subjects) and 120 mmHg in the IDACO (76.5% untreated) [57]. The use BP thresholds, which are higher than those from recommendations obtained in Caucasian subjects [56, 57], will lead to a lower prevalence of daytime, 24-h, and nighttime hypertension among African American adults. Consequently, the prevalence of white-coat hypertension (i.e. clinic hypertension without ambulatory hypertension) will increase, and masked hypertension (i.e. absence of clinic hypertension with ambulatory hypertension) will decrease. Although this important difference in the outcome-derived ambulatory BP thresholds is difficult to explain, the Jackson Heart Study reinforces the notion that ambulatory BP monitoring should be mandatory for the evaluation of African descent subjects with elevated BP.

In SSA migrants, the reduced nocturnal decline in ambulatory BP was found to be associated with altered sodium excretion and impaired adaptation of cardiopulmonary receptors following changes in sodium intake [23, 24]. Genome-wide association studies identified potential candidate genes or loci among hypertensive patients [58, 59], possibly contributing to the pathogenesis of impaired Na excretion in blacks [60].

11.2.2 South Asian

Regarding the South Asian (SA) population, an early systematic review [61] showed that HTN prevalence was lower in Bangladeshis followed by Pakistanis and Indians, than in EU. When absolute BP values were considered in a meta-analysis of observational studies conducted in Europe up to 2015 in nonselected adults, SA as a whole group had SBP values lower than EU (−4.57 mmHg) [7]. SA also tended to have lower, albeit not significantly, DBP values (−0.56 mmHg). This finding apparently does not fit with the higher incidence of stroke and CV death in SA living in Europe as compared with EU [8, 62–65]. However, the prevalence of diabetes mellitus in surveys was uniformly higher in SA than in many other populations [7] and may contribute to the high CV disease burden in SA [66, 67]. The close relationship between diabetes and obesity has driven the attention to the importance of body weight reduction [68]. The SA group is highly heterogeneous because SA ethnic roots originating from the Indian subcontinent, including subjects coming from a large geographic area, include countries (India, Pakistan, Sri Lanka, Nepal, and Bangladesh) characterized by important differences in diet, culture, lifestyle, and religions. In Europe, BP variations between SA populations originating from different countries have already been reported [69], and BP differences between Hindus and Muslims were found [15, 70]. When studies enrolling SA were grouped according to the dominant religion in the country of origin, participants from Muslim

countries showed significantly lower BP values than EU, regardless of gender, for both SBP (−9.22 mmHg) and DBP (−3.23 mmHg). Although data on alcohol consumption and diet are not available in most of included cohorts, the country of origin and religion can be considered proxies for other risk factors and behaviours (i.e. alcohol use, vegetarian diet, use of different cooking procedures) [71] that may explain some of the differences. Many studies have found that religious involvement is associated with lower risks of HTN. The link between religion and HTN has been attributed to a variety of factors including encouragement towards healthy behaviours such as avoiding tobacco, exercising regularly, and adhering to a particular diet [72], strengthening social ties and fostering supportive environments [73], and providing a sense of security and self-control [74]. It might thus be important to consider the role of religion in culturally specific strategies for CV prevention [75–77].

Lifestyle modification can also slow down the progression of diabetes mellitus. Although mean BMI seems comparable between SA and EU, it should be considered that compared with EU, SA subjects have increased abdominal visceral fat and greater insulin resistance at similar levels of BMI [78]. It is essential therefore to encourage the control of body weight in migrant populations because of its relationship with diabetes [78–82].

These results lead to three important considerations:

(a) Prevention strategies implemented in Europe played a key role in reducing BP in general population and in reducing the incidence of CV disease in Europe; however, the difference of BP levels between SSA and EU was consistent over years thus suggesting that new population-specific intervention strategies are needed.
(b) The finding of lower BP levels in SA Muslim populations suggests the importance of as yet untapped lifestyle and behavioural habits of such populations (religion being a likely proxy for them) that may represent an advantage reflecting a lower predisposition towards the development of HTN.
(c) The additive effect of diabetes, independent from origin, in explaining the findings of elevated BP levels emphasizes the need to develop new strategies for the prevention and control of HTN and ensuing CV disease in groups at higher prevalence of diabetes.

11.3 Hypertension Awareness, Treatment, and Control

The continuing debate/enigma is whether differences observed in SSA are because of inherent genetic differences; environmental factors such as excess dietary salt/reduced potassium, excess fructose, and sensitivity to alcohol; or limited access to healthcare and adherence to medication. An important aspect regarding reducing or eliminating CVD disparities has been the focus on awareness, treatment, and control of HTN. Whilst most studies found no differences in HTN awareness and treatment rates among the three ethnic groups, among treated hypertensives, blood

pressure (BP) control rates in the Netherlands were found to vary from, respectively, 37% for the Surinamese, 33% for the Ghanaians, and 47% for the whites [83, 84]. Evidence also indicates that large proportions of the hypertensive patients in the severe HTN category were not receiving treatment. Only about half of severe hypertensive Ghanaian migrants in Europe and under a quarter in rural and urban Ghanaian were receiving antihypertensive medication treatment [85]. The high prevalence of severe HTN accompanied by lack of medication treatment among this category population is worrying given high rates of complications associated with severe HTN. Poorly controlled HTN has been documented as the number one cause of stroke [86]. This also demonstrates that there is a need to address barriers to BP control among SSA who are treated for HTN. Poor adherence to prescribed medication and lifestyle recommendations has been identified as the most important modifiable cause for disparities in BP control and, consequently, the occurrence of HTN-related complications [87]. Enhancing patient adherence to therapeutic measures is an essential first step towards reducing the observed ethnic disparities in BP control [88]. Socioeconomic status and patient-provider communication were recently indicated as key parameters that may affect adherence [89].

Socioeconomic status has a profound impact on CVD morbidity, mortality, and medication adherence. Overall, medication adherence was higher in men, whites, older patients, and those living in areas with higher education rates and higher income [89]. Adherence improves when providers engage patients in their healthcare and patients are better educated, informed, and interactive in making healthcare decisions best suited to them. However, patient engagement may be a more difficult goal among minorities [90]. For ethnic minorities, the involvement of the families and community may be relevant. Given the complexity of the phenomenon, there is a pressing need to deepen the components of patient engagement at various levels (individual, relational, social community) considering their specific impact and interconnection [90].

Although non-scientific beliefs are common, structured evaluations of patient beliefs can help identify discordant beliefs. A systematic review of 22 studies, including 6516 participants, showed that the perception by African Americans that HTN was episodic and symptomatic led to unusual use of drugs. Studies from the UK and the USA have shown that patient beliefs about HTN and treatment can differ between ethnic groups [91–93]. In the patient education literature, there is increasing theoretical support for the notion that culturally adapted educational interventions may be better suited to support ethnic minority patients in chronic disease management than generic interventions. Reconciliation of differences between patient-provider understanding and cultural differences may improve adherence and acceptance of medical treatments among African patients with HTN [89]. General practitioners (GPs) play an important role in the treatment of HTN. Primary care guidelines recommend patient education as a means of enhancing patients' motivation and ability to adhere to HTN treatment goals [94]. Patient perceptions about the onset, symptoms, pathophysiology, course, and treatment of HTN can differ substantially from those of their healthcare providers [95], and this may have a profound impact on adherence to treatment [96]. HTN care providers

are therefore advised to employ "patient-centred" educational approaches that allow them to explore the individual beliefs and needs of their patients and to find common ground regarding treatment. A motivational interviewing according to the "5 A's" framework (i.e. ask, assess, advise, assist, and arrange) is recommended as the preferred method for HTN counselling for all patients [91].

Patients from different cultural backgrounds may be expected to have their own perceptions and beliefs which will affect their use of medicines. In addition, ethnic minority groups are associated with communication and language barriers and different experiences, needs, and expectations than the wider EU population which may influence their ability to manage their medicines effectively [97]. In a qualitative study in Amsterdam, African-Surinamese and Ghanaian residents perceived psychosocial stress as an important contributor to their high blood pressure levels [93]. Because of this perception, some Ghanaians and African-Surinamese admitted to discontinue their antihypertensive medication use when visiting their homelands. In addition, Ghanaian and African-Surinamese hypertensive men admitted lowering or stopping their prescribed antihypertensive medications because they worried about the negative effects of antihypertensive medications on their sexual performance [98]. These findings suggest that medication prescription alone is not enough to improve BP control among ethnic minority groups and highlight the need for further studies to unravel the key factors that may positively influence BP control among these populations including adherence and provision of alternative antihypertensive medicines for individuals who are worried about the side effects especially among men who are concerned about the impact of some antihypertensive medicines on their sexual life. Such information is crucial for developing appropriate culturally tailored patient education programmes to encourage patients to take their antihypertensive medications as prescribed [99].

Culturally appropriate patient education typically combines the principle of "patient-centred" care with that of "culturally competent" care [100]. Although guidelines for HTN management have been produced for several organizations [101], most guidelines have been primarily based upon the total population without accounting for ethnicity/race, providing little insight into the risks, responses, and social influences present in each unique racial milieu.

11.4 Issue for Prevention

Effective communication is essential in establishing a diagnosis and treatment plan [102]. Cultural differences between the physician and patient may create communication barriers so significant that our patients leave the office not knowing what we are telling them. Culture has been defined as "beliefs and behaviors that are learned and shared by members of a group" [103]. Gestures are not universal; personal space, the space between individuals during a one-on-one private conversation, is much closer in many cultures (i.e. Latin American or Middle Eastern); direct or prolonged eye contact with the patient may be thought to signify disrespect [102].

Certain conditions, such as overweight, women having high odds of obesity and abdominal obesity in most low-income countries [104], and gender differences starting at puberty, may be "acceptable" or even desired [105]. Abdominal obesity was found in nearly 80% of Iranian women living both in Iran and in Sweden [106]. Likewise in the Netherlands, the prevalence of central obesity was higher in women than in men, sex differences being particularly larger in ethnic minority groups, especially in African-Surinamese than in white Dutch [107]. Investment in women's education may present an important long-term investment in obesity prevention. Given the beneficial effects of physical activity on weight reduction, promotion of physical activity may help to bridge the gender gap in the metabolic syndrome, particularly in ethnic minority women in whom obesity is highly prevalent but physical activity levels are low [107]. Even whilst attempting to learn about specific cultural norms, the dangers of stereotyping need to be acknowledged, realizing that factors such as socioeconomic status, educational level, occupation, family values, and belief systems have an important role for the patient. The intervention should thus not be focused only on the individual but rather on the context (the family and the community); otherwise, change may not be sustainable.

Conclusion

How best to respond to the rising prevalence of HTN in ethnic minorities is a topic of ongoing public health debate and discussion. According to the Disease Control Priorities Project, two prevention strategies at population level, salt reduction and tobacco control, and a multidrug strategy to treat patients with high-risk cardiovascular disease meet the condition of cost-effectiveness [108, 109]. Population strategies supported by communication media might induce cultural changes and the adoption of healthy lifestyle. On the other hand, the approach to patients at high risk for cardiovascular disease requires the development of specific risk models. CVD risk-assessment models for a population rely on three components derived from a cohort representative of the same population: (1) mean levels or prevalence of risk factors, (2) average absolute CVD risk, and (3) relative risk of CVD associated with the risk factors. However, current tools are mainly developed on white population so that systematic errors may result when directly applied to populations with different profiles of the three components [110]. To better quantify this risk and develop more effective guidelines, we need to improve risk assessment and use risk scores validated for ethnic minorities. As in African patients, South Asians also develop hypertension at an earlier age, with more end-organ damage, but there are no known differences in the blood pressure-lowering response to antihypertensive drugs, and despite the greater mortality, there are no trials in South Asians with morbidity and mortality outcomes. Also, we need data on whether lower thresholds to start treatment or lower therapeutic goal blood pressures need to be applied [111].

There are 60 million citizens belonging to ethnic and religious minorities in Europe, and their presence in the physician's office is increasing. Policy initiatives should thus improve data collection, to adapt organization of health systems

to cultures and to provide information to ethnic minorities on health problems and services. Europe as a whole is often perceived as a group of wealthy countries where inclusive social protection systems provide comprehensive protection for the most vulnerable [4, 112, 113]. However, current budget restrictions may widen health inequalities, hurting population subgroups in the dominant ethnic groups (lower socioeconomic groups, the unemployed who comprise a very large group in Europe at present, those with limited education) [114]. Drive to cost-effectiveness should thus be coupled with seeing health as an investment, avoiding myopic short-term savings through arbitrary healthcare cuts.

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Type 2 Diabetes in Ethnic Minority Groups in Europe

12

Karlijn A. C. Meeks and Charles Agyemang

12.1 Introduction

Type 2 diabetes (T2D) is well established as an important risk factor for cardiovascular disease (CVD) by both observational and pathophysiological data. Those affected by T2D have a two- to fourfold increased risk for CVD [1, 2]. In addition, CVD accounts for 52% of mortality in T2D [3]. T2D increases the risk for CVD both directly and indirectly. The indirect pathway is confounded by T2D-related risk factors such as obesity, lack of physical activity, tobacco use, unhealthy diet, high blood pressure, increased cholesterol levels, etc. These factors independently contribute to both T2D and CVD. Hence, people suffering from T2D are at high risk to also suffer from hypertension and dyslipidaemia, which are major risk factors for CVD. Nevertheless, the risk for CVD remains twofold increased in those with T2D independent from conventional risk factors including age, sex, smoking, systolic blood pressure and Body Mass Index (BMI) [1]. There is evidence of an independent effect of increased blood glucose levels—the clinical manifestation of T2D—on CVD, [4] which is supported by pathophysiological data [5]. Poorly managed diabetes can in addition lead to blood vessel-related complications such as poor vision, kidney malfunction, neuropathy, (skin) infections and amputations [6]. An increased CVD risk in ethnic minority groups in Europe has been ascribed partly to a higher T2D risk in these population groups [7]. This chapter discusses the epidemiology of T2D in ethnic minority groups in Europe as well as underlying mechanisms and risk factors predisposing ethnic minority groups to T2D.

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12.2 The Global Burden of Type 2 Diabetes

Millions of people worldwide are affected by T2D and the numbers are increasing rapidly [8]. While in 1980 about 153 million people had T2D, 425 million people across the globe were diabetic in 2017, which corresponds to a global T2D prevalence of 8.8% [8–10]. Despite being perceived as a disease of the affluent, T2D no longer affects only high-income countries. As shown in Fig. 12.1, using data from the International Diabetes Federation (IDF) Diabetes Atlases 2000 through 2017, the T2D prevalence has since 2011 been higher than Europe in all world regions except Sub-Saharan Africa. Eighty percent of T2D cases live in low- and middle-income countries (LMIC) [11]. The IDF projects the largest increase in T2D prevalence to occur in countries that are moving from low-income to middle-income. In a comparison of the 80 most populous countries, the UAE was projected to have the highest increase in T2D from 2013 to 2015, namely, 245.3%, followed by Uganda with 166.9% [12]. On a regional level, the highest projected increase is for the Sub-Saharan African region with an estimated increase of 158% between 2017 and 2045. The lowest projected increase is for the European region with 16% [10]. This highlights that LMIC are rapidly catching up with high-income countries in terms of T2D burden. The rapidly rising levels of obesity are believed to underlie the high and increasing global burden of T2D [13, 14]. In 1975, about one in four countries worldwide had an overweight prevalence of over 40%; in 2014, this had expanded to more than half of the world's countries.

12.3 The Burden of Type 2 Diabetes in Ethnic Minority Groups

12.3.1 T2D Burden in Ethnic Minority Groups Compared to European Host Populations

Ethnic minority groups in Europe experience a higher burden of T2D compared to European host populations. A systematic review and meta-analysis compared the prevalence and odds of T2D among ethnic minority groups in Europe with their host

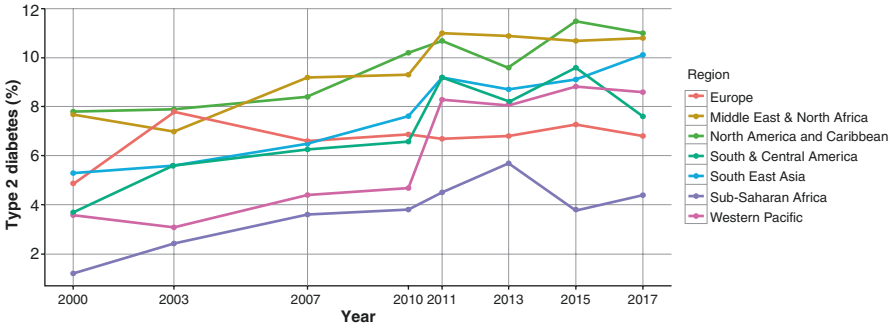

Fig. 12.1 Comparative type 2 diabetes prevalence by region as reported in IDF Diabetes Atlases 2000 through 2017

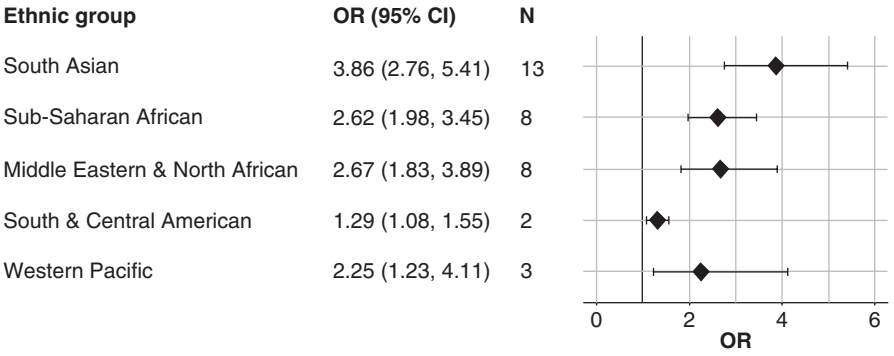

Fig. 12.2 Odds ratios for T2D for ethnic groups in Europe compared to the host European populations (adapted from Meeks et al. 2015 [15]). *N* number of studies included, *OR* pooled odds ratio, *CI* confidence interval

populations [15]. The ethnic minority groups were defined primarily by geographical origin as per categorization of IDF geographical regions [9] and included South Asian origin, Middle Eastern and North African origin, Sub-Saharan African origin, Western Pacific origin and South and Central American origin. All ethnic minority groups had higher prevalence and higher odds ratios of T2D than their host European populations (Fig. 12.2).

South Asian origin populations had the highest odds ratio of 3.9 compared to the other ethnic groups, followed by Middle Eastern and North African origin (OR = 2.7), Sub-Saharan African origin (OR = 2.6), Western Pacific (OR = 2.3) and South and Central American (OR = 1.3). The OR for T2D compared to Europeans was higher for women than for men in all ethnic groups except for South and Central American. The results of these meta-analyses showed that although ethnic minority groups in Europe experienced a higher burden of T2D compared to the European host population, South Asian, Middle Eastern and North African and Sub-Saharan African are more affected than Western Pacific and South and Central American.

In addition to a higher prevalence of T2D among ethnic minority groups, the age of onset is generally lower in these populations compared to Europeans [16, 17]. While in the age category of 31–40 years, T2D was still virtually absent among Dutch men and women, the T2D prevalence was up to 7% in South-Asian Surinamese men and 11% among African Surinamese men resident in the Netherlands [16]. The prevalence of T2D among Dutch does not rise up to 8% until the 51–60 age category and 12% in the 61–70 age category. Snijder et al. [16] note that in general, ethnic minority groups were about two decades younger to have a similar T2D prevalence as the host Dutch populations in a certain age category.

12.3.2 T2D Burden in Ethnic Minority Groups Compared to Nonmigrant Peers in Country of Origin

Another method of mapping the burden of T2D among ethnic minority groups in Europe is comparing these ethnic minorities with their peers still living in the

country of origin. Such a study design is less common, yet those that report geographical comparisons of a single ethnic group report stark differences between European residents and those living in the countries of origin in particular rural areas in countries of origin. In 1999, Mbanya et al. reported a T2D prevalence of 0.8% in rural Cameroon, 2.0% in urban Cameroon, 8.5% in Jamaica and 14.6% among African residents in Manchester. In 1995, Patel et al. reported higher fasting glucose among Indians in West London compared to their siblings in India [18]. A decade later, in 2006, the same authors reported a similar T2D prevalence between Indians in Britain and Indians in India [19]. Another decade later, in 2015, a higher T2D prevalence is reported in India than among Indian residents in the USA [20]. These data show that the initially increased burden of T2D among Indian ethnic minority groups compared to their compatriots in India is fading and even reversing rapidly. A similar trend seems to be occurring in the African region. The steep increase from rural to urban Africa to Europe as observed by Mbanya et al. had faded in the data from the RODAM study published in 2016. African migrants in Europe were found to have a T2D prevalence three times higher than in rural Africa, but similar T2D prevalence was observed between Africans in Europe and urban Africa [21].

12.4 Underlying Factors of High T2D Burden Among Ethnic Minority Groups

The causes for the disproportionate burden of T2D among ethnic minority groups are unclear but are thought to be a complex interplay between environmental factors and genetic factors (Fig. 12.3). The large disparities in prevalence between compatriots in the country of origin and ethnic minority groups in Europe exemplify the large role of environment and indicate that genetics alone cannot explain the high prevalence in ethnic minority groups compared to Europeans. The ethnic differences in T2D indicate that the differences in built environment alone cannot explain the high prevalence among ethnic minority groups either. Possibly specific behaviour (dietary habits, physical inactivity) by ethnic minority groups interacting with a particular built environment contributes to the high burden of T2D either directly or in interaction with genetic characteristics.

12.4.1 Pathophysiological Mechanisms

The pathophysiological mechanism that underlies T2D has been relatively well described for European populations. T2D is characterised by elevated blood glucose levels that cause micro- and macrovascular damage [22]. The elevated blood glucose levels have been attributed to an imbalance between insulin sensitivity and insulin production by the beta cells of the pancreas [23]. In a normal glycaemic state, there is a feedback loop between insulin-sensitive tissue and the beta cells of the pancreas. When insulin resistance increases, the beta cell initially compensates

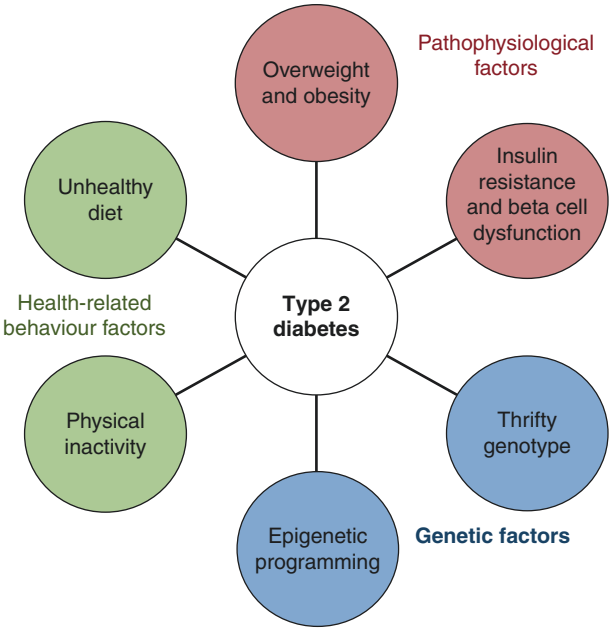

Fig. 12.3 Potential underlying factors for the increased T2D risk among ethnic minority groups

by increased insulin production. At the time when the beta cell is no longer able to compensate for increased insulin resistance, blood glucose levels increase, and T2D develops [23].

Most studies on the pathophysiology of T2D have been performed in Europeans. Studies among populations that constitute the largest ethnic minority groups in Europe have shown increased insulin resistance among South Asian origin and African origin populations even in a normal glycaemic state [24–28]. Nondiabetic South Asian men in the UK were found to have 1.4 times higher insulin levels in a fasting state than European men [17] and twice higher insulin levels 2 h after an oral glucose load [29, 30]. Despite these much higher insulin levels after glucose load, the blood glucose concentrations were higher in South Asian men compared to Europeans. Similarly, higher insulin resistance has been reported for African and Southern and Central American ethnic groups [31–33]. This suggests that ethnic minority groups are more insulin resistant compared with host Europeans and therefore at higher risk of developing T2D. The question then arises: What is driving insulin resistance in ethnic minority groups?

Among African origin, it was described that insulin resistance rather than beta-cell dysfunction contributed to geographical differences in impaired fasting glucose and thus seemed to be driving the increased T2D prevalence among African migrants compared to their compatriots in rural Africa [34]. In turn, the most strongly associated factors with insulin resistance in these analyses were BMI and waist circumference. This suggests that increases in body weight upon migration to Europe may play a role in increased insulin resistance and thereby higher T2D risk.

12.4.2 Obesity

A main driver of T2D risk among Europeans is overweight and obesity. Sixty-five to eighty percent of T2D new cases are thought to be accounted for by obesity [35, 36]. On the reverse, weight loss and increased physical activity have been shown to prevent or delay the onset of T2D among Europeans [37]. Similarly to T2D, obesity prevalence is higher in most ethnic minority groups compared to Europeans [38]. However, differences in overweight and obesity seem to only partially explain the higher risk of T2D among ethnic minority groups compared to Europeans. In the meta-analysis comparing T2D burden among ethnic minority groups with Europeans, we additionally studied the co-occurrence between T2D and obesity, defined as BMI > 30. Among Sub-Saharan African origin and Middle Eastern and North African origin populations, we observed co-occurrence; i.e. patterns in T2D in these populations corresponded to patterns in obesity. Among South Asian origin, South and Central American and Western Pacific origin, no clear pattern of co-occurrence was observed.

Studies in Europeans that have compared insulin-resistant and insulin-sensitive individuals with similar BMI found that the insulin-resistant individuals had a higher waist circumference, which was attributed to more abdominal fat [39]. Among African ethnic minority groups in the Netherlands, Ghanaian and African Surinamese, compared to Dutch, we found that body fat and body fat distribution only accounted partly for ethnic disparities in T2D [40]. In line with these findings, a much higher prevalence of T2D was observed among Ghanaian men (12.8%) and African Surinamese men (7.1%) with a low body fat percentage (≤25%) than among Dutch men (2.4%) with a low body fat percentage [40]. A similar pattern was observed among women. The T2D prevalence was even higher among those with a high body fat percentage (>25% for men and >35% in women). These findings suggest that although obesity is an independent risk factor for T2D also in ethnic minority groups, it cannot fully explain the disproportionate burden of T2D in these populations compared to Europeans.

Potentially, there is a differential effect of adiposity on insulin resistance and subsequent T2D in ethnic minority groups compared to Europeans. Studies comparing African descent with Europeans have shown that increases in abdominal fat negatively affect metabolism in African descent as it does in Europeans [41]. However, similar levels of general and abdominal adiposity for Sub-Saharan African origin, South Asian origin and Europeans were associated with higher levels of insulin resistance in Sub-Saharan Africans and South Asians compared to Europeans [41, 42]. Hence, the higher levels of insulin resistance among ethnic minority groups compared to Europeans cannot be attributed to higher adiposity levels. Potentially, small increases in BMI may have a more profound effect on insulin resistance in ethnic minority groups compared to Europeans putting ethnic minority groups at a higher T2D risk.

12.4.3 Health-Related Behaviour Factors

Multiple health-related behaviour factors, such as dietary intake, physical activity and stress, can increase T2D risk either mediated via obesity or directly. Differences in these health-related behaviours between ethnic minority groups and the European host population could contribute to ethnic disparities in T2D risk. It is suggested that the diet of migrants changes after migration towards a more Westernised diet. This change in diet is believed to increase T2D risk. Indeed, differences in dietary intake between South Asian and Sub-Saharan African origin ethnic groups in Europe and their compatriots in South Asia and Sub-Saharan Africa have been reported [43, 44]. Among Sub-Saharan Africans, adherence to a dietary pattern characterised by intake of roots, tubers and plantain was associated with rural African residence, while the dietary pattern associated with residence in Europe was characterised by intake of food items such as whole grain cereals, dairy products, potatoes, sodas and condiments [34]. Among South Asian migrants, higher energy intake and in particular energy intake from fats were reported compared to nonmigrants [19]. Higher intake of energy and fat compared to nonmigrants has been associated with changes in the insulin-like growth factor system [43], suggesting that dietary changes play a role in increased T2D risk upon migration. In a comparison of dietary patterns between ethnic minority groups in Amsterdam and their Dutch host population, similar dietary patterns were identified across ethnic groups [45]. However, the association between those dietary patterns and T2D differed between ethnic groups [45]. Possibly, the effect of dietary intake on T2D risk differs by ethnic group.

In addition to diet, another important health-related behaviour is physical activity. Physical activity of any kind has been shown to lower the risk of T2D [46]. Physical activity may contribute to weight loss efforts and has in addition the potential to improve insulin sensitivity directly. Physical activity improves skeletal muscle capillarisation, which can contribute to higher insulin sensitivity by increasing the available surface area for diffusion of insulin and glucose [47]. South Asian origin ethnic groups have been reported to be less physically active compared to other ethnic minority groups and the European host population [48, 49]. Reduced physical activity was associated with more insulin resistance in South Asian ethnic minority groups [50]. Differences in insulin resistance between South Asian origin and Europeans were found to be reduced—yet not abolished—when controlling for physical activity [50]. The role of physical activity in ethnic disparities in T2D between Middle Eastern and North African ethnic groups is less clear. Physical activity did not explain ethnic differences in T2D between Turkish and Moroccan ethnic minority groups in Amsterdam and the host Dutch [51]. Physical activity seems to contribute to ethnic disparities in T2D in some ethnic groups, but it cannot completely explain the high burden of T2D in ethnic minority groups.

12.4.4 Genetic Factors

To date, over 150 genetic loci have been associated with T2D [52]. However, the majority of these is in non-coding regions of genes and therefore difficult to pinpoint their role in the disease. Furthermore, the majority of genome-wide association studies (GWAS), the study design used for the discovery of novel genes associated with disease, have been performed in European populations [53]. Non-European populations make up only 19% of all participants in GWAS [53]. The majority of non-European individuals included in GWAS is of Asian origin (14%), while inclusion of African individuals is rare (2%) and Middle Eastern and North African origin individuals is nearly non-existent (0.08%). The thrifty genotype hypothesis is regularly mentioned as a genetic explanation for the higher risk of T2D among some populations [54]. This hypothesis suggests that a cluster of genetic mutations that were advantageous in an environment of scarcity are more common in some populations and thereby increase T2D risk in environments of affluence such as modern Europe. Only few studies have aimed to pinpoint what genetic mutations contribute to ethnic disparities in T2D risk. A GWAS that included South Asian migrants in the UK identified novel loci associated with T2D that had not been reported in other populations before (*GRB14, ST6GAL1, VPS26A, AP3S2, HMG20A* and *HNF4A*) [55]. These loci could play a role in ethnic differences in T2D risk, but that remains to be elucidated. One study that has compared the effect of a specific loci between South Asian origin and Europeans found that a polymorphism in the proliferator-activated receptor (*PPAR*)-y was protective against T2D among Europeans carrying the Pro12Ala variant but not among South Asians [56]. GWAS on T2D among Sub-Saharan African origin and Middle Eastern and North African origin are currently lacking. Increased diversity in genomics research is needed to elucidate the role of genetic factors in ethnic disparities in T2D.

Another hypothesis that is often referred to in the context of ethnic disparities in T2D is the "thrifty phenotype" or "developmental origins" hypothesis coined by Barker in 1986 [57]. This hypothesis postulates that poor living conditions in particular poor nutrition, during foetal and infant development lead to changes in genetic programming and thereby glucose metabolism that increases the risk for T2D [58]. These changes would have been advantageous in programming a child in that it would be well adapted to its future environment. Children exposed to undernutrition in the womb are according to this hypothesis programmed for an environment of scarcity. When they are, however, exposed to an environment of abundance in later life, they are mismatched to their environment and the programming that intended to be beneficial has become disadvantageous [59]. This is exemplified in that low birth weight has been associated with T2D in later life across ethnic groups [60]. The effects of in utero under nutrition on later-life T2D and other metabolic disease risks are clearly illustrated in the Dutch Hunger Winter studies [61]. These studies have shown that children born to mothers that had extremely low calorie intakes while pregnant during the Dutch hunger winter (1944) had higher risks for T2D in later life in the current Dutch obesogenic environment [62]. Similarly,

unfavourable living conditions in the countries of origin during childhood of first-generation migrants in Europe can increase the risk for obesity and T2D in later life when these individuals are exposed to an environment of abundance in Europe. The programming in response to environmental influence in utero is thought to occur via epigenetics. This thrifty phenotype hypothesis postulates that epigenetic processes occur mostly or at least more profoundly in early life and that once these changes are made, they are irreversible and even transferred over generations [63]. In this manner, these changes could affect multiple generations of migrants and contribute to increased T2D risk among ethnic minority groups in Europe. The first study to date investigating the role of epigenetics in the disproportionate burden of T2D among migrants is the RODAM study [64]. The RODAM study measured epigenetics processes in a subset of about 720 Ghanaian migrants and nonmigrants [65]. Epigenetics was found associated with obesity and T2D in this study population [65]. Potentially, migration from Ghana to Europe has caused epigenetic changes contributing to the high risk of T2D in this ethnic minority group. There is, however, still a long road ahead investigating epigenetic processes in relation to T2D among ethnic minority groups.

12.5 Prevention and Intervention

T2D is a preventive, and in some cases reversible, condition [66]. Prevention, timely detection and treatment are crucial in improving quality of life, reducing mortality and reducing health-care costs [9].

The clear disparities in T2D between ethnic minority groups and their compatriots in their countries of origin suggest that a population-based approach aiming at improving the environment to facilitate healthy behaviour may be needed. Population-based approaches usually involve actions such as policies and programmes that intervene in institutional processes to affect health-related behaviours in the society at large. They may include policies of governments and non-government organisations [67]. Promoting healthy eating and physical activity aiming at weight loss on a population-wide scale is therefore desirable. The goal of population-based obesity prevention is to lower and stabilise the mean BMI of the population in order to minimise the proportion of those who become overweight and obese [68]. The impact of population-based approaches on population health is usually very gradual, such as small changes in average population BMI. Multiple population-based approaches aimed at improving diet and physical activity, including, among others, media campaigns, taxation of unhealthy products and access to healthy food products in supermarkets, have been reviewed by the American Heart Association [69]. However, none of these targeted migrant communities and ethnic minority groups specifically. Studies that evaluated the implementation of lifestyle interventions in ethnic minority groups have found no or limited effect on T2D outcomes in these groups [70, 71]. More work needs to be done to evaluate the effectiveness of proven population-based interventions in ethnic minority groups. Cultural sensitivity of population-based approaches is an important element for success [72]. Successful implementation

needs to take social norms, language, gender roles, family ties and customs into account [72]. Further studies are needed to design, monitor and evaluate population-based approaches effective for ethnic minority groups in Europe.

As impact of health-related behaviour intervention is likely on the long term; on the short term, improved detection and timely treatment are crucial for the prevention of progression to microvascular and macrovascular complications contributing to CVD. Detection efforts should take the disproportionate burden of T2D among ethnic minority groups, at a relatively young age and low BMI, into account. Current guidelines for early detection differ between European countries and are limited in the ethnic groups probed to screen. The Dutch guidelines for general practitioners, for example, urge to test patients for T2D who are ≥45 years and have a BMI of ≥27 kg/m^2 and who are ≥45 years and of Turkish, Moroccan or Surinamese origin [73]. For Surinamese, these guidelines specify Hindustani (South Asian) origin, which is the largest South Asian population in the Netherlands, as high-risk T2D population. For Hindustanis, the guidelines advise to screen those aged 35 years and older. Other South Asian populations and Sub-Saharan African populations are, however, not specified and thus not considered a target group for early detection. Furthermore, evidence presented in this chapter showed a high risk for T2D even at low BMI levels and young age groups for not only South Asian ethnic groups. In the UK, guidelines for general practitioners and practice nurses recommend T2D risk identification for South Asians of 25 years and older [74]. Given the younger age of T2D onset in many ethnic minority groups [16], case finding for T2D would be desirable for younger ages than the European host population for all ethnic minority groups. Efforts to increase awareness of high T2D risk among health-care workers in Amsterdam seem to have paid off. Levels of awareness of T2D status and medical treatment were higher among ethnic minority groups compared to the host Dutch populations [16]. Despite these higher awareness and treatment levels, however, glycaemic control was lower than among Dutch, which is consistent with studies in other ethnic minority groups in Europe [16, 75]. Improving glycaemic control would be an important target to reduce vascular complications among migrant communities and ethnic minority groups in Europe.

Conclusion

This chapter highlights the high burden of T2D among ethnic minority groups in Europe. Most ethnic minority groups originating from all world regions are more affected by T2D compared to Europeans. The disproportionate burden of T2D among ethnic minority groups compared to their compatriots who have not migrated is rapidly fading. Although this highlights an important role of urbanisation along with a genetic predisposition, the exact underlying causes are still largely unclear. Health-related behaviour factors, such as diet and physical activity, likely interact with genetic factors contributing to underlying pathophysiological mechanisms such as unfavourable adiposity and high levels of insulin resistance. There is a need for more research regarding the specific health-related behaviour, genetic and epigenetic factors, causing the high burden of T2D among ethnic minority groups.

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13 Health Needs and Global Cardiovascular Risk of Chinese First-Generation Migrants in Europe: Which Peculiarities?

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13.1 Chinese in Europe

According to a traditional paradigm, the burden of noncommunicable diseases (NCDs) and their associated risk factors among immigrants is characterized by a transition from a low occurrence in the first period after arrival to a progressive convergence toward the epidemiological profile of the host country, changes being associated with the adoption of a Westernized, energy-rich diet and a more sedentary lifestyle [1]. However, socioeconomic changes experienced by most LMIC in the last decades (i.e., the epidemiological transition associated with urbanization and Westernization of lifestyles) [2] probably introduced a new element of complexity. It is now evident that in most LMIC, NCD-related mortality considerably exceeds mortality due to communicable diseases and maternal, neonatal, and injury-related deaths combined [1–4]. As an example, in the last two decades, stroke rates declined in high-income and increased in LMIC [3, 4]. In 2010, the highest rates of stroke were registered in Asia [5, 6]. In China, where stroke is currently the first

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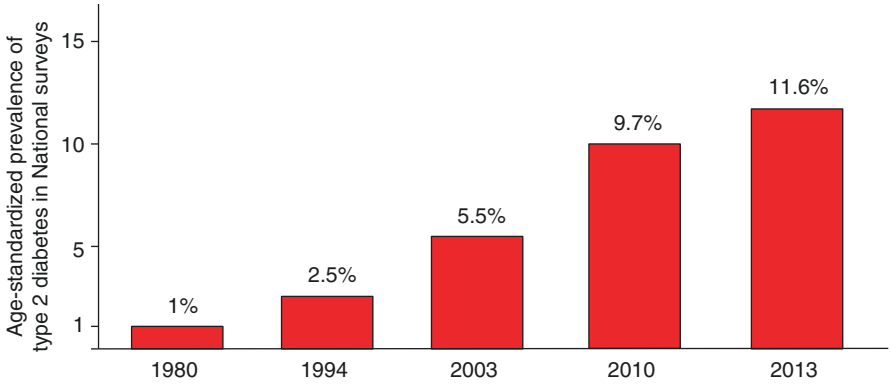

Fig. 13.1 Epidemics of diabetes in China: age-standardized diabetes prevalence in China in 1980 [7], 1994 [8], 2003 [9], 2010 [10], and 2013 [11]

cause of death, the prevalence of diabetes in the general population has risen from 1% in 1980 [7] to 11% in 2013 [8–11] (Fig. 13.1).

China now bears a significant proportion of hypertension-related global mortality and morbidity. According to the Global Burden of Disease Study 2013 (GBD 2013) [12–14], 20% of total Chinese DALYs are related to cardiovascular diseases [13]. Of the 230 million Chinese diagnosed with such diseases, 200 million have high BP, and 7 million suffer from stroke. Some data also seem to suggest that the Chinese population has a greater genetic predisposition toward a more precocious development of metabolic diseases linked to obesity.

Notwithstanding these accumulating evidences, Chinese immigrants living in Europe are still traditionally reported to have a low cardiovascular risk. This position moves from early surveys performed in Northern Europe. In 1997, Chinese living in the UK were found to have a favorable pattern of type 2 diabetes and other risk factors compared to the population of UK origin [15, 16]. More recent surveys [17, 18] reported a low rate of diabetes among Chinese (3.8% in men, 3.3% in women). However in these studies, only rates of physician-diagnosed type 2 diabetes were reported because blood sampling was not performed and total rates of T2DM were thus not available. Furthermore, Chinese people investigated in the above studies were mainly born in the UK, no information being available for first-generation migrants [19]. This point is probably crucial because socioeconomic difficulties and barriers in the access to healthcare systems are mainly experienced by first-generation migrants [20]. Finally no data were available for Southern Europe where migration flows from China is now mainly directed. Nowadays, the Chinese community in Italy and Spain, mostly represented by first-generation migrants, is numerically consistent. Data for cardiovascular risk in Chinese living in Southern Europe are needed [21]. Should the prevalence of type 2 diabetes among Chinese living in Europe be as high as in China, new prevention and intervention strategies could be a need for European health systems. The potential consequences of ineffective prevention and management of diabetes and other cardiovascular risk factors in Chinese

communities living in Europe on the future burden of cardiovascular diseases might be remarkable. When considering this scenario, the recent CHInese in Prato (CHIP) study [22] bears great interest. The project led to the development of a new approach to investigate and treat cardiovascular risk in an ethnic community.

13.2 A New Approach to the Chinese Community: The CHInese in Prato (CHIP) Project

Many minority patients have difficulty communicating with their healthcare providers, and cultural barriers may exist [23]. The approach to high-risk patients belonging to minority groups is limited by costs of the screening procedure, low compliance at follow-up, and the problematic contact with undocumented migrants. Undocumented migrants are usually not included in population statistics (hidden population of undocumented migrants), in trials, and in cost-effectiveness analysis. The conventional sampling procedure adopted in epidemiological studies indeed leads to exclude undocumented migrants from surveys because the ability to go back to a list of individuals in some form is lacking. Finally, this population is also excluded from healthcare provision for chronic disease in most EU countries, and this is an obstacle to prevention strategies [24, 25].

On the other hand, although the individual approach to high-risk subjects is know to be effective, limitations may exist when this approach is pursued in elusive, collectivist minority groups. A new perspective for an approach specifically involving the whole communities is probably now needed for high-risk minority groups living in Europe [26]. Health promotion, usually based on assumptions of an individual self-investment, should thus leave the approach to individuals to orient themselves towards the whole community. This position is particularly important when the aim is to involve societies with a collectivist history [27]. In 2014, the CHIP (CHinese in Prato) project was launched. The creation of a participatory research where Chinese population directly participates in the formation of a group of citizens involved in designing and conducting the survey allows overcoming difficulties due to the lack of official demographic files. Secondly, and most important, this approach makes it possible to effectively pass a prevention message to an elusive population. Its implementation required the development of a new organizational and management system according to gradual and integrated involvement of the various components participating in the project itself. The community-based participatory research was an instrument to provide equitable, accessible, and culturally competent healthcare and gave the opportunity to all undocumented migrants found to be affected by chronic diseases to have access to the public healthcare system for required needs. A screening service hosted and managed within the Chinese community was thus created through an agreement between the University of Florence and the Consulate General of the People's Republic of China [22]. The first CHIP survey, performed on first-generation Chinese migrants aged 16–59 years and settled in Central Italy, showed a prevalence of cardiovascular risk factors comparable to what was recently reported in China [11, 28–33].

Participants were born in the province of Zhejiang (80%), Fujian (12%), or Liaoning (5.2%) and had left China at an average age of 30.9 ± 9.7 years. Only 18.0% had lived in Chinese urban areas, the large majority (82.0%) coming from rural China. The participants were mainly occupied in light manual works in the textile industry, a minority being manager or self-employed professionals, students, or housekeepers. Overall, 548 out of 846 women (64.8%) self-reported at least one previous abort for unwanted pregnancy, and only 10 out of 635 women in premenopausal age (1.6%) used contraceptives. Current smokers and alcohol drinkers were mainly men. Overall, 57.1% of the participants had no health insurance, and only 29% were able to speak Italian.

13.3 Main Cardiovascular Risk Factors

13.3.1 High Blood Pressure

Overall, 21.7% of participants in the CHIP survey fulfilled criteria for hypertension. As expected, age-specific prevalence of hypertension increased with age from 3.4% in subjects aged 20–25 years to 47.4% among subjects aged 55–59 years (Fig. 13.2).

Age-standardized (WHO 2001 population) prevalence of hypertension was 19.2%, being 21.7% in men and 17.3% in women [34].

The proportion of hypertensive subjects aware of their condition was 54.3% (52.7% in men and 55.9% in women). Among aware hypertensives, 70.4% were treated with antihypertensive drugs (65.2% of men and 75.0% of women). Overall, 39% of hypertensive subjects treated with drugs had their BP values controlled (43% and 36% among men and women, respectively). When considering the age group 35–59 years, Chinese had higher hypertension prevalence than Italians (27.2% vs 21.3%, $p < 0.01$), with comparable levels of awareness (57.4% and 48.4%), although lower treatment rates (70.6% and 90.0%, respectively) [35]. In both ethnic groups, age

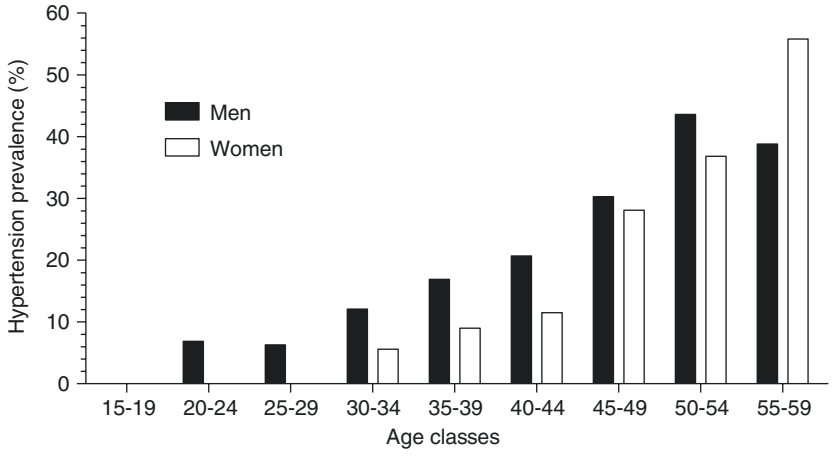

Fig. 13.2 Age-specific prevalence of hypertension in the CHIP study population by gender

and parental history of hypertension were predictors of awareness and treatment, body mass index being predictor of hypertension diagnosis. Health insurance coverage plays an important role in reducing health disparities, though it does not ensure access to equivalent healthcare resources. However, in the CHIP survey, hypertension awareness and allocation to drug treatment among participants aware of hypertension were not associated with healthcare insurance [34, 35]. Equal provision of care, with the removal of the administrative burden currently limiting the access to health services to undocumented migrants in the majority of European countries, might thus be insufficient to reduce hypertension burden in the absence of specific information programs. Prevention programs addressed to resident population might be inefficient for ethnic minorities. Importantly, only the capability to speak Italian was associated with years spent in Italy, whereas hypertension was not associated with years in Italy. It seems thus conceivable that first-generation Chinese immigrants do not easily assimilate Western (Italian) lifestyle. Subjects might rather keep much of their native country's traditions, including behavioral and nutritional habits.

13.3.2 24-Hour Urinary Sodium Excretion

The control of salt intake is a significant point for hypertension prevention and treatment, and salt intake was recently reported to be high in China. Using the 24-h urinary sodium excretion method, the INTERMAP study that China participated in the 1990s showed the average salt intake from three sites was 10.1 g/day varying from 12.0 g/day in Northern China (Beijing and Shanxi) to 6.3 g/day in Southern China (Guangxi) [36]. In the China Health and Nutrition Survey cohort including 16,869 adults aged 20–60 years from 1991 to 2009, the nationwide salt intake was 10.7 g/day based on the dietary record from three consecutive days. A North-South gradient in 24-h urinary sodium was observed in the country (Fig. 13.3) [36–42].

Chinese living in Prato mainly originate from the Zhejiang and Fujian provinces where the average salt intake in 2015 was found to be 8.9 g/day and 7.6 g/day, respectively [43]. We observed comparable values of 24-h salt excretion in the CHIP cohort (7.7 g/day), where 84% of Chinese had daily salt excretion higher than the limit value strongly recommended by WHO (5 g/day) [44]. Quartiles of daily sodium excretion were related to hypertension diagnosis and blood pressure values (Fig. 13.4).

Importantly, salt excretion in the CHIP cohort was not modified by the time spent in the host country. This pattern, clearly showing that first-generation migrants maintain their dietary habits in the host country, introduces a possible difficulty for public health interventions directed at reducing sodium intake in the Chinese migrant population. Furthermore in the CHIP cohort, although hypertension awareness was a powerful drive to pharmacologic treatment, as already reported for Chinese living in Europe [34] and in China [45], it was not associated with sodium excretion or with the voluntary habit of using salt at the table showing that Chinese hypertensive patients were not familiar with the importance of reducing dietary sodium. Finally Chinese migrant workers consumed together foods prepared in the workplaces [34] so that their possibility to change their diet individually is limited. It is thus probably unrealistic that sodium intake of Chinese immigrants may be

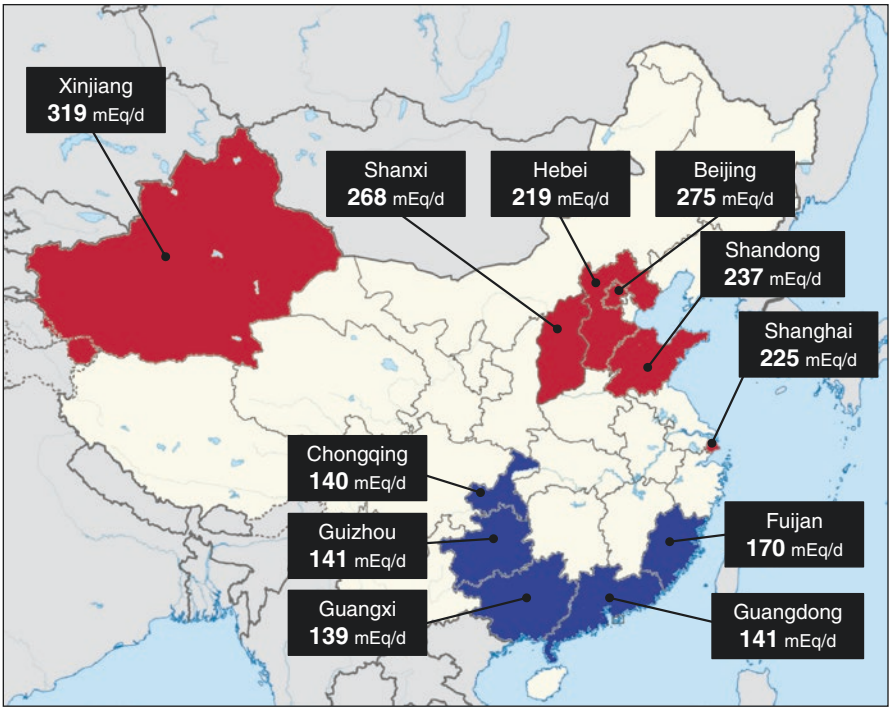

Fig. 13.3 North-South gradient of 24-h urinary sodium excretion in China [36–42]

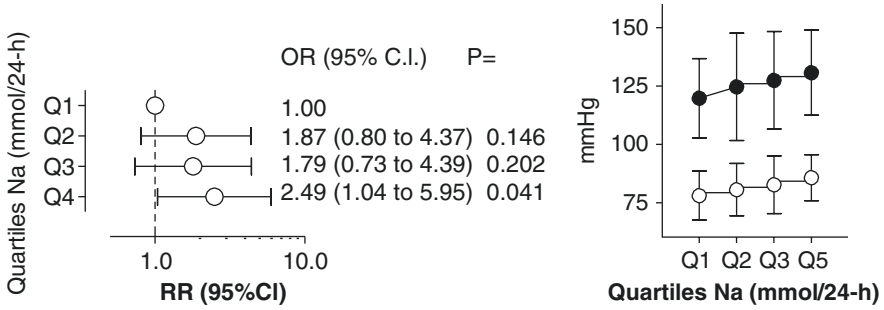

Fig. 13.4 ***Left graph***: odds ratio (95% C.l.) for hypertension by quartiles of absolute daily sodium excretion (Q1 < 97.5; Q2 97.5–124.9; Q3 125.0–156.4; Q4 > 156.5 Na mmol/day) in the CHIP Chinese cohort at binary logistic regression adjusted for age, gender, and education level (including 194 participants). ***Right graph***: relationships of quartiles of absolute daily sodium excretion (upper right panel) with systolic (black circles) and diastolic (empty circles) blood pressure of Chinese first-generation migrants who were not taking antihypertensive drugs (n = 182)

reduced in the short term with actions addressed at the patient level. Education on the risks of sodium should probably be focused to reach people responsible for preparing foods in the workplaces.

13.3.3 Atrial Fibrillation

Hypertension was an important predictor for atrial fibrillation. All participants aged 18–59 years underwent recording of 60 s of a single-channel ECG. Of the 1608 participants, 12 had AF (0.75%; 95% CI 0.33–1.17) – 4 men and 8 women. Prevalence of AF might be considered low. However, all subjects with AF were unaware of their arrhythmia and were not treated with anticoagulant. All subjects with AF had a CHA2DS2-VASc score ≥1. This element is especially relevant for prevention because, although no participant with AF had contraindications to oral anticoagulation, none was treated with oral anticoagulants. At multivariable-adjusted logistic regression, AF was associated with hypertension with an OR of 4.40 (95% CI 1.09–17.81; $p = 0.038$). The lack of awareness of individuals regarding their arrhythmia was independent from being registered to healthcare system (5 out of the 12 subjects with AF were registered to healthcare system).

13.3.4 Type 2 Diabetes

Of the 1608 Chinese participants in the CHIP survey, 177 had T2DM (11.0%) crude prevalence being higher in men (13.8%) than in women (8.8%) [46]. Crude prevalence for newly diagnosed T2DM was 7.4% (9.3% in men and 5.9% in women), with 3.6% for known T2DM (aware) (4.5% in men and 2.9% in women). Age-standardized (World Health Organization 2001 population) prevalence of T2DM was 9.6% (95% CI 9.1–10.2%), being 12.0% (95% CI 11.0–12.9%) in men and 7.8% (7.1–8.4%) in women.

Among the participants with known T2DM, 79.3% were treated with glucose-lowering drugs (81.2% among men and 76.9% among women). However, only 11 out of the 46 patients treated with drugs had their fasting glucose (FG) values lower than 130 mg/dL [36]. Among the participants aware of T2DM, those who had a health insurance more prevalently used glucose-lowering drugs. At adjusted logistic regression, diabetes was associated with hypertension, current smoking, adiposity indices (waist circumference, waist-to-hip ratio, waist-to-height ratio, and body mass index), and high triglycerides. T2DM, adiposity indices, and high triglycerides were not associated with duration of stay in Italy. The high prevalence of prediabetes in young people between 18 and 25, as well as high total cholesterol and triglycerides, could lead to a further increase in T2D in the near future [46] and makes specific prevention programs necessary.

A comparison with the Italian population was made in the age group between 35 and 59 years. Age-standardized (35–59 years) prevalence of T2D was markedly higher among the Chinese (12.9%) than the Italians (6.6%) (Fig. 13.5).

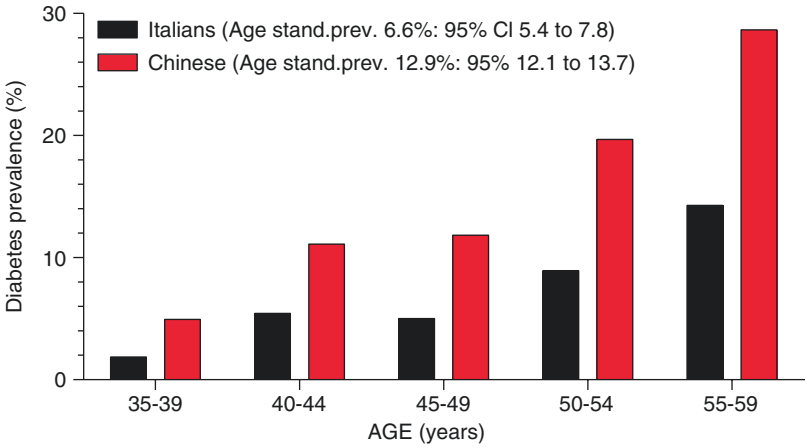

Fig. 13.5 Age-specific and age-standardized (to WHO population 2001) prevalence of type 2 diabetes in the CHIP study population aged 35–59 years

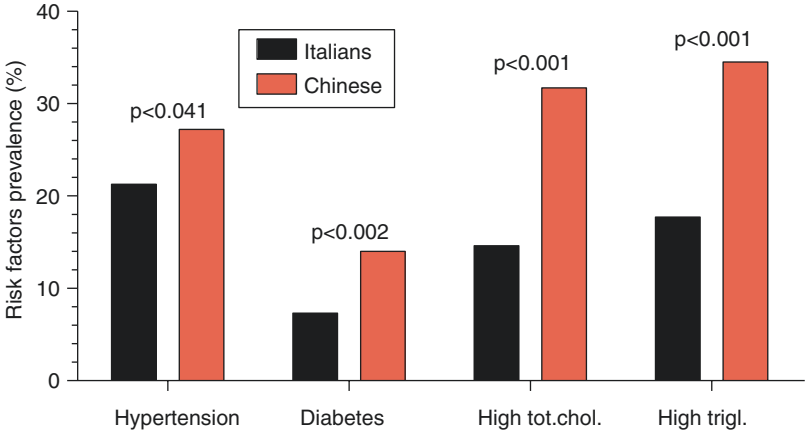

Fig. 13.6 Prevalence of hypertension, type 2 diabetes, hypercholesterolemia (total cholesterol ≥240 mg/dL), and hypertriglyceridemia (triglycerides ≥200 mg/dL) in Chinese and Italian subjects aged 35–59 years

Prevalence of hypertension, diabetes, hypercholesterolemia (total cholesterol ≥240 mg/dL), and hypertriglyceridemia (triglycerides ≥200 mg/dL) in Chinese and Italian subjects aged 35–59 years is shown in Fig. 13.6.

The awareness for T2DM was lower among Chinese than Italians (33.9% and 71.4%, respectively; age- and sex-adjusted OR 0.21; 95% Cl 0.08–0.59). Among participants with T2DM aware of their condition, 78.9% and 80.0% patients were treated with glucose-lowering drugs in the Chinese and Italian cohort, respectively (age- and sex-adjusted OR 1.45; 95% Cl 0.30–6.91). The OR of Chinese vs Italians

for T2DM increased when socioeconomic indicators were included in the model. A further increase was observed when controlling also for obesity indices (BMI and waist) and other risk factors. T2DM was independently associated with waist circumference in both ethnic groups.

13.4 Issues for Prevention

Type 2 diabetes mellitus (T2DM) in East Asians was reported to be characterized by β cell dysfunction with a reduced capacity of insulin secretion after ingestion of glucose or meal [47]. Likewise the appearance of diabetes seems to occur for a lower body mass index than in the American or European population [11, 28–33]. This pattern could render East Asians sensitive to the development of diabetes in conditions of overnutrition [48]. In addition, Chinese and South Asians display a greater amount of visceral adipose tissue for a given waist circumference than Europeans [49, 50] suggesting that they easily accumulate visceral fats. Thus, a subtle increase in insulin resistance due to visceral fat accumulation might easily trigger onset of T2DM [48]. These pathophysiological differences have an important impact on prevention and therapeutic approaches.

Overweight and obesity are main risk factors for the development of new T2DM [51], and the importance of body weight control is well recognized in prevention [52]. Modest weight loss (5–10% of body weight) and modest physical activity (30 min daily) indeed offer a variety of benefits in addition to the possibility to prevent or delay T2DM [51]. Rendering targeted advice to at-risk individuals is thus especially imperative for physicians. The main question is: Who is to be considered at high risk? Subjects originating from South Asia, China, and Africa develop T2DM at a higher rate, at an earlier age, and at lower ranges of BMI than their European counterparts [53]. A clustering of different genetic defects or polymorphisms, "thrifty gene" hypothesis [54], a genetic susceptibility to insulin resistance and higher central adiposity at similar BMI levels [55], or epigenetic changes occurring during gestation might play a role in influencing metabolic phenotypes of Asian populations [56]. For these reasons, the WHO consultation group recommends a lower cutoff of BMI for Asian with respect to native European populations [57]. The identified diagnostic cutoff for overweight is 23 kg/m^2 in India [58] and 24 kg/m^2 in China [59]. Proper consideration of the lower cutoff values of obesity indices in Chinese than in Europeans [52, 60] might increase diagnostic opportunities in the office of European physicians. Weight control and physical activity should also be specially suggested for East Asian migrants now living in Europe [61]. European physicians facing these new patients in their offices have opportunities for education, intervention, behavior, and lifestyle change [62]. The main scientific societies in Europe should give attention to prevention plans for ethnic minorities [51].

Many minority patients have difficulty communicating with their healthcare providers [23], and other cultural barriers may exist. A qualitative study performed in the UK [26] identified a main barrier for the Bangladeshi community in the complex

value hierarchy of what is accepted to be healthy (small portion size, limited rich and fatty food, regular activity) and what is important for the social norms of hospitality, the religious requirement for modesty, and the cultural rejection of a "sporting" identity or dress (especially for women, older people, and senior members of society). Contemporary health promotion, usually based on assumptions of a self-investment, should thus leave the individualistic approach when the aim is to involve societies with a collectivist history [27]. On these bases, a new strategic plan aimed at the prevention of new T2DM in the Chinese community settled in Prato is now active in Italy in the Regione Toscana. The project aim is to encourage weight control and physical activity with interventions on the Chinese community. Objectives for action include the reduction of 5% loss of body weight through the control diet (total intake of fat less than 30% of energy consumed, fiber intake per day of 15 g/1000 kcal) and the promotion of moderate exercise (30 min/day with resistance exercises such as walking, jogging, cycling) [61]. A paradigm change is now required by an ever-changing society.

Conclusions

The Chinese community in Italy and Spain, mostly represented by first-generation migrants, is numerically consistent. The prevalence of prediabetes and type 2 diabetes mellitus in this ethnic group was recently found as high as in China. The potential consequences of ineffective prevention and management of diabetes and other cardiovascular risk factors in Chinese communities living in Europe on the future burden of cardiovascular diseases might be remarkable. However, cultural factors may limit the possibility to reach minority groups with interventions addressed to the native population so that implementation of specific intervention strategies is specifically needed.

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14 Overweight and Obesity in Ethnic Minorities: Ethnic-Specific Cut-off Values of Obesity Indices

Aletta Elisabeth Schutte

14.1 Burden of Obesity

It is now well established that elevated levels of adipose tissue in children and adults pose a significant risk for non-communicable diseases, including cardiovascular and renal diseases, diabetes, some cancers and musculoskeletal disorders [1]. In a recent report by the Global Burden of Disease Study collaborators, it was found that nearly 70% of deaths related to obesity were due to cardiovascular disease [2]. Based on these and similar reports over the past decades [2–5], there is consensus among global public health initiatives to reduce the burden of obesity. In fact, due to the obesity-related adverse health outcomes, adiposity was included among the global non-communicable disease targets, with a target to stop the rise in the prevalence of obesity by 2025, to its level in 2010 [6].

The global burden of obesity has increased so dramatically over the past decades that the NCD Risk Factor Collaboration recently indicated the probability of meeting the global obesity target to be virtually zero [4]. If current trends continue, it is expected that by 2025, the global obesity prevalence will reach 18% in men and 21% in women [4].

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14.2 Contributors to Obesity

Exposure to unhealthy environments was recognised by the Lancet Commission on Hypertension as one of the main focus areas to reduce hypertension and non-communicable disease. This would require multisectoral collaboration to create health-promoting environments [5]. This action encapsulates concerted and unified strategies to make it easier to make healthy food choices (e.g. fruit and vegetables) and discourage unhealthy foods (e.g. introducing sin taxes). The main drivers of the increasing trends in obesity are recognised as changes in the food environment, with increased accessibility, availability and affordability of energy-dense foods [2]. Another challenge is that there are not everywhere sufficient safe environments to enable the promotion of physical activity in daily living [5]. The development of obesity is, however, much more complex than dietary intake and energy expenditure, with many social factors driving the epidemic.

An important aspect highlighted in several obesity reports is socioeconomic status [2, 5], as many countries with the highest increases in obesity prevalence were those from low- or middle-income countries, with large proportions of the populations also having a lower socioeconomic status. Within these countries, there are usually limited finances to initiate nutrition programmes [2] with countries generally suffering from overburdened health systems.

But not only within low- and middle-income countries are such trends observed, as reports from high-income countries such as the United States and European countries show disparities in obesity prevalence in ethnic minority groups residing in these countries [7–9]. It therefore seems that a complex interaction between ethnicity and socioeconomic status is apparent, as it has been shown that ethnic differences in socioeconomic status are an important contributor to ethnic disparities in health. This is potentially due to stigmatised ethnic minorities experiencing higher rates of illness, impairment and death [10].

14.3 Assessing Adiposity

Advanced techniques have been developed to assess an individual's level of adiposity, such as magnetic resonance imaging or computed tomography. However, to assess large volumes of patients, several cheap and easily obtained anthropometric measurements have been proven to correlate well with advanced techniques. These typically include body weight and height used to calculate body mass index (BMI in kg/m^2) and waist circumference as an estimate of abdominal or central obesity. The World Health Organization (WHO) [11] has established widely used cut-offs for BMI to distinguish between underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese class I (30–34.9 kg/m^2), obese class II (35–39.9 kg/m^2) and morbid obesity (≥40 kg/m^2). Global trends in obesity are also generally reported using BMI as a preferred index due to the ease in obtaining weight and height estimates [2–4]. Although this is done due to overall good correlations with more precise measures, BMI is

also met with criticism for not being able to distinguish between a lean muscular person and a person with high adiposity [12].

Another well-established measurement that can easily be obtained is waist circumference, where it is argued that obesity-related health risk is better captured by this measure of abdominal obesity [13]. The ATP III criteria in the United States [14] has defined waist circumference cut-offs for men (>102 cm) and women (>88 cm), which are different from the definitions set by the Consensus Metabolic Syndrome Criteria of the International Diabetes Federation (IDF), which are ≥94 cm for men and ≥80 cm for women [15].

Although the majority of epidemiological reports use BMI and waist circumference to report obesity estimates and related risk, other easily obtainable measurements have also been proposed and validated. Examples include waist-to-hip ratio [16] and waist-to-height ratio (WHtR) [17]. Although it is beyond the scope of this chapter to focus on the usefulness of these estimates, it should be highlighted that waist-to-height ratio was proven to be particularly effective when comparing different ethnic groups with different body composition and fat distribution. By incorporating height into the central obesity assessment, one is likely to reduce the variability observed between populations due to differences in height. Furthermore, based on a systematic review, WHtR may be a better discriminator than waist circumference or BMI for metabolic risk in adults of both genders and varying ethnic groups [18].

14.4 Using BMI and Waist Circumference Cut-Offs Across Populations

When trying to establish the prevalence of obesity or when taking individual obesity measurements in ethnic minority groups, it is important to take into account significant differences in body composition. With BMI derived from height and weight measurements, it is noteworthy that not only body fat distribution may differ between ethnic groups, but there are also variances in, e.g. muscle mass [19] and height [20]. A review on human height over the past century clearly indicated a gap of 20 cm within each sex between different regions of the world, with the tallest and shortest men being from the Netherlands and Timor-Leste (and Yemen), respectively. For women, the tallest and shortest were from Latvia and Guatemala, respectively [20]. It is due to these ethnic differences that reports from several countries have shown BMI cut-offs not being appropriate for certain regions, with different BMI cut-offs linked to adverse health outcomes. These include reports for advising ethnic-specific BMI cut-offs for, e.g. Maori, Pacific Islanders [21], Asian Indians [21, 22], Tongans [23], Japanese [24] and Africans [25]. Yet, despite these reports, it remains difficult for global prevalence reports to include varying BMI cut-offs, resulting in the traditional WHO cut-offs being used across the board [2, 4, 14, 26]. However, many ethnic-specific cut-offs are validated, and it is encouraged that these be used in the clinical setting to ensure that patients with increased adiposity be detected early on. This is particularly important since many of the changes in cut-offs have proposed a lowering of, e.g. overweight cut-offs from 25 to, e.g. 22 or 23 kg/m^2.

Similar to BMI, different population-specific waist circumference cut-offs have also been proposed. In the IDF's Metabolic Syndrome Criteria, the prerequisite for being diagnosed with the metabolic syndrome is exceeding a specific waist circumference cut-off [15]. As mentioned earlier, the proposed cut-offs indicated for Europeans are ≥94 cm for men and ≥80 cm for women. The IDF should also be applauded for including ethnic-specific waist circumference cut-offs for South Asians, Chinese and Japanese. It is suggested that for ethnic South and Central Americans, the South Asian cut-offs be used, but for sub-Saharan Africans and Eastern Mediterranean and Middle East (Arab) populations, the suggested European cut-offs be used until more specific data become available [15]. New reports are constantly generated with a recent collaboration paper from sub-Saharan Africa defining ethnic-specific cut-offs for Africans [27], suggesting a similar cut-off of 80 cm for both African men and women. Taking this cut-off as example, the difference in the cut-off for European men of 94 cm signifies the dramatic gap of 14 cm when compared to the 80 cm advised for African men, thereby demonstrating the importance in using ethnic-specific waist circumference cut-offs when classifying individual patients with obesity.

14.5 Summary

The obesity epidemic in the world is taking on significant proportions, with one in every five adults expected to be obese by the year 2025 [4]. The resultant effects on non-communicable diseases, especially cardiovascular disease, will have significant implications on economies and health systems of countries around the world. Obesity affects all populations, also minority populations residing outside of their home countries. To accommodate these patients, it is important to take into account different body composition estimates such as height and fat distribution. Hence, ethnic-specific cut-offs for widely used obesity estimates, such as BMI and waist circumference, should be used to identify patients at early phases of obesity development.

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Part IV

Ethnic Specific Issues for Prevention and Treatment of Hypertension and Global CV Risk

New Notions on Salt Sensitivity

15

Gert van Montfrans and Lizzy M. Brewster

15.1 The Classical View of Salt Sensitivity

The history of the study of *hypertension*, starting as a simple risk factor for cardiovascular disease and, if untreated, progressing to an assembly of lesions of the heart and vessels, runs parallel with the cumbersome struggle of governments to reduce daily *salt consumption* of the general public from a current average of 10 to a preferred 5 g. Few will contest the strong correlation between sodium intake and blood pressure since the Intersalt study found 2 g higher daily sodium intake associated with BP increases of systolic 6 and diastolic 3 mmHg, respectively [1]. Of note, the systolic BP rise normally seen with ageing was absent in various, indigenous populations consuming very low-sodium diets, such as the indigenous Yanomami people in Brazil. Many studies have shown a dose relation between sodium reduction and decreasing BP levels [2, 3]. While the feasibility of this ambitious goal may be questioned, the WHO aims to lower global sodium intake to less than 2 g daily by 2025.

However, the effect of sodium intake on BP varies considerably among individuals. Those who see their BP rise after an acute salt load and go down after salt depletion are called salt-sensitive (SS), and the others are salt-resistant (SR). Being salt-sensitive not only bears on individualising blood pressure-lowering treatment but also appears to be a cardiovascular risk factor irrespective of the level of blood

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pressure. In a study with 27-year follow-up, Weinberger et al. showed that SS individuals, even when normotensive, had similar mortality rates as hypertensive individuals. SR normotensive subjects showed the best survival [4].

Salt sensitivity affects about one quarter of the normotensive adult population and more than half of all hypertensive patients. Salt sensitivity is higher than average in the elderly, hypertensives of African ethnicity (Afro-American or Afro-Caribbean: sub-Saharan origin) and patients with diabetes and kidney disease or when nephron number is low, such as in small-for-date infants [5]. In humans, the trait is normally distributed; therefore, the distinction between SS and SR members of the population has to be made by choosing an arbitrary magnitude of the salt-induced change in BP to define the groups. Regardless of possible causation by abnormalities of sodium handling, the SS phenotype is not usually characterised by alterations in salt balance (e.g. impaired natriuresis or expanded plasma volume) but rather by a hypertensive response to maintain it [6].

Mechanisms driving the sodium-induced increase in BP have been proposed more than 50 years ago by the internist Borst and the physiologist Guyton, who both demonstrated that long-term control of blood pressure is closely related to body fluid homeostasis [7, 8]. In their now considered classical view, a high-salt diet causes sodium accumulation, volume expansion, increased preload and cardiac output and then autoregulation for flow maintenance. The autoregulation in all vascular beds increases systemic vascular resistance, causing the kidneys to excrete more salt and water, thus reducing systems to normal and minimising any changes in blood pressure [9]. In SS, however, a new steady state of sodium homeostasis after a salt load takes about 3–5 days, with the kidney matching sodium intake and excretion, at the expense of an increased extracellular volume and gradual increase of blood pressure, by increased cardiac output and systemic peripheral resistance. In this classical textbook view, the kidney is central, particularly concerning the regulation of renal pressure natriuresis, demonstrating in SS an intrinsic (still unknown) abnormality of the kidney to excrete appropriate levels of salt at the appropriate time. An abnormal increase of the amount of renal salt reabsorption/retention is usually an early, critical abnormality that enables increased salt intake to initiate hypertension. The prevailing viewpoint then has mostly been that the increase in BP produced by salt loading in SS is a compensatory response to maintain salt balance via pressure natriuresis, owing to an underlying defect in a single or multiple physiological natriuretic systems. This explanation would explain the nonparallel, rightward-tilted shift in pressure natriuresis curves observed in SS models of hypertension.

At this point in summarising the classical viewpoint on mechanisms in SS and SR, it is fitting to mention that renal pressure natriuresis in no way equals the blood pressure changes over time [10]. As Weinberger demonstrated in 1986, increased or reduced sodium excretion in terms of SS or SR seems to be a function of ‘when and how you look’: in 347 healthy black and white subjects, they found that after an acute salt load, 4-h natriuresis was no different. However, within 24 h, black subjects excreted less of the salt load than white subjects, although after volume contraction with furosemide, the black subjects excreted enough salt to make up the difference.

15.2 Abnormal Vascular Responses in Salt Sensitivity

As discussed by Titze and Luft [9], Kurtz and others have challenged the above discussed ideas. They advance as a dominant BP-increasing mechanism in SS individuals on salt loading, rather than abnormal salt retention, a diminished vasodilatatory response [11]. They point out that during experimental increases in salt intake, healthy SR subjects undergo substantial salt retention and do not excrete salt more rapidly, retain less sodium or undergo less volume expansion than SS subjects. According to Kurtz and coworkers, compared with SR subjects, in SS individuals, the failure of vascular resistance to normally decrease during salt loading is the first hemodynamic abnormality occurring. As Laffer and coworkers in a recent study point out, studies of SS versus SR subjects failed to show abnormally increased sodium retention or increased cardiac output in the SS subjects. Actually, the haemodynamic pattern of SS hypertension is one of relative vasoconstriction or impaired vasodilation in response to a normal salt-induced increase in cardiac output [12]. To pursue this issue further, they investigated SS and SR normotensive and hypertensive subjects during a 24-h salt loading followed by 24-h salt deprivation and volume contraction by furosemide. Cardiac output was assessed by echocardiography. After salt loading, mean arterial pressure was higher in SS than in SR, owing to higher peripheral resistance in SS, with similar cardiac output in the two groups. Following salt depletion, cardiac output was equally reduced in the two groups, and peripheral resistance increased in SR, whose mean arterial pressure remained unchanged. In contrast, in SS, total peripheral resistance did not change. Thus, their mean arterial pressure normalised because of the reduction in cardiac output, abolishing the difference in MAP between the two groups. Laffer and coworkers concluded that SS are unable to modulate total peripheral resistance in response to either salt loading or salt depletion [12]. These results support vascular dysfunction, as opposed to total body autoregulation, as the predominant underlying mechanism in SS.

15.3 A Third Salt-Storage Compartment Under the Skin

Recent ultra-long-term sodium balance studies have shown that sodium homeostasis is more complicated than the classical two-compartment model: current thinking dictates that body water is divided over the intracellular (2/3) and extracellular compartment (1/3). Within the extracellular compartment, sodium is the principal cation. The principal cation in the intracellular compartment is potassium. Because cell membranes are permeable for water, the osmolality is equal in both compartments. To control body water osmolality after a salt load, water will shift from the intra- to the extracellular compartment, resulting in a slight rise of body water osmolality and plasma sodium concentration [13]. This two-compartment model, supporting the notion that sodium intake and excretion are perfectly matched by the kidney during stable sodium intake, no longer holds. Recent long-term sodium balance studies in 10 healthy young men, accurately measuring sodium intake and excretion

during 200 consecutive days (Mars flight simulations) in an enclosed habitat, were revealing. It was demonstrated that daily sodium excretion fluctuated continually, up to 100 mmol (about 2 g), although dietary salt intake was constant at about 9 g/day [14]. Daily sodium excretion exhibited inverse aldosterone-dependent weekly rhythms.

As a result, net total body sodium (determined from differences in intake and excretion) varied up to 400 mmol, without any change in body weight, blood pressure or extracellular volume: contrary to current thinking that changes in total body sodium are always accompanied by changes in extracellular volume and weight.

The authors suggested the existence of a sodium reservoir, capable of storing large amounts of sodium non-osmotically (without water retention). Eventually, Na + MRI studies found such a reservoir to exist in the skin, directly under the keratinocyte layer and muscle [15]. Na + stores increase with age in both sexes, without concomitant changes in water content, changes in serum Na + or readily apparent volume expansion. Men store more sodium than women, and hypertensive patients have higher Na + stores than matched control subjects (Fig. 15.1). This 'third compartment' can be reduced by dialysis and diuretics. In an earlier study, the same authors showed that hyperaldosteronism leads to water-free Na + storage in the muscle, which can be reversed by removal of the culprit adenoma or spironolactone [16]. The sodium stores in the muscles and the skin were bound as osmotically inactive sodium to negatively charged polysaccharides, called glycosaminoglycans. As a result of this binding, sodium retention is not accompanied by water retention.

Titze and coworkers found that the skin storage was dynamic and regulated by macrophages acting as local osmosensors, leading to VEGF-C growth factor production stimulating lymph capillary density to facilitate clearance of salt from skin stores. For details, see Fig. 15.2, from [9]. For the record, Titze and Luft draw our attention to a publication 30 years ago in which Russian researchers arrived at similar findings, albeit in white rats.

These findings imply that although the kidneys regulate the sodium content of the body, they are not the sole organs participating in the process [9]. The fact that groups of subjects known with classical salt-sensitive hypertension may also be those with large amounts of stored sodium in the skin and muscles adds a new chapter to the mechanisms driving salt-sensitive hypertension. When in animal experiments the skin storage site was disrupted by whatever mechanism, a salt load invariably increased blood pressure. At this point in time, the teleological advantages of the described third sodium compartment are not easy to understand nor its clinical ramifications. Whether the architecture of pigmented skin of African ancestry patients might be related to salt transport to and from the skin as a possible mechanism for the excess SS hypertension found in black people seems an intriguing research possibility.

Yet, to stay on *terra cognita*, as if saluting the erstwhile pioneers of renal pressure natriuresis, Titze and Luft conclude their summary of 15-year ground-breaking research by presenting on the basis of their ultra-long-term balance studies, an old fashioned but modified steep pressure natriuresis curve with a period of 60 days [9].

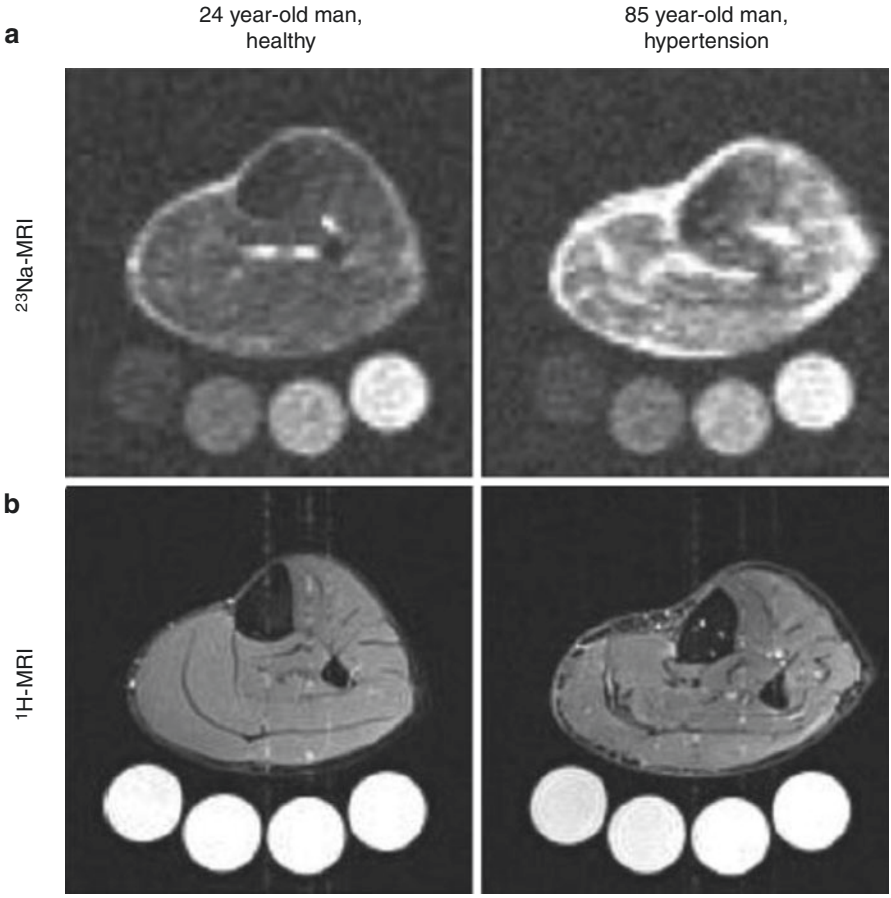


Fig. 15.1 From [16]. Two examples of 23 Na magnetic resonance imaging (^{23}Na-MRI) of tissue Na^+. (**a**) representative image of the lower leg of a young hypertensive man vs an older hypertensive man. Tubes with solutions containing 10, 20, 30 and 40 mmol/l of NaCl are arranged below the extremity for calibration. Tissue Na^+ content is increased in the old compared with the young subject. (**b**) tissue water **in** the same subjects detected with conventional ^{1}H-MRI. No difference in muscle water content is visible to the naked eye [16]. (By permission from Kopp C, Linz P, Dahlmann A et al. ^{23}Na magnetic resonance imaging of tissue sodium. Hypertension. 2012;59:167–72. Copyright *Hypertension*, AHA)

15.4 Sulodexide as a Novel Drug Target for (Salt-Sensitive?) Hypertension

Based on this briefly outlined framework, it seems but a small step to aim for a proper functioning endothelial surface layer (ESL), as a potential drug target for hypertension [17]. The ESL is a dynamic cell layer on the luminal side of the endothelial cell that is in continuous exchange with blood flow. It comprises a network

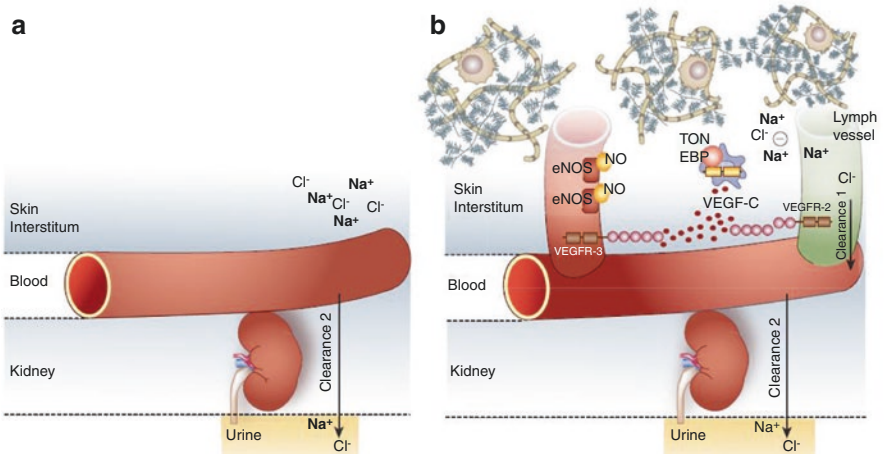


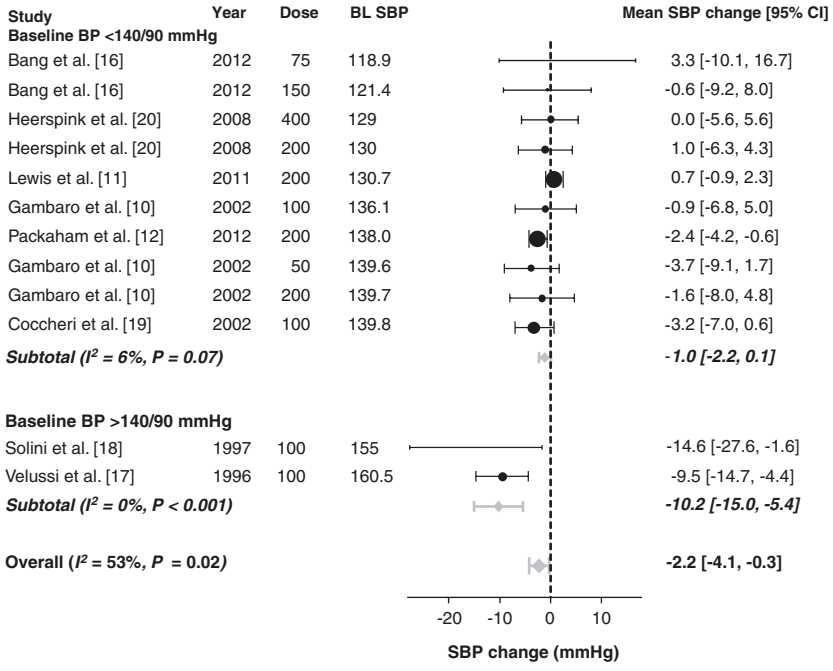
Fig. 15.2 From [9]. Panel (**a**), illustrates the traditional research approach for body electrolyte balance and blood pressure homeostasis, based on the concept of passive body fluid equilibrium in closed systems where known forces are balanced and electrolyte concentrations are not remarkably different between blood volume and interstitial volume. (**b**) Extended research approach for body electrolyte balance and blood pressure homeostasis, based on the finding that interstitial electrolyte concentrations are higher than in blood ('skin sodium storage'). Interstitial electrolyte balance is not achieved by renal blood purification alone but instead relies on additional extrarenal regulatory mechanisms within the skin interstitium. Macrophages act as local osmosensors that regulate local interstitial electrolyte composition via an endothelial growth factor C-dependent mechanism, enhancing electrolyte clearance via other growth factor's mediated modulation of the lymph capillary network in the skin. *Cl* chloride; *eNOS* endothelial nitric oxide synthase; *Na*$^+$ sodium; *NO* nitric oxide; *VEGF* vascular endothelial growth factor receptor (By permission from Titze J, Luft FC. Speculations on salt and the genesis of arterial hypertension. Kidney Int. 2017;91:1324–35. Copyright Kidney International, International Society of Nephrology)

of glycoproteins to which glycosaminoglycan (GAG) chains are attached. As mentioned earlier, GAGs are negatively charged polysaccharides that reversibly bind the abundant cation Na + at hand. The sodium binding capacity of the entire vascular ESL can be roughly estimated to store 30–900 mmol. Great variability in ESL volume has been reported in many different medical conditions. Most of these are characterised by an expanded extracellular volume, increased blood pressure or both, suggesting that variability in sodium homeostasis and salt sensitivity may be related to the quality of the ESL [18].

Sulodexide is a commercially available highly purified mixture of GAGs, consisting of 80% heparan sulphate and 20% dermatan sulphate. Sulodexide improves ESL function and lipid profiles and reduces platelet aggregation. Sulodexide has been used clinically for the prophylaxis and treatment of vascular diseases with increased risk of thrombosis, including intermittent claudication, peripheral arterial occlusive disease and post-myocardial infarction. The compound has also been investigated in the treatment of diabetic kidney disease and diabetic neuropathy.

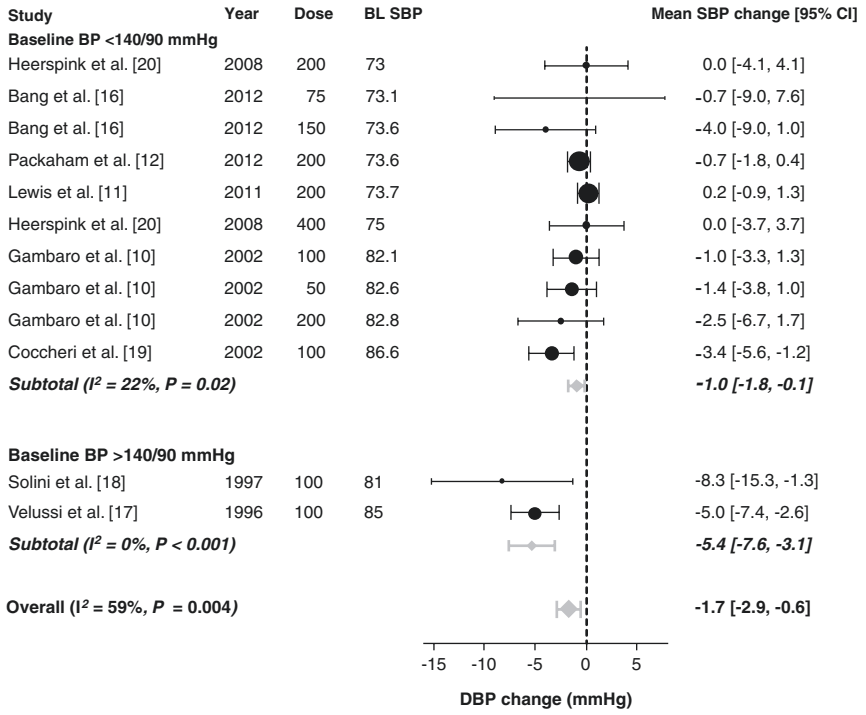
The available data were meta-analysed on BP-lowering effect, as some sort of off-label effect of sulodexide, focusing on the presumed beneficial increase of salt-storage capacity [17]. Randomised controlled trials were selected of at least 4-week duration. Of 93 full-text articles, 8 studies were included comprising 3019 participants. The main results are shown in Fig. 15.3 as forest plots of systolic and diastolic BP changes. Sulodexide treatment led to a significant BP reduction, of 2.2/1.7 mmHg. On pooling these findings for those with baseline BP <140/90 mmHg and two studies recruiting >140/90 mmHg, it was observed that in the latter two controlled studies, BP decrease was 10.2/5.4 mmHg. Sulodexide seems to be well tolerated. Most adverse effects reported were related to the GI system and seem to be transient in nature.

The authors understandably argue that these effects may clearly be related to improvement of the quality of the ESL, both in improving NO bioavailability, as increasing its non-osmotic sodium storage capacity. Considering its



Studies have been separated according to mean baseline BP as hypertensive (>140/90 mmHg) or non-hypertensive (<140/90 mmHg). Studies were weighted by the inverse of variance assuming random effects. The diameter of the point estimate (circle), representing mean BP changes, is proportional to the weight of the study. BL, baseline; DBP, diastolic, BP; SBP, systolic BP.

Fig. 15.3 Forest plot of systolic (upper panel) and diastolic (lower panel) BP changes after at least 4-week sulodexide treatment, compared to control (By permission of Olde Engberink RH, PhD Thesis, University of Amsterdam 2017, Clinical impact of non-osmotic sodium storage. Chapter 6, The blood pressure lowering potential of sulodexide—a systematic review and meta-analysis)



Studies have been separated according to mean baseline BP as hypertensive (>140/90 mmHg) or non-hypertensive (<140/90 mmHg). Studies were weighted by the inverse of variance assuming random effects. The diameter of the point estimate (circle), representing mean BP changes, is proportional to the weight of the study. BL, baseline; DBP, diastolic, BP; SBP, systolic BP.

Fig. 15.3 (continued)

anti-inflammatory and antithrombotic actions, it is conceivable that sulodexide may render additional cardioprotective benefits compared to the known classes of antihypertensive compounds. BP was not a major outcome in these studies, but notwithstanding a number of inherent methodological shortcomings, there is certainly scope for further work on this interesting new drug target in hypertension, probably in particular for more severe complicated forms of hypertension [17].

15.5 Creatine Kinase and Renal Sodium Excretion

Finally, it has been proposed that the reduced sodium excretion in salt-sensitive people following a high-salt diet might be related to high creatine kinase (CK) concentrations in some. CK is known to promote high blood pressure through greater vascular contractility and to regenerate ATP near tubular Na^+/K^+-ATPase for sodium

transport. These data provide first indications that differential CK activity might help explain the observed variation in sodium excretion in humans beyond ancestry or skin colour. This new development offers also interesting new possible drug targets to lower blood pressure.

There is a wide interindividual variation in the response to sodium intake, and some people display a slower urinary excretion of sodium after a standard sodium load than others, as we have seen earlier in this text. Brewster et al. proposed that these interindividual differences in renal sodium handling may be related to the variation in activity of the enzyme creatine kinase (CK) observed in humans [19].

CK catalyses the rapid transfer of a phosphoryl group from creatine phosphate to ADP, thereby forming creatine and ATP: creatine phosphate+MgADP↔creatine+MgATP.

CK connects sites of ATP production (glycolysis and mitochondrial oxidative phosphorylation) with subcellular sites of ATP utilisation, including myosin ATPase and myosin light chain kinase at the contractile proteins, and Ca2 + -ATPase and Na+/K + -ATPase at cellular membranes, where it rapidly regenerates ATP in situ from phosphocreatine. These ATPases preferably use ATP regenerated by CK. Thus, CK is thought to enhance ATP buffer capacity for cardiovascular contractility and renal sodium retention and increase hypertension risk [20].

Sixty healthy men (29 European and 31 African ancestry), almost all normotensive, with a mean age of 37 were assigned to low-sodium intake (<50 mmol/d) during 7 days, followed by 3 days of high sodium intake (>200 mmol/d). Sodium excretion (mmol/24 h) after high sodium was 260 (28.3) in the high CK tertile versus 415 (26.3) mmol/24 h in the low CK tertile (P <0.001), with a decrease in urinary sodium excretion of 98 mmol/24 h for each increase in log CK, adjusted for age and African ancestry.

Relatively high tissue and plasma CK activity is found in persons of African ancestry [20]. Also, persons of African ancestry are known to have an enhanced ability to retain sodium. This is accompanied by lower potassium excretion, whereas renin activity is, on average, lower in persons with African versus European ancestry. The enhanced capacity of the kidney to retain sodium is thought to play a major role in the greater prevalence of (sodium-sensitive) hypertension in this population subgroup.

These findings are certainly not meant for pleasing readers only interested in basic mechanisms: the first studies with specific CK blocking agents have been reported [21], and do not refute the hypothesis that CK plays a major role in blood pressure regulation, and may well be a future drug target to lower high blood pressure.

The clinical meaning of the new findings described in this brief overview will of course require long-term longitudinal prospective studies; to end aptly, we quote once more Titze and Luft: ‘how much there remains to be learned about salt’ [9].

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Body Image Perception in Ethnic Minorities: Implications for Prevention

16

Emanuela Gualdi-Russo

16.1 Introduction

Body image is a complex, subjective, and multidimensional psychological construct that includes self-perceptions and self-attitudes related to the body, as well as beliefs, feelings, and behaviors [1].

Procedures for the assessment of body image perception and satisfaction involve questionnaires and/or figure rating scales [2]. These procedures are generally completed by anthropometric evaluation, since relationships of body image perception with anthropometric data have been demonstrated [3–5]. Numerous anthropometric methods can be used to assess weight status and body fat distribution. In addition to the abdominal circumference and waist-to-hip ratio, the body mass index (BMI, calculated as weight, in kilograms, divided by the square of height, in meters) is currently the most used parameter for defining weight status in adults.

Based on the selection of actual and ideal figures, the assessment of body dissatisfaction is calculated by Feel minus Ideal Discrepancy (FID) index: negative scores indicate the desire to be fatter and positive scores the desire to be thinner (body image satisfaction has score 0) [6]. Inconsistency in the perceived weight status is assessed by the Feel weight status minus Actual weight status Inconsistency (FAI) index: negative scores indicate weight status underestimation and positive scores weight status overestimation (a realistic perception of weight status has a score of 0) [5].

The diffusion of weight disorders is often connected to body image misperception and distortion: thin subjects might overestimate their weight and, conversely,

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obese subjects might be unaware that their weight is too high. In such cases of misperception, as well as in cases of body image dissatisfaction, there is often an association with weight-related behaviors [7, 8].

Substantial sex differences have been found in body image perception. More women than men typically perceive themselves as fatter than they actually are [9]. Men are more likely to underestimate their weight. Consequently, men represent a high-risk group for the development of overweight. A clear discrepancy between body image perception and weight status was also found in overweight/obese children and adolescents demonstrating that some of them were completely unaware of their condition and indicating the need to carefully follow such cases during growth and development [3].

Furthermore, a lower perception of overweight/obesity especially in immigrants or generally in people with lower socioeconomic status (SES) was observed in Western countries [10–12]. In immigrants, a change in their beauty ideals and a distortion of their body image perception with consequent weight disorders can occur during the migration and acculturation processes in the new country. Overweight and obesity increase with length of time after migration because the acculturation in the host society favors the adoption of obesogenic behaviors [13, 14]. Parental migrant status contributes to greater prevalence of overweight and obesity in children. Unhealthy eating and physical activity (PA) habits are more frequent in immigrants [15–17]. Even in these cases, assessment of body image perception can be effective in revealing a health risk factor associated with misperception [18].

16.2 Ethnic Variability

There are anthropometric differences within and between ethnic groups [19]. In addition to genetic differences, environmental and cultural conditions and behavioral differences in diet and PA habits could contribute to disparities in the onset of obesity. The prevalence of overweight and obesity is higher in ethnic minority groups and, especially, in women of lower SES [20].

Although with some inconsistency of results, studies on body image and weight status generally report a preference of Caucasians for a thinner body ideal compared to African-Americans. Caucasians also show greater body dissatisfaction and body discrepancy than African- or Asian-Americans. In contrast, a similar ideal body size was reported among Caucasians, African-Americans, and Asian-Americans. After controlling for BMI, Caucasians and Asian-Americans showed greater body discrepancy than African-Americans [21], suggesting that Black males from the USA have a greater preference for a larger body size and a more positive image than White males from the same country based on 20 studies of 27 from literature [22]. No difference in body image perception was found between

Hispanic Americans and Whites. Native Americans show more body image concerns than Whites, and their dissatisfaction is associated with higher BMI values. According to three of four studies, Pacific Islanders tend to prefer a larger body size in comparison with Whites. Among populations from Middle Eastern countries, a preference for a large body size was observed in Bahraini male adolescents [23]. Discrepant findings emerge from literature reports on body image perception in Asians and Whites [22]. Although there is a common opinion that misperception and weight disorders typically affect subjects living in developed Western countries, the prevalence of body dissatisfaction and body image disorders are also increasing in developing non-Western countries, such as China [24]. Moreover, a study of Japanese adolescents revealed that the increasing body image disturbance is a public health concern [25].

A detailed picture of body image perception among Africans living in Africa or as immigrants in Europe is presented below.

16.3 Body Image in Africans

In a recent review [26], the body image perception and BMI of Africans living in their countries or as immigrants in Europe were analyzed. In southern Africa, a preference for a heavier body was expressed by women living in Zimbabwe and by Zulus in South Africa [27, 28]. Overweight was preferred by residents in rural areas in comparison with Cape Town residents [29, 30]. Residents in central African countries seemed to prefer a normal/slightly overweight body, showing a low level of dissatisfaction with their body [26]. North African residents in Tunisia, Moroccan women living in Casablanca, and Egyptian students were aware of their body size and wanted to be thinner [31–35]. Conversely, three studies on Moroccan residents reported a misperception of body weight and a preference for a heavier body [36–38]. North African female immigrants in Italy had a higher prevalence of overweight and a greater body image dissatisfaction than Italians or Africans living in Tunisia and Morocco [31].

In summary, the literature review shows different body preferences among African residents according to country and SES. An ancestral beauty ideal (shapely body) is still present in relation to a low SES or an isolation condition. Body image dissatisfaction is always higher in African immigrants than in residents.

In African women, the quantitative assessment of dissatisfaction shows an increase of FID values according to a geographical gradient from southern Africa to Europe (African immigrants) (Fig. 16.1).

These data show significant differences in body ideals of Africans and consequently in body dissatisfaction, which is particularly high in immigrants. This trend is consistent with the increase in their weight status from Southern to Northern Africa and to Europe (Fig. 16.1).

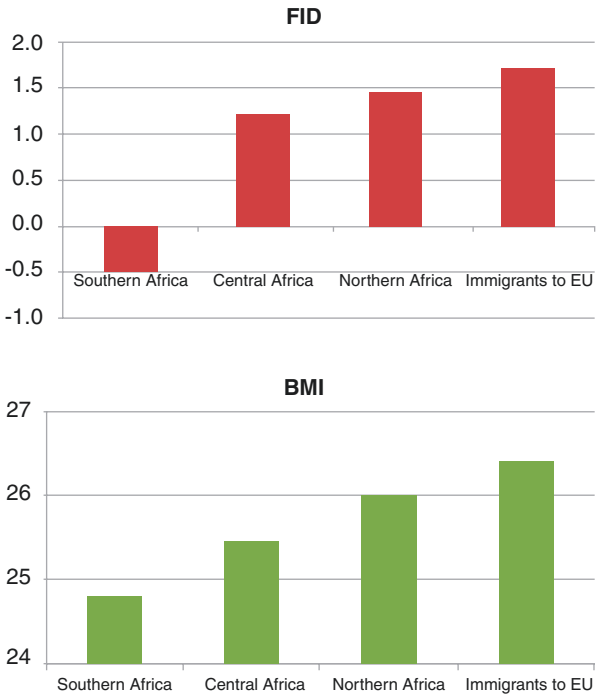

Fig. 16.1 Geographical pattern of body image dissatisfaction (FID) and BMI in African women from Southern Africa to EU (this original picture was obtained by combining data collected from a previous paper) [26]

16.4 Body Image Screening: A Tool for Control and Prevention of Weight Disorders

It is important to investigate the complex relationship between body image perception and weight status because of its influence on eating behaviors and health risk. In view of the significant correlations between body image and anthropometric traits, body image perception should be used as a proxy indicator of body weight or adiposity [39, 40]. Reducing body dissatisfaction and increasing body esteem are strategies to improve treatment effects: longitudinal follow-up may give important information on changes in the perception of body image following obesity treatment.

The importance of considering body image dissatisfaction and discrepancies should be emphasized on account of the associated health consequences. Particular attention should also be given to the sex and ethnic differences in cultural concepts of beauty, with the provision of sex- and ethnicity-tailored intervention programs. Monitoring the evolution over time of perceived and ideal body image represents a primary health goal to guarantee well-being and health in immigrants and minority groups.

In conclusion, the planning of health strategies for the management of noncommunicable diseases should also consider the body image perception. Greater efforts are needed to reduce health inequalities by promoting a healthy lifestyle and controlling associated risk factors in high-risk groups.

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Risk Assessment of Future Type 2 Diabetes and Implication for Prevention

17

Pietro Amedeo Modesti, Maria Calabrese, and Giorgio Galanti

17.1 Overweight and Obesity at the Global Level

Nutrition and lifestyle transition seem to play a role in disclosing the predisposition for the development of type 2 diabetes in different populations with special regard to Asian and African countries. Being overweight in childhood and adolescence is associated with greater risk and earlier onset of chronic disorders such as type 2 diabetes, and the incidence of new diabetes is growing at the global level [1, 2], and a special focus is now placed on low-income countries [3, 4]. The NCD Risk Factor Collaboration recently pooled 2416 population-based studies with measurements of height and weight on 128.9 million participants aged 5 years and older [5]. Data analysis revealed that mean BMI and prevalence of obesity increased worldwide in children and adolescents from 1975 to 2016, with the rate of change in mean BMI moderately correlated with that of adults until around 2000 but only weakly correlated afterward. Likewise the worldwide number of adult women with obesity increased from 69 (57–83) million in 1975 to 390 (363–418) million in 2016; the number of men with obesity increased from 31 (24–39) million in 1975 to 281

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(257–307) million in 2016. Most importantly, the regions with the largest absolute increase in the number of children and adolescents with obesity were East Asia, the Middle East and North Africa, and South Asia [5].

17.2 Overweight and Obesity Among Ethnic Minorities in Italy

According to the national survey "Status and social integration of foreign citizens in Italy," conducted by ISTAT between 2011 and 2012, 38.4% of the foreign population resident in Italy was overweight/obese (47.8% of males and 30.7% of females) [6]. Among men the highest percentage of overweight/obesity was observed among those coming from America (42.5% and 11.5% respectively), from Europe (42.4% and 8.6%), and from North Africa (41.0% and 7.6%). Among women, the highest rate of overweight/obesity was among those coming from North Africa (33.1% and 10.4%, respectively), from sub-Saharan Africa (30.0% and 10.4%), and from Central-Western Asia (29.9% and 5.4%).

Considering the ten most frequent foreign nationalities in Italy, among men, prevalence of overweight/obesity higher than the average value (47.8%) was observed among the Moldovans (53.8%), the Ukrainians (53.2%), the Romanians (52.1%), the Albanians (50.8%), and the Moroccans (49.1%). Among women, overweight/obesity prevalence higher than the average value (30.7%) was observed among Moroccans (42.3%), Moldovans (38.3%), Ukrainians (35.6%), (32.5%), Tunisian (31.7%), and Filipino (31.1%). Moreover, for some nationalities, the difference in absolute prevalence of overweight/obesity between males and females was over 20% (Romania and Albania), while for others (Morocco, Tunisia, and China), it was less than 10% [6].

Among men, the prevalence of overweight and obesity was always 50% higher in the 46–55 age group, with the exception of those coming from East Asia and Oceania. Among those who come from America, the prevalence of overweight or obesity was more than 50% for all age groups. Percentages above 60% are observed for Europeans over 35 years of age. With regard to women, a linear increase in the prevalence of overweight/obesity with increasing age was instead observed. Immigrants from North Africa had overweight or obesity prevalence values higher than average values for each age group, exceeding 60% over 45 years of age. The results of the multivariate models show that in the immigrant population, being a woman and living in a family with Italians were protective factor from the condition of overweight/obesity [6].

Similarly to other research, the results of this study also show that the probability of overweight/obesity was directly associated with the length of stay in Italy [7, 8]. The risk of overweight/obesity increases with age and is greater for those living in Italy for over 5 years [6].

A higher probability of being overweight or obese was then observed among those who had a low socioeconomic level, in terms of absence of employment and level of medium/low education. This modest evidence is in line with a Dutch study

[9] which found that overweight/obesity was associated with socioeconomic status only for some subgroups of the immigrant population, thus suggesting that prevention interventions should be targeted specifically for the individual communities, regardless of their social position.

Compared to Europeans, lower odds of overweight/obesity were observed among foreigners coming from sub-Saharan Africa and from Asia and higher odds among Americans. After adjusting for sociodemographic factors and lifestyles, the results showed a greater likelihood of overweight/obesity among American immigrants [6]. A study conducted in Peru showed a significant increase in obesity in the immigrant population from rural areas to urban areas, an effect perhaps similar to that observed in the Peruvian population that emigrates abroad [10]. The result is also consistent with a Swedish study reporting adjusted prevalence of BMI among Chileans higher than the native Swedes [11]. Moreover, a lower probability of weighting excess among the citizens coming from East Asia was observed, in line with what observed elsewhere [12, 13]. Chances of obesity in Italy were also slightly higher for former smokers than those who have never smoked and lower for those who smoke currently [6].

Overweight and obesity are the main risk factors for the development of new T2DM, and the importance of body weight control is well recognized in prevention [14–16]. Modest weight loss (5–10% of body weight) and modest physical activity (30 min daily) indeed offer a variety of benefits in addition to the possibility of preventing or delaying T2DM [15, 17]. Rendering targeted advice to at-risk individuals is thus especially imperative for physicians.

17.3 Who Is at High Risk of Type 2 Diabetes?

The main question is: Who is to be considered at high risk? Subjects originating from South Asia, China, and Africa develop T2DM at a higher rate, at an earlier age, and at lower ranges of BMI than their European counterparts [18]. A clustering of different genetic defects or polymorphisms, the "thrifty gene" hypothesis, a genetic susceptibility to insulin resistance and higher central adiposity at similar BMI levels, or epigenetic changes occurring during gestation might play a role in influencing metabolic phenotypes of Asian populations [16, 19, 20]. For these reasons, the WHO consultation group recommends a lower cutoff of BMI for Asians with respect to native European populations [21]. The identified diagnostic cutoff for being overweight is 23 kg/m^2 in India and 24 kg/m^2 in China [22, 23]. Consequently, the American Diabetes Association (ADA) recommended lowering the threshold for diabetes screening to a BMI of 23 kg/m^2 or more in Asian Americans [24], and the UK National Institute for Health and Care Excellence (NICE) has recommended thresholds to identify South Asians at an increased risk of diabetes (23 kg/m^2) and those at a high risk (27.5 kg/m^2) [25]. The main scientific societies in Europe still give little attention to the different cutoffs for overweight of ethnic minorities [15].

Proper consideration of this issue by European physicians when facing these new patients in their offices might increase opportunities for education, intervention, and behavior and lifestyle changes [26].

17.4 From Blood Glucose to Noninvasive Risk Scores

Although ethnic origin has a value "per se" in the estimation of the risk for T2DM, doctors often base their prediction on blood glucose measured at opportunistic screening [27, 28]. The risk of developing T2DM is over 5 times higher in subjects with impaired glucose tolerance (IGT) being 12 times higher in those with both IGT and impaired fasting glucose (IFG) compared to normoglycemic individuals [29]. However, blood glucose has limitations because:

(a) It is an invasive, costly, and time-consuming procedure.
(b) It has a large random variation.
(c) When taken in the aggregate, age, family history of T2DM, ethnicity, waist-to-hip ratio, BMI, blood pressure, and lipid levels, combined with plasma glucose levels, are more predictive of future T2DM than glucose levels by themselves.
(d) Most importantly, the opportunities for an immigrant to have a blood test may be low, because of cultural barriers (varying rates of literacy, limited motivation linked to the lack of education on healthy lifestyle) and socioeconomic status [30, 31].
(e) Finally, primary prevention should be addressed at high-risk subjects when they are still in a normoglycemic state, and interventions should prevent their transition from normoglycemia to IFG and IGT.

For these reasons, inexpensive, easily administered, cost-effective, and validated noninvasive risk scores (based on non-laboratory clinical variables) have been made available [32, 33].

These noninvasive scores identify a high risk of T2DM (C statistics 0.8) with acceptable to good discriminatory power across diverse settings in Europe [33–38]. Five noninvasive scores, the ARIC 2005, ARIC 2009, AUSDRISK, DPoRT, and QDScore, include the ethnic origin in the model [39–42]. To screen subjects at risk for T2DM, the American Diabetes Association (ADA) currently recommends a noninvasive tool that includes ethnicity (available at the URL http://www.ndep.nih.gov/am-i-at-risk/diabetes-risk-test.aspx). A study performed in the USA compared three risk scores in a multiethnic population living in the same country [43]. In Europe, noninvasive tools were validated in different settings, although none of the diverse setting included ethic minority groups [33].

17.5 Issue for Health Policies: Limitations for the High-Risk Approach in High-Risk Minority Groups

Current randomized clinical trials seem to indicate that T2DM can be prevented with lifestyle interventions in Asian individuals who are at high risk [17]. However, when the intervention is targeted at Asian communities living in Europe, some aspects have to be considered. The main limitations in the high-risk approach to

minority groups are represented by costs of the screening procedure, the problematic contact with undocumented migrants, and low compliance at follow-up.

17.5.1 Cost-Effectiveness

A comparison of potential screening strategies and subsequent interventions for the prevention and treatment of T2DM was performed by Gillies et al., who considered a hypothetical population of the UK, aged 45 years, at the time of screening [44]. In their estimation, lifestyle intervention strategy shows a small clinical potential benefit in terms of average years spent without T2DM and cases of T2DM prevented, because discounted QALYs gained compared with no screening were 0.09 (0.03–0.17) for screening and lifestyle interventions. The hypothetical population had 17% of either IGT or undiagnosed T2DM at the time of screening. However, as noted by Gillies et al., when an increased prevalence of IGT and T2DM is considered, the QALYs decrease, and most importantly the total costs of the screening strategy increase [44]. When the model was run for a South Asian cohort, with high prevalence of T2DM, the results for QALYs were reduced, and costs of screening increased. Notwithstanding these limitations, Gillies et al. consider lifestyle interventions to be cost-effective compared with no screening in an "at-risk" population [44]. A recent trial performed in the Netherlands studied the effectiveness of an intensive, culturally targeted lifestyle intervention in general practice for weight status and metabolic profile of South Asians at risk of T2DM [45]. Although T2DM incidence is not included among outcomes, the trial is of great interest because limitations connected with the high-risk approach in minority groups are clearly shown. Low initial response rate and laborious recruitment, high dropout rate, and the lack of effect of the lifestyle intervention on weight change and other metabolic parameters indeed led the authors to raise the question whether the high-risk strategy is the optimal approach to prevent T2DM in minority groups [45]. Admiraal et al. concluded that health gain might be better achieved by focusing on prevention strategies that tackle the high risk of T2DM among South Asians at an earlier stage [45].

17.5.2 Undocumented Migrants

The large number of subjects not included in population statistics (hidden population of undocumented migrants) is also often not considered in trials and cost-effectiveness analysis. Approximately, 1.7 million Chinese people are now estimated to live in Europe, mostly in the UK, France, Italy, Germany, and Spain, and migration from China to Europe has now been mainly concentrated in countries of Southern Europe, e.g., Italy and Spain [46]. In China, a prevalence of T2DM of 11.6%, with over 40% of young adults (aged 18–29 years) at risk was found in 2010 [47]. The high prevalence of prediabetes and T2DM in the Chinese living in Europe made the prevention of T2DM a need for our health system [48–50]. Many minority patients have difficulty communicating with their health-care providers, and other cultural barriers may exist [51].

17.5.3 Cultural Barriers

A qualitative study performed in the UK identifies a main barrier for the Bangladeshi community in the complex value hierarchy of what is accepted to be healthy (small portion size, limited rich and fatty food, regular activity) and what is important for the social norms of hospitality, the religious requirement for modesty, and the cultural rejection of a "sporting" identity or dress (especially for women, older people, and senior members of the society). Contemporary health promotion, usually based on assumptions of a self-investment, should thus leave the approach to individuals when the aim is to involve societies with a collectivist history [52]. This paradigm change is now required by an ever-changing society. On this basis, a new strategic plan aimed at the prevention of new T2DM in the Chinese community settled in Prato has been approved recently in Italy by the Regione Toscana. The project aim is to encourage weight control and physical activity with interventions on the Chinese community. The local Chinese schools are the setting to contact families for distribution of training materials on T2DM and the correct rules on nutrition and lifestyles, training courses on the importance of nutrition in the prevention of T2DM directed at teachers, and promotion of physical activity through the creation of sports group aggregation. Objectives for action include the reduction of 5% loss of body weight through the diet control and the promotion of physical exercise.

Conclusion

Two major strategies in CVD prevention, a population-based strategy and an individual-based strategy, have been recommended by the WHO and experts on the prevention of noncommunicable diseases. Both strategies have contributed substantially to the declining CVD mortality in Western countries. Evidence is now revealing that ethnic origin is an important element for the risk of future T2DM, and there are now the need and unprecedented opportunity to prevent future T2DM and CVD in these populations now present in Europe. This opportunity is to be communicated to the public and to policymakers. When the targets are societies with a collectivist history, the effectiveness of health promotion based on approach to single high-risk individuals may be limited, and effective partnerships and collaborations with the whole ethnic communities are to be supported to pursue a common goal. An approach specifically involving the whole communities is a new opportunity for Europe to limit the development of new T2DM.

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Screening Strategies for Type 2 Diabetes and Risk Stratification in Minorities

18

Andre Pascal Kengne

18.1 Introduction

Diabetes mellitus is an increasingly common condition worldwide, affecting 425 million adults in 2017 [1]. The global burden of diabetes is not uniformly distributed, with the largest and fast-growing population of people with diabetes currently residing in developing countries, where access to prevention, detection, management, and ongoing support through public health and clinical services for diabetes is generally below optimal. Within countries, disparities exist in the burden of diabetes, with, for instance, high prevalence, low detection, and poor outcomes of care for diabetes regularly reported in ethnic minorities, compared with nonminority ethnic groups [2–4]. Where access and financial barriers have been overcome and where recommended by guidelines, ethnic minorities at high risk of diabetes and regular contact with the health system do not receive increased screening for diabetes [5].

The current understanding of diabetes mellitus and type 2 diabetes (T2DM) in particular is that of a condition occurring as the result of the interplay between a genetic predisposition and environmental factors [6]. The precise interaction of these risk factors is a complex process that varies both within and across populations [7–9]. In this interplay, diabetes ultimately occurs when the inability of insulin to act on target organs (insulin resistance) is not matched by a sustained increase in pancreatic production of insulin (insufficient insulin production). The natural course of T2DM is very insidious, leading to many people with the diseases remaining

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undiagnosed for several years, in the absence of proactive screening. Regular expansion and refinement of the therapeutic armamentarium and strategies over time have substantially improved the quality of life and survival among people with diabetes, who are increasingly enjoying long and healthy life, although these benefits are not equally enjoyed by all people with diabetes across settings. In spite of these improvements, a significant proportion of people with diabetes are still cut down prematurely, succumbing essentially to cardiovascular disease (CVD). Compared with their nondiabetic counterparts, people with diabetes have a two- to fourfold higher risk of experiencing a cardiovascular event [10].

Early detection of diabetes followed by the implementation of control and ongoing monitoring strategies can potentially reduce related morbidity and mortality and improve quality of life [11]. Furthermore, progression to the full stage of overt diabetes among people with prediabetes, which include impaired fasting glycaemia (IFG) and/or impaired glucose tolerance (IGT), can be postponed by lifestyle changes and/or pharmacotherapy [6, 12–14]. Early identification of individuals with undiagnosed diabetes or future high risk of diabetes may be cost-effective, hence the need for developing strategies to identify individuals at high risk for diabetes and/or with undiagnosed diabetes. Prospective epidemiological studies have highlighted the limitation of the use of IGT as the sole mean for identifying individuals at high risk for T2DM, as only three to four out of ten of individuals with IGT ultimately develop diabetes [15–17]. Furthermore, 40% of those who develop T2DM have a normal glucose tolerance at baseline [15]. This variable of prognosis has prompted the search for alternative methods to accurately estimate diabetes risk. Risk prediction models including multiple risk factors have therefore emerged as practical tools to classify and predict diseases.

This chapter is on strategies for diabetes risk screening and stratification in minority groups. The principles of diabetes risk screening are similar across population and settings. The chapter therefore provides a broad perspective on diabetes risk screening and stratification and, where appropriate, discusses the specificities of minority groups. Risk screening for prevalent undiagnosed diabetes as well as for future diabetes occurrence is presented simultaneously due to the substantial overlap between strategies. While this presentation focuses on both biochemical tests and absolute risk models for diabetes risk screening, the two last sections of the chapter are also dedicated to risk screening for two major diabetes complications using absolute risk models.

18.2 Specificities of the Natural History of Diabetes Among Ethnic Groups

The natural history of T2DM includes an asymptomatic phase comprised of prediabetes lasting on average 8–10 years [18] and preclinical latent diabetes stage that could go on for about 9–12 years [19]. In various populations, prediabetes states are less likely to revert to normoglycemia and are associated with a high risk of progression to overt T2DM, with an annualized relative risk of 4.7–12% and absolute

annual risks of 5–10% [20]. This progression rate has been reported to be particularly high in populations like South Asians, with annual progression rates approaching 18.5% in some reports [21]. Studies mostly in Caucasians with newly diagnosed diabetes have revealed the presence of chronic diabetes complications in up to 50% of cases at the time of diagnosis [22]. This indicates that tissue damages occur during the preclinical stages of diabetes. Considering the susceptibility of some ethnic groups (e.g., South Asians) to diabetes-related complications and their high progression rate [21], the prevalence of complications among screen-detected patients from these groups is likely higher than that observed among Caucasians.

18.3 A Historical Perspective on Diabetes Risk Screening

Until the late 1970s and early 1980s, there was a lot of controversy surrounding early identification of people with diabetes, treatment of those with less severe form of the disease, and little or no difference between interventions for diabetes prevention and those for diabetes control. Furthermore, the definition, classification, and diagnostic criteria for diabetes varied substantially. In this context, recommendations for diabetes detection, prevention, and treatment were very loose, and accordingly little effort was invested in improving diabetes risk screening and stratification [23]. In 1979, the National Diabetes Data Group (NDDG) of the US National Institute of Health proposed the first uniform classification and diagnostic criteria for diabetes mellitus [24], largely adopted by the World Health Organization (WHO) a year later and subsequently revised a few times by both the American Diabetes Association (ADA) and WHO. One defining event appears to be the change of stance on community screening for diabetes by the ADA in 1989, in the wake of the accumulating evidence, by issuing a position statement recommending that "all people with one or more diabetes risk factors or having any diabetes symptoms should be identified and referred for medical evaluation" [25]. This was followed by a shift of focus toward developing appropriate strategies for diabetes risk screening.

18.4 Current Diabetes Diagnosis Tests

Diabetes risk screening has relevance only when diabetes status is unknown or not up to date. Thus, screening aims to establish the presence of diabetes or estimate the chances of future occurrence in those free of diabetes. As such, establishing the presence of or ruling out existing diabetes is an inherent component of diabetes risk screening strategies. For this purpose, the World Health Organization (WHO) currently recommends three options for diabetes diagnosis:

- Fasting plasma glucose (FPG) ≥ 7.0 mmol/l (≥126 mg/dl)
- 75 g oral glucose tolerance test (OGTT) with FPG ≥ 7.0 mmol/l (≥126 mg/dl) and/or 2-h plasma glucose ≥11.1 mmol/l (≥200 mg/dl)
- Glycated hemoglobin A_{1c} (HbA_{1c}) ≥ 6.5% (≥48 mmol/mol)

WHO further advises that in asymptomatic people with a single abnormal test, unless the results are unequivocally elevated, the abnormal test should be repeated to confirm the diagnosis [26, 27]. Apart from these formally established tests, diabetes mellitus can also be diagnosed based on random plasma glucose levels ≥11.1 mmol/l (≥200 mg/dl), in the presence of classical symptoms of diabetes [26]. Other possible diagnostic tests, but not currently validated for this purpose, include fructosamine levels, glycated albumin (GA), and 1,5-anhydroglucitol (1,5AG) [28]. HbA_{1c} results from nonenzymatic glycation of hemoglobin in red cells, while fructosamine and GA result from the modification of serum protein and albumin in particular by glucose and reflect exposure to endogenous glucose over the preceding 2–4 weeks. 1,5AG is a monosaccharide present in foods, which in normal physiology is filtered through the kidneys but also completely reabsorbed by renal tubules. However, the affinity of proximal renal tubules is higher for glucose than 1,5AG. It follows that in states of hyperglycemia, when the renal threshold is reached and glucose is filtered through the kidneys, it is preferentially reabsorbed at the detriment of 1,5AG which is excreted in the urines. As a consequence, the blood levels of 1,5AG drop. Therefore, 1,5AG levels decrease with increasing blood glucose levels. 1,5AG levels reflect the blood glucose levels over the preceding 10–14 days.

Alternative tests are developed among others to compensate for the limitations of established tests, some of which are ethnic specific. Ethnic disparities in HbA_{1c} levels regardless of diabetes status have been long recognized. A recent meta-analysis of 12 studies involving 49,238 individuals without prior diabetes found that compared with Caucasians, HbA1c was significantly higher by 0.26% in Blacks, 0.24% in Asians, and 0.08% in Latinos [29]. While these differences appear small, their impact can be substantial when diagnosing diabetes in other ethnic groups using cutoffs derived from Caucasians [30]. These ethnic disparities in HbA1c levels have fueled an ongoing debate on whether different HbA1c decision-making thresholds should be established for different ethnic groups [31–34].

18.5 Diabetes Screening Tests

Available test for diabetes screening includes biochemical tests and diabetes risk questionnaires and scores.

18.5.1 Biochemical Tests

Several biochemical tests are available for diabetes risk screening. Each test has its practical advantages and limitations.

Urine glucose: This test by the current standard is inappropriate for diabetes. It has a low sensitivity ranging from 16% to 64% and a low predictive value ranging from 11% to 37% [35]. With such a performance, a large proportion of people with undiagnosed diabetes will be misclassified and their diagnosis delayed when using urinary glucose for screening.

Random blood glucose (*RBG*): RBG is easy to obtain as it does not require fasting. Its use for diabetes screening is compromised by the low sensitivity. At a threshold of ≥6.9 mmol/l which has been considered to be cost-effective, RBG has a sensitivity of 41% and a specificity of 93% in detecting OGTT-diagnosed diabetes. For prediabetes, the specificity remains high at 94%, while the sensitivity drops to 23% [36]. The RBG ≥ 7.2 mmol/l threshold has been recommended, which has a sensitivity of 63% and specificity of 87%, based on validation against OGTT [37].

Fasting plasma glucose (*FPG*): FPG is highly correlated with the risk of diabetes complications and has modest sensitivity when used for hyperglycemia screening [38]. Compared to OGTT, a FPG threshold of ≥7 mmol/l may detect only 55.7% of people with diabetes, but with 100% specificity [39]. At the recommended optimal cutoff for FPG of >6.1 mmol/l, the sensitivity increases to 85.2%, but specificity also decreases to 88.5%. For the identification of IGT, FPG is less sensitive than OGTT [40]. At a threshold of >5.6 mmol/l, FPG may detect only about 28.9% of IGT cases, while OGTT would detect 87% or more.

Glycated hemoglobin: The American Diabetes Association (ADA) has adopted HbA_{1c} as a diagnostic test for diabetes at a threshold of ≥6.5% [41]. The ADA criteria using HbA_{1c} do not specifically define IFG and IGT categories, but rather a "high-risk" category corresponding to an HbA_{1c} between 5.7 and 6.4%. The WHO has also recommended the 6.5% threshold of HbA_{1c} for diabetes diagnosis, as an alternative to plasma glucose measurements when stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement. A value less than 6.5% does not exclude diabetes diagnosed using glucose tests. However, the WHO does not make any formal recommendation on the interpretation of HbA_{1c} levels below 6.5% [42].

HbA_{1c} is an appealing screening tool, as it does not require to be measured in fasting samples, has values that are not affected by short-term lifestyle changes, may only require a point-of-care testing capillary sample, and has a lower intraindividual variability than fasting plasma glucose. However, the costs, unavailability of the test, and absence of national glycohemoglobin standardization programs in low-resource settings are severe limitations to the worldwide use of HbA_{1c} [37]. HbA_{1c} test results can be affected by a number of factors that may be more prevalent in some ethnic groups such as hemoglobinopathies, other conditions that shorten the lifespan of erythrocytes, iron deficiency, and chronic kidney disease [33, 43].

75 g oral glucose tolerance test (*OGTT*): Oral glucose tolerance test (OGTT) is currently considered the gold standard for diabetes and dysglycemia diagnosis. It is the only method to formally detect or diagnose IGT. OGTT identifies about 2% more individuals with diabetes than does FPG [44]. However, OGTT has poor reproducibility compared to other glucose-based tests or HbA_{1c} [45]. OGTT also has many practical limitations, including the required 8-h fast before testing, commitment of staff, and the length of the test itself. For all these reasons, OGTT has been less favored as a screening test.

Capillary blood (point-of-care) testing: The utility of capillary blood testing for screening remains unclear, largely because of concerns of imprecision in the few

existing studies and the lack of standardization. An Indian-based study comparing capillary fasting and 2-h post-load blood glucose measurements with fasting and 2-h post-load venous plasma glucose measurements in screening for diabetes and prediabetes showed a moderate-to-acceptable correlation between a fasting capillary and venous values. Based on the ADA fasting criteria, 31.9% versus 21.1% (capillary vs. venous) had diabetes, whereas based on the WHO criteria, 43.2% versus 38.6% had diabetes [46]. In terms of performance at detecting hyperglycemic states, the C-statistics for prediction of dysglycemia and diabetes were 0.76 and 0.71 for capillary FPG and 0.87 and 0.81 for venous FPG, respectively, in an Australian population [47]. However, a much larger study among South Asians found a much better performance of capillary FPG (C-statistic 0.87 [95% CI 0.81–0.93]) to be significantly better at predicting diabetes than risk scoring models based upon clinical variables alone (C-statistic for the best clinical model including age, BMI, hypertension, waist circumference, 0.69 [95% CI 0.62–0.77]) [48].

18.5.2 Risk Scores and Questionnaires

18.5.2.1 Evolution of Diabetes Risk Questionnaires and Scores

The field of diabetes risk screening questionnaires and prediction models has developed essentially in line with the recognized need for more proactive identification of people with undiagnosed diabetes and/or at high risk of it [25]. This development appears to have been very fast. Following its 1989 statement on diabetes screening [25], the ADA in 1993 issued the risk factor questionnaires for diabetes risk screening [49], thereby embracing the concept of multivariable approaches to diabetes risk screening. The first published multivariable diabetes risk models aimed to prove that conventional diabetes risk factors can predict future diabetes as well as, if not better than, impaired glucose tolerance [50]. These models were developed in randomly selected Mexican Americans and non-Hispanic Whites within the San Antonio Heart Study cohort, for the overall population and separate for each sex and ethnic group, all containing fasting plasma glucose (FPG) as a variable. Following this, and based largely on the ADA questionnaire, Herman and co-workers used the classification regression tree to develop a model to predict undiagnosed diabetes based on data from the second Nutrition and Health Examination Survey (NHANES) in 1994 [51]. This marked the beginning of the absolute risk model development explosion.

18.5.2.2 Absolute Risk Assessment: Overview

Global (or absolute) risk assessment is based on the combination of predictive information from several risk factors, using mathematical equations (models) [52, 53], to estimate the chance that a disease or condition of interest is present (diagnostic prediction model) or will develop in the future (prognostic prediction model). In those models (risk scores), the coefficient of each included risk factor indicates their relative contribution to the overall disease risk [52, 53]. Once developed, a risk model normally requires a validation both on the derivation sample (internal validation) and on independent populations (external validation). Validation consists of

testing whether the model correctly estimates the risk of the targeted disease in one or several populations [52, 53].

The performance of absolute risk models is commonly assessed in terms of discrimination, calibration, and more recently reclassification [52, 53]. Discrimination is the ability of the model to correctly classify individuals who have (or who go on to develop) the disease of interest and those who are (or remain) disease-free [52, 53]. For example, if there are two individuals without diabetes, with one developing the disease after certain time of follow-up and the other remaining diabetes-free, a model with a high discriminative ability will systematically assign a higher risk to the first subject compared to the second. Discrimination is commonly characterized by the area under the receiver operating characteristic curve (AUC) or the C-statistic. The C-statistic ranges from 0.5 (lack of discrimination) to 1.0 (perfect discrimination) [52–54]. In general, a C-statistic of 0.7 or greater is considered acceptable.

Calibration refers to the agreement between predicted risk and observed risk and is assessed by comparing risk estimates from the model with actual event rates in the test population [52–54]. For instance, a 5-year estimated risk of diabetes of 20% for a patient means that, in a given group of patients with similar characteristics, 20% will be diagnosed with diabetes within a 5-year period of follow-up. The most commonly reported measure of the calibration is the Hosmer-Lemeshow statistic. Estimates of calibration are sensitive to differing baseline levels of risk. For instance, if a given risk model is derived in a high-risk population but tested in a low-risk population, the predicted risk estimates might be unreliably high. Recalibration of the risk model by adjusting the baseline risk estimates to fit the target population may help correcting the over- or underestimation of risk [52, 54].

18.5.2.3 Overview of Diabetes Absolute Risk Models

Various risk screening tools based on the combination of several risk factors have been developed to identify people at high risk of having or developing prediabetes or T2DM [55–57]. There has been significantly more focus on incident diabetes risk models, and as expected, risk prediction research has been concentrated in Western countries, with a small spike in developing countries like India, China, and Taiwan [56, 58]. These models have been examined in recent comprehensive reviews on diabetes risk prediction modeling [55–59].

Hitherto, studies have been mostly undertaken in the USA and European countries on Caucasian individuals [55–59]; however multiethnic studies [51, 60, 61] and studies focusing on minorities in a country are available [62–64]. The age range of included participants has mainly encompassed middle-aged individuals (40–65 years); however some studies did include a younger population (adults over 20 years of age) [56–58]. Variables included in diabetes risk models have ranged from simple demographic information such as age or family history to more complex and invasive markers such as triglyceride levels and genetic polymorphisms. The most commonly included risk factors have been age, family history of diabetes, body mass index (BMI), hypertension, waist circumference (WC), and gender [55–59]. The defining criteria for diabetes used in risk model studies have included those of the World Health Organization [11] and those by the American Diabetes

Association [65]. The C-statistics in model development samples have ranged from as low as 0.64 in the Chinese Diabetes Risk Score [66] to as high as 0.917 for the women's Clinical and Biologic Risk Score in the Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort [67]. The performance of noninvasive models ranged from 0.7 to 0.8, while models containing biochemical measures ranged from 0.68 to 0.85, not displaying substantial gain from inclusion of more invasive variables [55]. Well-recognized and externally validated incident diabetes models are the ARIC Study Diabetes Risk Score, the Cambridge Diabetes Risk Score, and the Framingham Offspring Diabetes Risk Score and prevalent diabetes risk models Cambridge Diabetes Risk Score and Finnish Risk Score (FINDRISC) [68]. A comprehensive review explored the extent of use of diabetes risk assessment tools, showing that implementation mostly happened in Europe in a general practice or healthcare setting, with the American Diabetes Risk Score being the most frequently used tool [69]. This review illustrates the fact that relatively few prognostic models are currently used in clinical practice, as highlighted by the Prognosis Research Strategy group [70].

18.5.3 Which Diabetes Screening Strategy to Adopt in Ethnic Minorities

Different approaches have been used alone or in combination in screening programs [22]. Screening may be conducted at the community level (population-based) or in the context of medical care (opportunistic). None of these two approaches can meet the screening needs in all circumstances.

Population-based approaches attempt to screen the entire population at risk. This can be done by directly testing the entire population using a biochemical method as usually done in epidemiological studies of diabetes prevalence, although a country like Brazil has implemented nationwide screening in the segment of the population aged 40 years and above, using biochemical testing [71]. Another approach to population-based screening can also be undertaken in a stepwise manner combining several testing methods in various stages. A possibility is to use a risk score or a questionnaire to limit the population that would undergo biochemical testing, as done in the ADDITION study [72]. Another possibility in the stepwise approach is the use of less expensive biochemical tests, namely, capillary testing, as initial tests, and then followed by more accurate venous testing. Several biochemical tests could also be combined in parallel at the initial screening stage for the detection of hyperglycemia, to improve the yield. For example, the best approach to the use of HbA_{1c} for diabetes detection in non-Caucasians may be a combination with traditional glucose criteria. Indeed, screening studies have indicated that in combination with either RBG or FPG, HbA_{1c} may add value in identifying the subgroups of individuals that need to undergo an OGTT [22]. Depending on the method used for screening, population-based approaches can be costly and potentially inefficient.

Opportunistic screening involves screening individuals during routine encounters with the healthcare system for other purposes, such as primary care visits or

periodic health appraisals. Opportunistic screening may require fewer additional resources to reach high-risk groups, to conduct screening tests, and to perform follow-ups. However, it may have poor coverage and a tendency to be misdirected, with some people getting too many tests too often while others get too few tests too infrequently. There is little empirical information about the benefits of such screening within current healthcare systems. Based on various cost-effectiveness simulations conducted in Western countries, the best case has been made for opportunistic screening. This screening strategy has been recommended by Western professional organizations, generally at a 3-year frequency [22]. Implementing opportunistic screening supposes an almost universal access to healthcare providers for those to be screened, which is not the case in most developing countries with underdeveloped primary care systems. Consequently, community screening may represent a more viable option in developing countries, as it will allow an initial linkage of patients to the healthcare system. However, efforts are needed to ensure proper referrals for subjects who screen positive and appropriate repeat testing for subjects who screen negative. Otherwise, community screening may not have a positive long-term impact on health.

The segment of the population to be targeted by screening may differ across ethnic groups, considering the age distribution of diabetes. In non-Caucasians populations in developing countries, diabetes predominantly affects younger age groups than Caucasians in developed countries. The large majority of people with diabetes are within the age range 40–59 years, as compared to aged 60 years or older in developed countries [73]. Furthermore, increases in diabetes numbers are expected for all age groups in other ethnic groups, whereas in Caucasians, an increase is only expected among persons older than 60 years.

18.6 Absolute Risk Screening for Major Diabetes Complications

Cardiovascular disease (CVD) and chronic kidney disease (CKD) are two major diabetes complications for which screening using absolute risk models is increasingly advocated.

18.6.1 Cardiovascular Disease (CVD) Risk Screening in Diabetes

Until very recently, strategies for CVD prevention in people with diabetes were guided by the principle that future chances of experiencing a CVD in people with diabetes were similar in magnitude to those in nondiabetic individuals with existing CVD. Based on this principle, people with diabetes were eligible for risk-reducing therapy prescriptions such as statins without accounting for their absolute CVD risk levels. This principle, however, was inspired by evidence from earlier cohort studies [74–76], which may no longer reflect the modern era of diabetes care. Indeed, subsequent and more recent studies have shown variable results, with more indications that

the presence of diabetes mellitus may not be a CVD risk equivalent in all circumstances [77]. These new findings have refocused the interest on the need for multivariable approach as an appropriate basis for risk stratification for the purpose of CVD prevention in people with diabetes. This even has more relevance in the current era characterized by a gradual shift in the management of diabetes mellitus from a glucocentric focus to an intensive multifactorial strategy targeting reduction in the risk of both macrovascular and microvascular complications of diabetes [78, 79].

18.6.1.1 Contemporary Approaches to Absolute CVD Risk Screening in Diabetes

Three main approaches can be distinguished in contemporary strategies for cardiovascular disease risk evaluation in people with diabetes [80]. These include the CVD risk equivalent approach, the stepped approach, and the interaction approach.

In the CVD risk equivalent approach, all people with diabetes are classified as having a 20% or higher 10-year absolute CVD risk. This corresponds to the projected risk of recurrent CVD in people with prior CVD. Based on this assumption, people with diabetes are then eligible for CVD risk-reducing therapies without further objective assessment of their risk.

In the stepped approach, unifying multivariable absolute risk models are constructed for use to assess CVD risk in people with or without diabetes. This approach assumes that risk factors for CVD affect the risk in similar ways in people with and without diabetes. Therefore, everything else being equal, a person with diabetes will not always have higher CVD risk than a nondiabetic subject with the same level of other CVD risk factors like blood pressure, lipids, etc., with excess risk, if any, conferred by the diabetes status itself. This belief forms the basis of popular CVD models such as the Framingham cardiovascular risk models [80].

In the interaction approach, multivariable absolute risk models are constructed separately for people with and without diabetes. This approach assumes that risk factors for CVD affect the disease risk in different ways in people with and without diabetes. This approach in people with diabetes was initially used by the United Kingdom Prospective Diabetes (UKPDS) investigators [81, 82]. Their assumption was that a unit increased in the known duration of diabetes contributes more to risk estimates than a unit increment in age [81]. Therefore to allow a more accurate use of predictive information from age in people with diabetes, it has to be distinguished into two components: the age at diabetes diagnosis and known duration of diabetes. While the assumption has not necessarily been tested and confirmed in other studies, this consideration has other useful applications.

Available studies largely suggest that classical cardiovascular risk factors including smoking, blood pressure, and lipid variables and even some novel risk factors [80, 83–86] affect the risk of CVD in similar ways in people with and without diabetes, with no evidence of statistical interaction. Some risk factors or characteristics are likely to be more frequent in people with diabetes and may justify separate cardiovascular risk models for people with diabetes. These diabetes-specific characteristics include prescriptions of cardiovascular risk-reducing therapies, which may differ in people with and without diabetes. Additional specific factors including

hemoglobin A1c (HbA_{1c}), urinary albumin excretion, and markers of microvascular complications of diabetes in general (especially retinopathy) have been demonstrated to be associated with cardiovascular disease risk and can contribute useful information to predictions [87–92].

18.6.1.2 Performance of Existing Global Risk Tools for Cardiovascular Risk Estimation in People with Diabetes

At least two systematic reviews have examined the performance of CVD risk estimation models applicable to people with diabetes [93, 94]. The most recent and comprehensive review described 45 risk models applicable to people with diabetes [94]. Of these, 12 were specifically developed for patients with type 2 diabetes (including the ADVANCE model), and 33 were developed in the general population accounting for diabetes as a predictor. These models vary greatly in their quality and the methodology used to develop them. Numbers of the prediction models were developed before the advent of novel and more appropriate statistical methods for assessing model performance. Only about a third of the existing CVD risk tools applicable to people with diabetes have been externally validated in a population with diabetes.

The discriminative ability of both diabetes-specific CVD prediction models and general population prediction models that use diabetes status as a predictor was generally acceptable-to-good (i.e., C-statistic $\geq$0.70). However, the methods used to assess the performance in validation studies and the discriminative ability in these models varied widely (C-statistics, 0.61–0.86). The discrimination of prediction models designed for the general population was moderate (C-statistics, 0.59–0.80) and their calibration generally poor.

The most commonly validated models were the general population-based Framingham cardiovascular risk equations and the diabetes-specific UKPDS risk engines. The Framingham prediction models also showed a low-to-acceptable discrimination and a poor calibration. Although the discriminative power of UKPDS engines was acceptable it has a poor calibration and a tendency toward systematic overestimation of risk, particularly in recent cohorts. The models with best external validity were more contemporary, but these had been validated in other patient populations only once [94]. Therefore, more validation studies on the performance of these prediction models in different diabetes populations are needed.

18.6.2 Chronic Kidney Disease Risk Prediction in Diabetes

Screening for prevalent kidney damage by monitoring using urinary albumin excretion (UAE) and estimated glomerular filtration rate (eGFR) is already a well-accepted practice in routine diabetes care worldwide, and will not be discussed further here. It is of note however that ethnic variations in the diagnostic performance of these indicators and eGFR in particular are well-known, with the introduction of the ethnicity correction factor in recent estimators of kidney function such as the Modification of Diet in Renal Disease (MDRD) [95, 96] and

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [97] equations, aiming to correct for these discrepancies. There has been increasing need in recent years, both in the general population and in people with diabetes, to accurately identify, among people without UAE and eGFR-defined chronic kidney damage, those who are likely to develop such a damage in future and, among people with a chronic damage, those who are more likely to progress to the advanced stages of the disease requiring kidney transplantation or renal replacement therapy. This emerging need has positioned absolute multivariable risk models as attractive and likely cost-effective approach for wide-scale CKD risk stratification. Unlike the field of CVD however, the development and uptake of renal absolute risk score are still a developing story both in the general population and in people with diabetes [98].

The first published systematic review on renal risk models identified 30 CKD occurrence prediction models and 17 CKD progression prediction models from 16 studies published between 1980 and 2012 [98]. Those of these models applicable to people with diabetes used diabetes status as a risk factor in models (step approach) for most, while only a few were developed exclusively in people with diabetes (interaction approach). Models had been overwhelmingly developed in Caucasian populations, with only four studies reporting on models developed exclusively in Asian populations [99–102]. Very few of existing models had been externally validated [103], and none had been advocated for CKD risk screening in guidelines [98]. Subsequent efforts following the review have expanded the scope of developed and validated renal models for people with diabetes. Recent models specifically developed in people with diabetes include the Chinese National Diabetes Care Management Program (NDCMP) model [104], the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) model [105], the New Zealand models [106], the Hong Kong Hospital Authority [107], and the ADVANCE-ON risk model [108].

The few renal risk models developed in multiethnic population with diabetes suggest possible effects of ethnicity on model performance. In the New Zealand renal risk models, for instance, relative to Caucasians, hazard ratios for incident end-stage renal disease were always higher in Maori, Pacific, and Indo-Asians and lower in East Asians and other ethnicities [106]. The ADVANCE-ON model derived using the entire eligible cohort had variable calibration performance across participants from established market economies, Asians and Eastern European participants [108]. These two observations suggest that possible changes in both discrimination and calibration should be expected when renal risk models developed in a specific ethnic group are applied to a population of different ethnic backgrounds. Renal risk models developed from general diabetic populations have shown acceptable-to-good discrimination and good calibration when applied to the derivation sample [104, 106, 107] and mostly similarly during external validation by the same investigators. Renal risk models developed for people with diabetes included in clinical trials and likely receiving many modifying therapies for CKD risk factors have rather shown modest discrimination both in derivation sample and during external validations where conducted [105, 108].

Independent external validation studies of renal risk models in people with diabetes are lacking. However, the few validation studies conducted in the general population tend to support a preserved discrimination and to some extent calibration performance of CKD models [109, 110]. In the Hong Kong Hospital Authority of people with diabetes, the sample-derived models to predict ERSD had similar acceptable-to-good performance like equivalent models from ADVANCE [111] and New Zealand [106]. In the South and West New Zealand diabetes audit sample, the New Zealand [106] and ADVANCE [111] models equally performed well at predicting renal outcomes [106]. This limited available evidence suggests that, unlike CVD risk models, available renal models offer more flexibility for application/adaptation in diverse settings and populations. The more consistent measurement of potent CKD predictor (eGFR and UAE) and renal outcomes across settings are likely driving the consistent performance of renal risk models across settings.

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Cardiovascular Risk-Assessment Models and Ethnicity: Implications for Hypertension Guidelines

19

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19.1 CVD Risk-Assessment Models

The mathematical basis of a CVD risk-assessment model rely on three main components: (1) the mean levels or prevalence of risk factors, (2) the average absolute CVD risk (incidence or mortality), and (3) the relative risk associated with the risk factors. Reliable quantitative estimation of the CVD risk is theoretically determined by these components, so that systematic underestimation or overestimation might occur if a model derived from one population cohort is applied to a population with different profiles of these components. This point is now becoming crucial for both ethnic minorities in Europe and for low-income countries.

Differences in the first two elements, the mean risk factor levels and mean rates of CVD, have been consistently reported between native European populations belonging to ethnic minorities. Differences are also evident between the different minority groups, such as between South Asians and African descents. ACC and AHA released separate predictive models for non-Hispanic white American individuals and African-American individuals [1]. The SCORE project only developed separate models for populations living in the different European countries

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characterized by high or low CVD risk [2]. Furthermore, the composition of CVD can vary between populations. Particular countries in Asia had a considerably high mortality from stroke and low mortality from ischemic heart disease [3]. For example, the rate of stroke and ischemic heart disease in China was 157 and 63 per 100,000 population, respectively, compared with 30 and 98 per 100,000 population, respectively, in the USA [4].

As regards the third element, only little information is available for ethnic minorities in Europe. Although major risk factors for CVD have been identified for more than half a century and their association with CVD has been repeatedly verified in diverse populations, heterogeneity in the relative risks or the β coefficient of risk factors (indicating the strength of the associations) between models derived from different populations has been reported [5, 6].

As regards blood pressure, the Asia Pacific Cohort Studies Collaboration, which involved more than 500,000 individuals followed for several years on average, has demonstrated direct continuous associations of usual levels of systolic and diastolic blood pressure with the risks of coronary heart disease and stroke in both white and Asian populations [7, 8]. Overall, the association of blood pressure with stroke risk was about twice as steep as that with coronary disease risk, and whereas the association with coronary risk was identical in the Asian and white populations, the association with stroke risk was steeper among Asians [9]. More recently, a high relative risk of stroke associated with high blood pressure was observed in South Asians living in the UK because blood pressure was found to be more strongly associated with stroke in South Asians than Europeans [10]. Over a median of 20-year follow-up, SBP, and particularly DBP and MAP, were more strongly associated with stroke risk in South Asians than Europeans, independent of other cardiovascular risk factors [10].

Unsurprisingly, given the differences in relative risks, risk factors, and rates of CVD between populations, a systematic overestimation or underestimation of CVD risk has been observed when a model designed for one population is directly applied to another population. As noted in the validation of Framingham models in six US cohorts, a significant overestimation of CHD risk was found in Japanese-American [5]. A similar overestimation was reported when the Framingham models were used to predict CVD risk in Chinese [11] and Spanish [12] populations. The SCORE models generally overestimated the risk of cardiovascular death in the Japanese general population [13]. The Framingham and SCORE cardiovascular risk prediction models did not accurately predict an excess risk in minority ethnic groups in the UK [14–16].

One pragmatic and advocated solution to the need to base clinical decisions on risk prediction is to use equations derived from studies on white Europeans (SCORE) but to multiply the result by correction factors (1.4 for Southern Asia, 1.3 for sub-Saharan Africa and the Caribbean, 1.2 for Western Asia, 0.9 for Northern Africa, 0.7 for Eastern Asia or South America) to account for the mismatch between expected and actual prediction in ethnic minorities [17]. This is conceptually equivalent to using a lower threshold of predicted risk [14].

19.2 Availability of Algorithms Derived from Different Populations

The pioneering creation of the Framingham Heart Study led to recognize the importance of "prospective cohort studies" as the main methodological tool in etiological research in epidemiology [18]. Since then, several versions of the Framingham Risk Equations have been developed [5]. Furthermore, in 2013, the ACC/AHA released the Pooled Cohort Equations for non-Hispanic white American and African-American individuals [1]. In Europe, the SCORE system was developed to estimate the 10-year risk of fatal CVD events for low-risk and high-risk populations separately, based on data from 12 European cohorts [2]. In addition to the integrated SCORE project, several models were also developed based on cohorts from other European countries, such as PROCAM in Germany [19]; the HellenicSCORE in Greece [20], in Iceland [21], in the Netherlands [22], in Switzerland [23], and in Turkey [24]; and QRISK in the UK [25, 26] and in former Yugoslavia [6]. CHD risk-assessment models have also been developed for South American populations, specifically in Chile [27] and Puerto Rico [6]. In Asia, predictive models of CVD have been established based on large cohort studies in Chinese [11, 28], Indian [29], Iranian [30], Israeli [31], Japanese [32], Korean [33], Singaporean [34], and Thai [35] populations. Although a predictive model for CVD risk in the African population is not yet available, a model incorporating all major CVD risk factors has been developed to predict all-cause mortality [36]. These widely available prospective cohorts with developed risk-assessment models from different geographical regions and ethnic groups have provided the opportunity for the development of population-specific risk-assessment tools for local practice.

Regarding outcome, SCORE was designed to predict 10-year risk of any atherosclerotic CVD death, PROCAM to predict 10-year risk of hard CHD or stroke, QRISK to predict 10-year risk of CVD event, Framingham to predict 5-year risk of hard CHD event, and the Pooled Cohort to predict 10-year risk of CVD event [37]. Considerable heterogeneity in the definition of total CVD was observed between the studies. For example, the SCORE risk-assessment system included any kind of fatal atherosclerotic CVD, whereas the Pooled Cohort Equations included nonfatal myocardial infarction or CHD death and fatal or nonfatal stroke.

After a risk-assessment model has been developed, its predictive capacity should be evaluated in the dataset from which it is derived (internal validation) and in a population other than that on which the model was based (external validation). Among the available models, the Framingham [38], Pooled Cohort [1], SCORE [2], QRISK [25], PROCAM [19], and AusSCORE [39] models reported internal validation results. As regards the external validation, the Framingham, Pooled Cohort, SCORE, QRISK, and PROCAM models retained acceptable discrimination performance in external validation cohorts, but calibration was usually poor among cohorts at different levels of risk or of other ethnicities [1, 5, 11, 12]. Recalibration of a risk-assessment model would involve the replacement of the mean CVD risk and risk factor levels of the source model with data for the local population, but retaining the variable coefficients.

19.3 Guidelines for Risk Assessment

Clinical guidelines have an essential role in guiding clinical practice by providing physicians with recommendation based on the latest data. The first integrated clinical guidelines for CVD prevention that recommended total CVD risk assessment in clinical practice were developed and issued by the European Society of Cardiology, the European Atherosclerosis Society, and the European Society of Hypertension in 1994 [40], which provided not only a risk-assessment chart and a definition of high risk based on equations developed from Framingham Heart Study data but also total CVD risk-based clinical management strategies. Since then, different guidelines for hypertension treatment have been issued by different organizations and different countries. Guidelines can effectively bridge complicated mathematical-based risk predictive models with understandable and useful tools for clinicians and patients. However, notable differences may exist in the list of risk factors, as well as in the recommended algorithms for risk assessment. Among 8 guidelines on hypertension, the risk factor list ranged from 1 risk factor (blood pressure only) to 15, with an additional 3–6 indicators for target-organ damage [41–48]. The hypertension guidelines issued from some LMICs included a higher number of risk factors for risk assessment than those from developed countries [41, 44–46]. An increase in systolic blood pressure, a commonly and easily measured parameter, is often the initial reason for a risk assessment. Some guidelines require physicians to collect information only on age, sex, systolic blood pressure, total cholesterol, and smoking status for risk assessment, but other guidelines require up to 15 other risk factors [37, 49]. An increase in the number of measurements required for risk assessment necessitates additional time and resources; such facilities might not be available in the primary care setting in many LMICs. Furthermore, the varied risk factor measurements required by different guidelines might also be a source of confusion to physicians administering the CVD risk assessment [37]. Efforts are needed to develop hypertension guideline(s) for the LMIC [49]. The expected guideline(s) should be broad based, flexible, adaptable, socioculturally acceptable, and economically attainable for better health-related outcomes in patients with hypertension [49].

19.4 Defining High-Risk Thresholds

Defining the threshold for high risk is of paramount importance, given that it is closely related to selection of candidates for treatment. However, inconsistencies may exist between recommended risk factors, algorithms for risk classification, and CVD risk thresholds to define high risk among the population in different regions and countries or the same regions or countries but different organizations. For example, a Chinese patient aged 48 years with systolic blood pressure of 150 mmHg and an LDL cholesterol level of 4.2 mmol/L would be classified as high risk based on the risk algorithms of the Chinese guidelines for dyslipidemia, but medium risk based on the Chinese guidelines for hypertension, and low risk by the Chinese risk score [28, 45, 50]. Whether a physician would immediately prescribe drugs to lower

his blood pressure and LDL cholesterol level would potentially depend on which guidelines the physicians were following and which risk calculators they used in practice. Furthermore, a high-risk threshold should be assessed not only for its capacity to define a high-risk population for CVD but also the cost-effectiveness of drug treatment strategies for the defined high-risk population, the resources available, and the extent to which evidence from randomized controlled trials can be generalized, in addition to the economic status, the health-care system, and the health insurance plans, especially in LMICs [51].

In one study, the proportion defined as high risk ranged from 0.4 to 4.8% in eight low-income countries when a CVD risk of ≥30% was used as the threshold of high risk (as recommended by the WHO), but the proportion increased to 7–33% if a blood pressure of ≥160/100 mmHg or total cholesterol level >8 mmol/L was added to the criteria for high risk [52]. Using the WHO criteria of CVD risk of ≥30% in these countries would presumably result in a very small proportion of CVD events being prevented by an intervention strategy in high-risk patients.

Conclusions

An appropriate and feasible risk-assessment tool is of critical importance for effective implementation of a CVD prevention strategy in a high-risk population. Country-based or ethnicity-based CVD risk prediction models are needed because of substantial variations in mean CVD risk, mean levels of major risk factors, relative risk of a risk factor, and epidemiology of CHD and stroke among different countries or ethnic groups. Differences exist in the recommendations for risk assessment between clinical guidelines issued by different regions, countries, or organizations which partly reflect the prevailing attention to the conditions of local populations. Prospective cohort studies with localized risk-assessment models are widely available and might be used to develop localized risk-assessment tools in different regions, countries, or ethnic groups.

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Antihypertensive Drug Therapy in Patients of African and South Asian Ethnicity: A Systematic Review

20

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20.1 Hypertension in Patients of African and South Asian Ethnicity

Patients of sub-Saharan African or South Asian descent tend to have more hypertension and diabetes leading to early organ damage and premature cardiovascular mortality, compared to patients of white European descent [1–22]. Abundant data indicate that greater salt sensitivity, blunted nocturnal dipping, and enhanced vasoconstriction in patients of African descent lead to higher mean blood pressures with early stroke, heart failure, and premature death [1–8, 10, 12–14, 16–22], while hypertensive South Asian patients are reported to be at a higher risk for early ischaemic end organ damage [1, 2, 5, 9, 11, 15, 22]. Thus, hypertension seems to be a more aggressive disease in these ethnic groups. This could have important implications for hypertension screening and management. Non-pharmacological interventions to reduce blood pressure and cardiovascular risk, including dietary adjustments, physical exercise, weight reduction, smoking cessation, and stress

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reduction, should be applied [1, 23–33], but most hypertensive patients need drug therapy aside from lifestyle measures. Therefore, we reviewed the evidence on randomized trials of antihypertensive drug treatment in African and South Asian ethnicity patients.

20.2 Methods

The participation of patients of ethnic minority groups in major international clinical trials is generally too low to calculate the primary outcome with sufficient power [34]. Therefore, we systematically reviewed the evidence on the efficacy of antihypertensive drug therapy to reduce blood pressure and morbidity and mortality outcomes and pooled the existing data.

Systematic searches were conducted in September 2017, with our previous systematic reviews on patients of African and Asian ethnicity [16, 17, 19] updated. In brief, we used the Cochrane systematic review methodology [35] and defined a highly sensitive search strategy to retrieve original reports of randomized controlled trials in hypertensive African and South Asian ethnicity patients, providing original quantitative data on the effect of antihypertensive monotherapy on blood pressure (trial duration at least 2 weeks) versus concurrent placebo treatment or antihypertensive monotherapy or combination therapy on morbidity or mortality outcomes (trial duration at least 1 year).

We included only trials with major drug classes in adult men and non-pregnant women with uncomplicated primary hypertension (no history of or current cardiovascular event or ESRD). Trials that considered oral antihypertensive treatment with thiazide and thiazide-like diuretics, calcium channel blockers, centrally acting agents, peripheral adrenergic neuron antagonists, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers were eligible for inclusion.

We conducted separate searches and data analysis for these two ethnic groups. Searches were performed in electronic databases (Embase, PubMed, Cochrane Library CENTRAL, Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS), African Index Medicus, and, for South Asian patients, IndMED) from their inception through September 2017, without language restriction.

These databases have different software and therefore different search languages, but a typical search strategy for trials in patients of African ethnicity was "(Black* OR Afri* OR AFRO* OR Creole OR Carribean OR Caribbean OR negr* OR ethnic* OR blacks) AND (hypertension OR antihypertensive) AND randomized"; and for South Asians, the first step was "(South Asian OR South Asians OR India OR Indian OR Hindustani OR Bangladesh OR Nepal OR Sri Lanka OR Ceylon OR Pakistan)".

Search yields from different databases were considered and analysed separately to prevent merging errors and to enhance trial retrieval. Furthermore, we performed hand search including contacting experts. We did not include trials in diabetics only, with experimental drugs, or with complementary medicines.

We used data extraction forms to collect trial data in duplo. With pilot searches, we retrieved very few placebo-controlled trials in South Asians and decided to review drug versus drug trials in this group. For drug versus drug trials with multiple treatment arms, we followed the Cochrane handbook methodology and combined the comparison groups into one group of "other drugs" [35]. African or South Asian descent (ancestry or ethnicity) was defined as, respectively, of sub-Saharan African descent or Indian subcontinental descent as indicated by the authors. We included only randomized controlled trials, and methodological quality was further assessed using the Jadad score, based on the description of randomization, blinding, and accountability of all patients, including withdrawals in each of the treatment arms and the underlying reasons. Subgroups were based on sex and geographical location.

20.2.1 Statistical Analysis

Quantitative analysis of outcomes was based on intention-to-treat results (primary) and per protocol analysis (secondary). We included data from the first part of crossover studies when such data were available; if not, we included the data these studies provided. Our measure of effect for each study was difference in means (in mmHg) for systemic arterial blood pressure (continuous measure) and relative risk (RR) for dichotomous data. In addition, we calculated achievement of target diastolic blood pressure (DBP <90 mmHg, or reduction of ≥10 mmHg, or ≥10%, as defined by the author) as the weighted mean of placebo-corrected results per drug class, or in South Asians, versus other drug types.

Missing standard deviations were imputed per drug class. We clinically assessed studies for heterogeneity in patient characteristics, interventions, and outcomes, to decide whether studies should be pooled. Furthermore, we used I^2 statistics to quantify the proportion of total variation in the estimates of treatment effect that was due to heterogeneity. We planned to not aggregate results with a high variation across studies ($I^2 \geq 75\%$) [17, 19, 35]. When we aggregated studies, we conservatively used the random effects model to estimate the average intervention effect. Data in square brackets are 95% confidence intervals, unless indicated otherwise. We used Review Manager (RevMan) software, version 5 (Cochrane Collaboration, Oxford, United Kingdom) for the analyses.

20.3 Results

20.3.1 Patients of African Ethnicity

20.3.1.1 Search Yield

Full reports or abstracts from 5311 references of papers yielded 35 trials with 7 classes of antihypertensive drugs, in 25,540 patients [36–89]. Blood pressure was the main outcome measure in 28 trials (Figs. 20.1 and 20.2; Table 20.1) [36–66] and

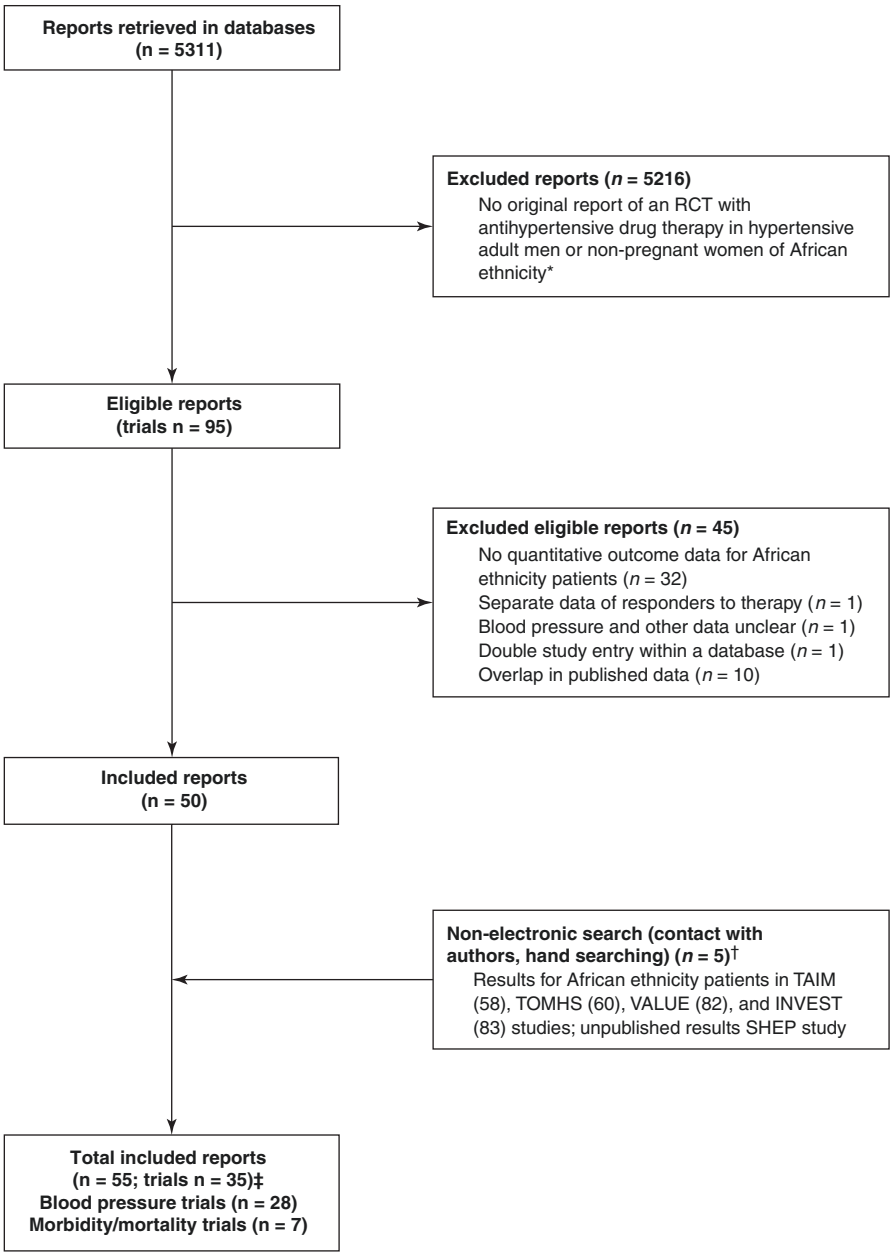

Fig. 20.1 Trial flow: patients of African ethnicity. *Most excluded papers were not a randomized controlled trial (RCT) fulfilling the inclusion criteria in the method section or multiple overlapping reports concerning these trials. †Eligible data and papers were either not published, not included in the electronic databases searched, or lacked electronic bibliographic indexing terms referring to African ethnicity. ‡Some studies reported data on African ethnicity patients in more than one paper

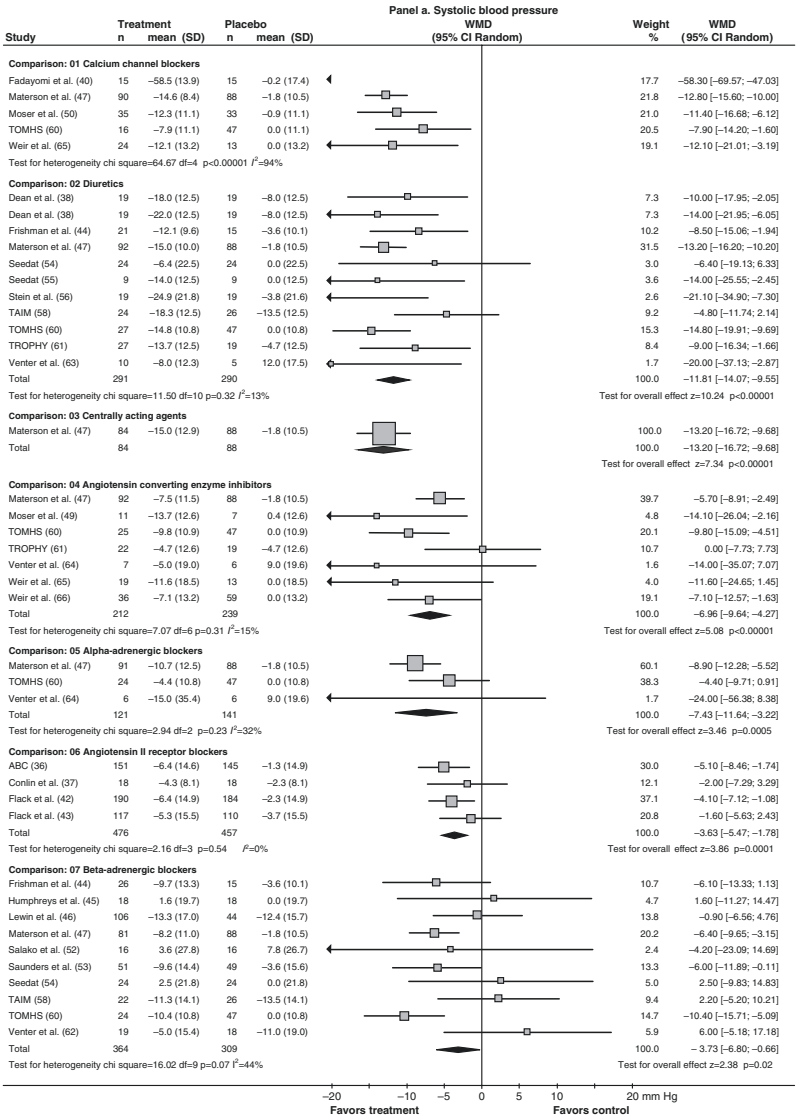

Fig. 20.2 Effect of different antihypertensive drugs on blood pressure in patients of African ethnicity. Panel (**a**). Systolic blood pressure. Panels (**a** and **b**). Random, random effects model. Results are reported as weighted mean differences in reduction of systolic and diastolic blood pressure (mmHg) from baseline to endpoint with the use of different antihypertensive drugs compared to placebo. Squares are weighted mean differences in reduction of SBP/DBP (mmHg). The size of the squares represents study weight, and horizontal lines represent 95% CIs. Arrowheads depict data outside the scale. When a study provided only the placebo-drug difference, we entered a "nil" for placebo results. Results for Materson and colleagues' study and Weir and colleagues' study are weighted means of older and younger people and patients receiving a high- and a low-salt diet, respectively. Black diamonds are pooled estimates. Results for calcium channel blockers were not pooled because the size of the effect is heterogeneous. *ABC* Association of Black Cardiologists; *TAIM* Trial of Antihypertensive Interventions and Management; *TOMHS* Treatment of Mild Hypertension Study; *TROPHY* Treatment in Obese Patients with Hypertension [36–66]

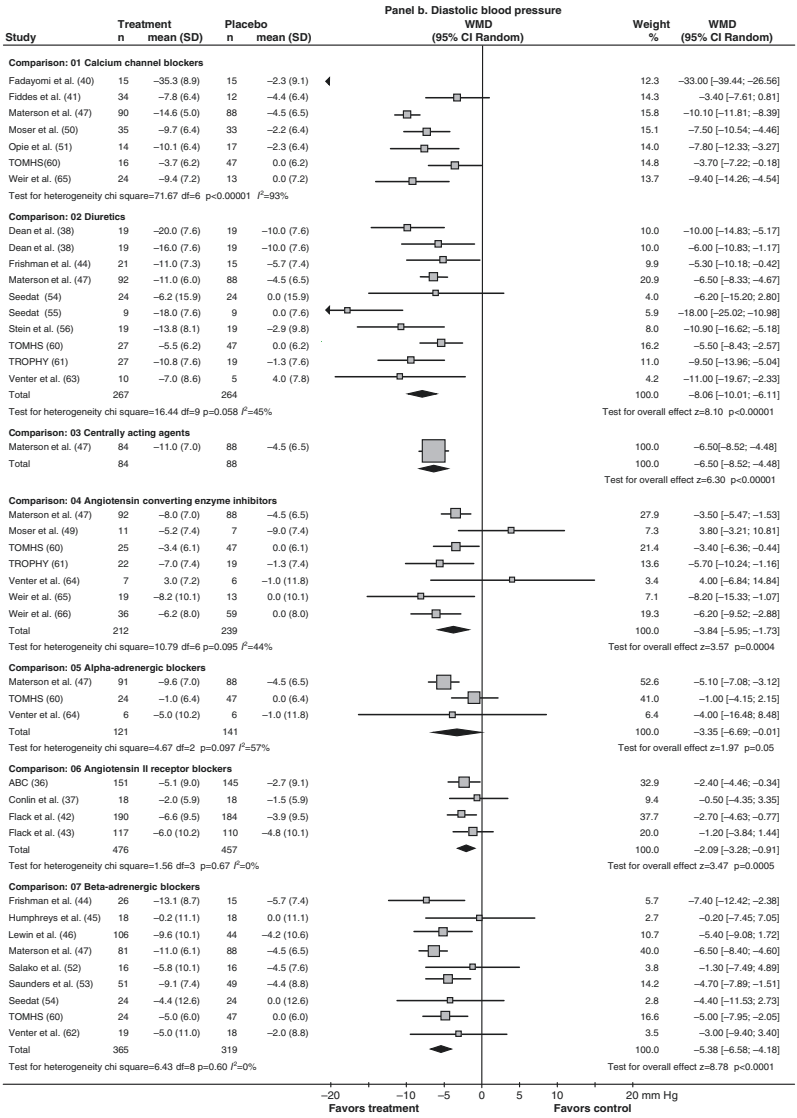

Fig. 20.2 (continued)

morbidity or mortality in 7 trials (Fig. 20.1 and Table 20.2) [67–89]. Most included patients were older than 50 years with risk factors for cardiovascular disease, followed for 3–5 years. Cardiovascular events and mortality were the main outcome measures. Jadad score ranged from 1 to 5 (Table 20.2). Trials were clinically comparable in describing the results of randomized controlled interventions with antihypertensive drugs in African ethnicity patients with hypertension, but the age range, inclusion blood pressure, drugs, and drug dose varied (Tables 20.1 and 20.2).

Table 20.1 Characteristics of studies in African ethnicity patients: blood pressure outcomes

	Participants of African ethnicity				Drug intervention vs. placebo total daily dose, mg§	Treatment duration	Outcome measure (BP)	Analysis of results	Adverse effects	Jadad score					
Study, y	N	Country	Age, y	BP, mm Hg						RA	MR	DB	MB	DO	Total
ABC 2000 [36]	304	USA	Mean 52	DBP 91–105	Candesartan cilexetil 32	8 w	Cont./ dichot.	ITT	Reported	1	–	1	1	1	4
Conlin et al. 2003 [37]	18*	USA	Mean 52	DBP 90–109	Losartan 50‖	4 w	Cont.	ITT	n.d.	1	–	1	1	1	4
Dean et al. 1971 [38]	60	RSA	Adults	DBP 100–116	Hydrochlorothiazide 50 Mefruside 25	2 w	Cont.	PP	n.d.	1	–	1	1	–	3
Drayer et al. 1983 [39]	58*	USA	Mean 53	DBP 95–115	Captopril 200	8 w	Dichot.	PP	n.d.	1	–	1	–	1	3
Fadayomi et al. 1986 [40]	32	Nigeria	Mean 48	DBP > 100	Nifedipine 40	6 w	Cont./ dichot.	PP	Reported	1	–	1	1	–	3
Fiddes et al. 1994 [41]	46	USA	≥55	DBP 95–114	Diltiazem XR 480	8 w	Cont.	ITT	n.d.	1	–	1	–	–	2
Flack et al. 2001 [42]	381	USA	Mean 50	DBP 95–109	Losartan 150	12 w	Cont./ dichot.	ITT	Reported	1	–	1	–	1	3
Flack et al. 2003 [43]	233*	USA/RSA	Mean 52	DBP 95–109	Losartan 50–100	16 w	Cont.	ITT	n.d.	1	–	1	1	–	3
Frishman et al. 1995 [44]	62*	USA	≥21	DBP 95–115	Hydrochlorothiazide 25 Bisoprolol 5	4 w	Cont./ dichot.	ITT	n.d.	1	–	1	–	–	2
Humphreys et al. 1968 [45]	18	Jamaica	46–63	DBP 100–155	Propranolol 360‖	2 m	Cont./ dichot.	ITT	Reported	1	–	1	1	1	4
Lewin et al. 2013 [46]	152	USA	Mean 51	SBP 160–180 DBP 90–100	Nebivolol 20 mg	6w	Cont./ dichot	ITT	Reported	1	1	1	1	1	5

(continued)

Table 20.1 (continued)

Study, y	Participants of African ethnicity				Drug intervention vs. placebo total daily dose, mg§	Treatment duration	Outcome measure (BP)	Analysis of results	Adverse effects	Jadad score					
	N	Country	Age, y	BP, mm Hg						RA	MR	DB	MB	DO	Total
Materson et al. 1993 [47, 48]	621	USA	Mean 58	DBP 95–109	Diltiazem 360 hydrochlorothiazide 50 clonidine 0.6 Captopril 100 Prazosin 20 Atenolol 100	8 w/1 y‡‡	Cont./ dichot.	ITT	n.d.	1	–	1	–	1	3
Moser et al. 1982 [49]	20	Bahamas	32–60	DBP 101–119	Captopril 450	4 w	Cont./ dichot.	PP	Reported	1	–	1	–	–	2
Moser et al. 1984 [50]	77	USA	26–70	DBP 90–114	Nitrendipine 40	5 w	Cont./ dichot.	PP	n.d.	1	–	1	1	–	3
Opie et al. 1997 [51]	31*	RSA	18–75	DBP 95–114	Nisoldipine 30	6 w	Cont.	ITT	n.d.	1	–	1	1	–	3
Salako et al. 1979 [52]	20	Nigeria	37–60	DBP 95–120	Alprenolol 400‖	8 w	Cont.	PP	Reported	1	–	1	1	1	4
Saunders 2007 [53]	301	USA	Mean 51	DBP 95–109	Nebivolol 40 mg	12 w	Cont.	ITT	Reported	1	–	1	–	1	3
Seedat 1980 [54]	24	RSA	Adults	DBP 100–115	Chlorthalidone 100 Atenolol 25‖	4 w	Cont.	ITT	Reported	1	–	1	–	1	3
Seedat 1980 [55]	9	RSA	Mean 44	DBP ≥ 110	Mefruside 25 Debrisoquine 20‖	4 w	Cont./ dichot.	ITT	n.d.	1	1	1	–	1	4
Stein et al. 1992 [56]	25	Zimbabwe	<70	DPB 96–114	Hydrochlorothiazide 50‖	6 w	Cont./ dichot.	PP	n.d.	1	–	1	–	1	3
TAIM 1991 [57, 58]	98*	USA	Mean 46	DBP 90–100	Chlorthalidone 25 Atenolol 50¶	6 m	Cont.	ITT	n.d.	1	1	1	1	–	4

TOMHS 1997 [59, 60]	177	USA	Mean 54	DBP 90–99	Amlodipine 10 Chlorthalidone 30 Enalapril 10 Doxazosin 4 Acebutolol 800**	1 y	Cont.	PP	Reported for women only	1	–	1	1	–	3
TROPHY 1997 [61]	68†	USA	21–75	DBP 90–109	Hydrochlorothiazide 50 Lisinopril 40	12 w	Cont.	PP	n.d.	1	–	1	1	–	3
Venter et al. 1990 [62]	50	RSA	25–65	DBP 95–115	Penbutolol 80†	12 w	Cont./ dichot.	PP	Reported	1	–	1	1	1	4
Venter et al. 1991 [63]	15*	RSA	25–65	DBP 95–115	Xipamide 20	12 w	Cont.	PP	Reported	1	–	–	–	1	2
Venter et al. 1991 [64]	29	RSA	21–65	DBP 95–115	Enalapril 40 Prazosin 20	10 w	Cont./ dichot.	PP	Reported	1	–	1	1	1	4
Weir et al. 1998 [65]	56*‡	USA	Mean 52	DBP 95–115	Isradipine 20 Enalapril 40††	4 w	Cont.	PP	n.d.	1	1	1	1	–	4
Weir et al. 1998 [66]	96*	USA	Mean 54	DBP 95–114	Trandolapril 16	6 w	Cont.	ITT	Reported	1	–	1	–	1	3

Y (publication) year(s); *ABC* Association of Black Cardiologists; *N* number of African ethnicity patients randomized or *evaluated in this review; *USA* United States of America; *RSA* Republic of South Africa; *(D) BP* (diastolic) blood pressure; *mg* milligram; *W* weeks; *m* months; *ITT* intention to treat; *PP* per protocol analysis; *ND* no data reported for African ethnicity patients; Jadad score: *RA* randomization; *MR* method of randomization; *DB* double blind; *MB* method of blinding; *DO* dropouts; *TAIM* Trial of Antihypertensive Interventions and Management; *TOMHS* Treatment of Mild Hypertension Study; *TROPHY* Treatment in Obese Patients with Hypertension; †obese patients; ‡salt-sensitive patients; §highest daily dose. ‖crossover trial; ¶other drugs added in 12.5% of participants. **Second drug added in 9.2% of participants, plus lifestyle interventions. ††Plus high–/low-salt diet; ‡‡BP as continuous (cont.)/dichotomous (dichot.) outcome

Table 20.2 Trials with morbidity and mortality outcomes in African ethnicity patients

Participants of African ethnicity*			Inclusion criteria	Treatment arms¶	Primary endpoint	Jadad score††						Follow-up (y)	Primary outcome
Study	*N* (%)	Country				RA	MR	DB	MB	DO	Total		
SHEP	657 (14)	USA	>60 ISH	Chlorthalidone Placebo	Fatal/non-fatal stroke	1	–	1	1	–	3	4.5	ns
LIFE	533 (6)	7 countries†	55–80y LVH	Losartan Atenolol	MI, stroke, CVM	1	1	1	1	–	4	4.8	ns
AASK	1094 (100)	USA	18–70y GFR 20–65‖	Ramipril Metoprolol Amlodipine	GFR (usual vs. low BP goals)	1	1	1	1	1	5	4.1	ns
ALLHAT	15,094 (35)	USA	>55y CHD risk	Lisinopril Amlodipine Chlorthalidone Doxazosin	MI + CHD death	1	1	1	1	1	5	4.9	ns
VALUE	639 (4)	31 countries‡	≥50y CVD/risk	Valsartan Amlodipine	Time to first cardiac event	1	1	1	1	–	4	4.2	ns
INVEST	3029 (13)	14 countries‡	>50y CAD	Atenolol** Verapamil	Death (ACM), MI, or stroke	1	–	–	–	–	1	2.9	ns
ACCOMPLISH	1414 (17)	5 countries§	>55y TOD	Benazepril/ HCT Benazepril/ Amlo	CVD, CVM	1	–	1	–	–	2	3.0	ns

Country, †98% USA; ‡not reported; §USA. ‖mL/min/1.73m^2. ¶Parallel treatment arms with initial monotherapy, except SHEP (vs. placebo) and ACCOMPLISH (initial combination therapy). **Primary add-on drug trandolapril (verapamil arm) and HCT (atenolol). †† Jadad score: *RA* randomization; *MR* method of randomization; *DB* double blind; *MB*, method of blinding; *DO* dropouts in African ethnicity patients. *ISH* isolated systolic hypertension; *LVH* left ventricular hypertrophy; *GFR* glomerular filtration rate; *CA(H)D* coronary artery (heart) disease; *CV(D)(M)* cardiovascular (disease) (mortality); *TOD* target organ damage; *HCT* hydrochlorothiazide; *Amlo* amlodipine; *BP* blood pressure; *MI* myocardial infarction; *ACM* all-cause mortality; *ns* no significant difference. *SHEP* The Systolic Hypertension in the Elderly Program [67–69]; *LIFE* The Losartan Intervention for Endpoint reduction in hypertension study [70–73, 85, 87]; *AASK* African American Study of Kidney Disease and Hypertension [74–76, 81]; *ALLHAT* Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial [77–80, 86, 88, 89]; *VALUE* Valsartan Antihypertensive Long-term Use Evaluation trial [82]; *INVEST* The International Verapamil-Trandolapril Study [83]; *ACCOMPLISH* Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension trial [84]

20.3.1.2 Trials with Blood Pressure Outcomes

Monotherapy Versus Placebo

The aggregated data showed a greater effect of calcium blockers and diuretics, while beta-adrenergic blockers and ACE inhibitors were the least effective drugs to lower systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively [17, 19, 36–66], as depicted in Fig. 20.2a, b. As a post hoc outcome, nebivolol was analysed separately because of the presumed different mechanism of action [46, 53]. Nebivolol is thought to promote nitric oxide generation, which is reported to be attenuated in African ethnicity patients [16, 46, 53]. However, the pooled weighted mean difference in systolic and diastolic pressure versus placebo of these two trials was, respectively, −3.38 mmHg, 95% CI [−8.38; 1.62] (I^2 = 33%) (SBP) and -5.00 mmHg, 95% CI [−7.41; −2.59] (I^2 = 0%) (DBP).

Achievement of target DBP differed by drug class, calcium channel blockers 46% (RR 3.39 [2.35; 4.90]), diuretics 31% (RR 2.49 [1.68; 3.69]), beta-adrenergic blockers 24% (RR 1.97 [1.43; 2.72]), centrally acting agents 23% (RR 2.22 [1.35; 3.63]), angiotensin II receptor blockers 19% (1.77 [1.41; 2.21]), alpha-blockers 13% (RR 1.71 [1.02; 2.86]), and ACE inhibitors 10% (RR 1.35 (0.81; 2.26), with a RR of >1.0 indicating a beneficial effect.

Blood Pressure Outcomes by Sex

We predefined subgroups based on sex and on geographical location. However, only 3 small trials out of 28 trials with blood pressure outcomes reported data for men and women (N = 146 patients), and this was not further analysed [40, 45, 66].

Blood Pressure Outcomes for US Versus Non-US Citizens

When we separately analysed US versus Caribbean studies, calcium channel blockers changed SBP by −11.89 mmHg (CI, −14.12 to −9.67 mmHg), and beta-blockers led to a change of −4.83 mmHg (CI, −7.91 to −1.75 mmHg), while the size of the effect of alpha-blockers on DBP became heterogeneous. When we separately analysed data from African studies, however, only calcium channel blockers remained more effective than placebo for all outcomes analysed. Diuretics did not significantly differ from placebo in achieving the DBP goal (relative risk, 3.55 [CI, 0.41 to 31.05]), and ACE inhibitors, beta-blockers, and alpha-blockers did not significantly differ from placebo in reduction of SBP and DBP. None of the African studies used a cut-off baseline DBP of less than 114 mmHg, compared with 7 of the 15 US and Caribbean studies (Table 20.1). Thus, we could not determine whether the response of African continental ancestry patients was truly different from that of US African-American and Afro-Caribbean patients or rather related to higher baseline blood pressure levels.

20.3.1.3 Trials with Morbidity and Mortality Outcomes

Blood Pressure Reduction with Combination Therapy

Patients of African ancestry more often needed multidrug regimens to reach goal blood pressure than patients of European ancestry [83, 86]. In ALLHAT, the

majority of the participants of African descent (54–63%) reached blood pressure control, but 56–70% needed combination therapy, depending on the treatment group [86]. In line with the blood pressure lowering efficacy of monotherapy, more patients on calcium blocker-based treatment reached goal blood pressure at 24 months than with beta-adrenergic blocker-based treatment in the INVEST study [83], while a reduced blood pressure lowering response in treatments based on initial monotherapy with angiotensin II receptor blockers or ACE inhibitors was observed in ALLHAT and in VALUE [82, 86].

20.3.1.4 Effect on Cardiovascular Morbidity and Mortality

Primary Outcomes

There was no statistical difference between treatment arms in primary morbidity and mortality outcomes for patients of African ethnicity (Table 20.2). In the SHEP study, the overall effect of diuretics on the primary outcome stroke in African ethnicity patients was not significantly different from placebo.

Subgroup Analyses by Antihypertensive Drug Class

Treatment reduced cardiovascular events in patients of African ethnicity in the SHEP study, analysed as a secondary outcome (hazard ratio for all cardiovascular events, 0.50 (CI, 0.32; 0.78) (unpublished results, SHEP trial investigators).

Furthermore, in the ACCOMPLISH trial, there was no significant difference in African ethnicity patients between the two treatment strategies in retarding the rate of progression of kidney disease, in contrast to patients of other ethnicities where amlodipine−/benazepril-based therapy was more effective than hydrochlorothiazide/benazepril [84].

Although ACE inhibitor-based treatment resulted in better clinical outcomes in kidney disease in the AASK trial [75], there was no difference in prevention of cardiovascular events by drug type [81], while the results of the ALLHAT trial indicated cardiovascular morbidity outcomes were worse with treatments based on inhibitors of the renin-angiotensin system [86]. The use of lisinopril-initiated treatment versus chlorthalidone in patients of African ethnicity was associated with greater relative risk of morbidity: combined CHD (1.15 [1.02; 1.30]), combined CVD (1.19 [1.09; 1.30]), stroke (1.40 [1.17; 1.68]), and angina (1.24 [1.07; 1.44]). Heart failure risk was lower with chlorthalidone [86]. No data were provided for these outcomes for lisinopril versus amlodipine in African ethnicity patients.

In line with these findings with ACE inhibitors, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study had showed that losartan-initiated therapy was superior to atenolol-initiated therapy in reducing stroke risk in hypertensive patients of European descent. However, among patients of African descent, losartan-initiated treatment was associated with a nearly significant increase in stroke events compared with atenolol unadjusted hazard ratio, 1.99 [1.00; 3.98] [85], similar to the findings of the primary outcome, a composite outcome including stroke [17, 19, 73]. In addition, the risk for sudden death was 97% higher in patients of African descent in the LIFE trial, with, at this relatively small sample size

($n = 533$), a trend towards increased risk with losartan [87]. These data indicate that therapy initiated with blockers of the renin-angiotensin system is associated with greater cardiovascular morbidity and mortality in patients of African ethnicity.

Subgroup Analyses with Add-On Lipid Lowering Therapy

Participants treated for hypertension in ALLHAT were eligible for add-on lipid lowering therapy with pravastatin 20–40 mg versus usual care when fasting LDL-C levels were 120–189 mg/dL (3.1–4.9 mmol/L) or 100–129 mg/dL (2.6–3.3 mmol/L) for those with known coronary heart disease. There was no difference in the primary outcome all-cause mortality between pravastatin ($n = 1769$) and usual care ($n = 1722$) in African ethnicity patients, relative risk (RR) 1.01 [0.85–1.19]). Adding pravastatin did result in significantly greater stroke risk in African ethnicity patients (relative risk 1.12 versus 0.74 in other patients, confidence intervals not reported; $p = 0.03$). However, the relative risk for atherosclerotic coronary heart disease events with pravastatin was lower in patients of African ethnicity than in other patients (RR 0.73 [0.58–0.92] versus 1.02 [0.81–1.28]; $p = 0.03$). As a result, there was no significant effect of add-on pravastatin treatment on combined cardiovascular disease outcomes in hypertensive patients of African ethnicity [89]. No data were provided for outcomes with add-on lipid lowering therapy by antihypertensive drug type.

Subgroup Analyses by Sex

In a subgroup analysis of the SHEP trial, diuretics were not significantly different from placebo in preventing stroke in African ethnicity men (relative risk, 0.98 [CI, 0.39; 2.44]) but reduced stroke risk in women of African ethnicity (relative risk, 0.36 [CI, 0.16; 0.83]) [69].

In ALLHAT, men of African descent had the highest absolute stroke risk (mean 6y rate/100 patients 7.73, 5.90, 5.81, and 5.90, in African ethnicity men, African ethnicity women, white men, white women, respectively) and the highest stroke risk with lisinopril of all sex-ethnic groups (6y rate/100 patients for lisinopril 9.41, 7.25, 5.32, and 5.59, respectively) [88].

Furthermore, pharmacogenetic outcomes differed by sex in the AASK trial; only women randomized to a usual blood pressure goal (mean arterial pressure 102–107 mmHg), and with an A allele at *CYP3A4* A392G, were more likely to reach a target MAP of 107 mmHg (adjusted hazard ratio of AA/AG compared to GG: 3.41 (95% CI: 1.20 to 9.64; $p = 0.02$). Among participants randomized to a lower MAP goal, men and women with the C allele at *CYP3A4* T16090C were more likely to reach the target MAP of 107 mmHg (adjusted hazard ratio 2.04 (95% CI 1.17–3.56; $p = 0.01$). Finally, the polymorphisms Arg65Leu, Ala142Val, and Ala486Val of the G protein-coupled receptor kinase gene, *GRK4*, were studied in the AASK Study. Only in men randomized to the usual blood pressure goal (mean arterial pressure 102 to 107 mmHg), the adjusted "hazard" ratio to reach goal blood pressure with metoprolol was 1.54 (95% CI 1.11–2.44; $p < 0.01$) with Ala142Val. There was no association between *GRK4* polymorphisms and blood pressure response to metoprolol in women [16].

Subgroup Analyses in US Versus Non-US Citizens

Morbidity and mortality trials were conducted in the USA only or included only a very small number of non-USA patients (Table 20.2). Hence data on European patients are lacking, and we are not informed whether responses are similar.

Adverse Effects

Risk of new-onset diabetes was higher with diuretics, respectively; 9.6% of the participants on diuretics, 7.4% on calcium blockers, and 5.8% on ACE inhibitors developed diabetes in 2 years [80]. There was a significantly greater occurrence of cough and angioedema with ACE inhibitors, 72 per 10.000 (0.72%), versus diuretics (0.04%) and calcium blockers (0.06%) in African ethnicity patients in ALLHAT [86].

20.3.2 Patients of South Asian Ethnicity

20.3.2.1 Search Yield

Electronic searches retrieved 2188 papers (Fig. 20.3). We additionally retrieved three trials with hand search, which were not eligible for inclusion. Seventeen randomized controlled trials were included, with blood pressure as the main outcome. Only one trial was placebo controlled; other trials assessed monotherapy with a drug from one drug class versus a drug from another class. We did not include trials comparing two drugs within one antihypertensive drug class. The 17 included trials (Fig. 20.3 and Table 20.3) were 4 weeks' to 9 months' duration (median 8 weeks), containing original data of 6 classes of antihypertensive drugs in 1819 South Asian hypertensive patients without a history of or current cardiovascular events (n = 37 diabetics) [55, 90–105]. Blood pressure at inclusion was generally between 140 and 180 mmHg systolic and 90–110 mmHg diastolic. Most trials were conducted in India. The methodological quality of the trials was lower than the trials in African ethnicity patients, with Jadad scores between 1 and 4 (median 2). No trial had a Jadad score of 5, and only two were double blinded. Most trials reported side effects and dropouts, but intention-to-treat analysis was reported in only one (Table 20.3).

20.3.2.2 Trials with Blood Pressure Outcomes

There were no significant differences between drug classes in blood pressure lowering efficacy in South Asian patients, as analysed per comparison presented in the trial data [35] (data not shown). Calculation of the blood pressure lowering effect per drug class was hampered by the limited data and heterogeneity that could not be well accounted for but was partly due the small number of trials and sample sizes. However, as South Asian ethnicity patients represent a population subgroup with high cardiovascular mortality, aggregated data on the average effect is of clinical relevance. Therefore, we allowed for heterogeneity in an a posteriori analysis and used the random effects model to calculate the inverse variance-weighted mean blood pressure lowering effect of the different drug classes (Table 20.4) [35]. Other effects described included that lisinopril reduced microalbuminuria (−33% vs. −10% in amlodipine) [95], while

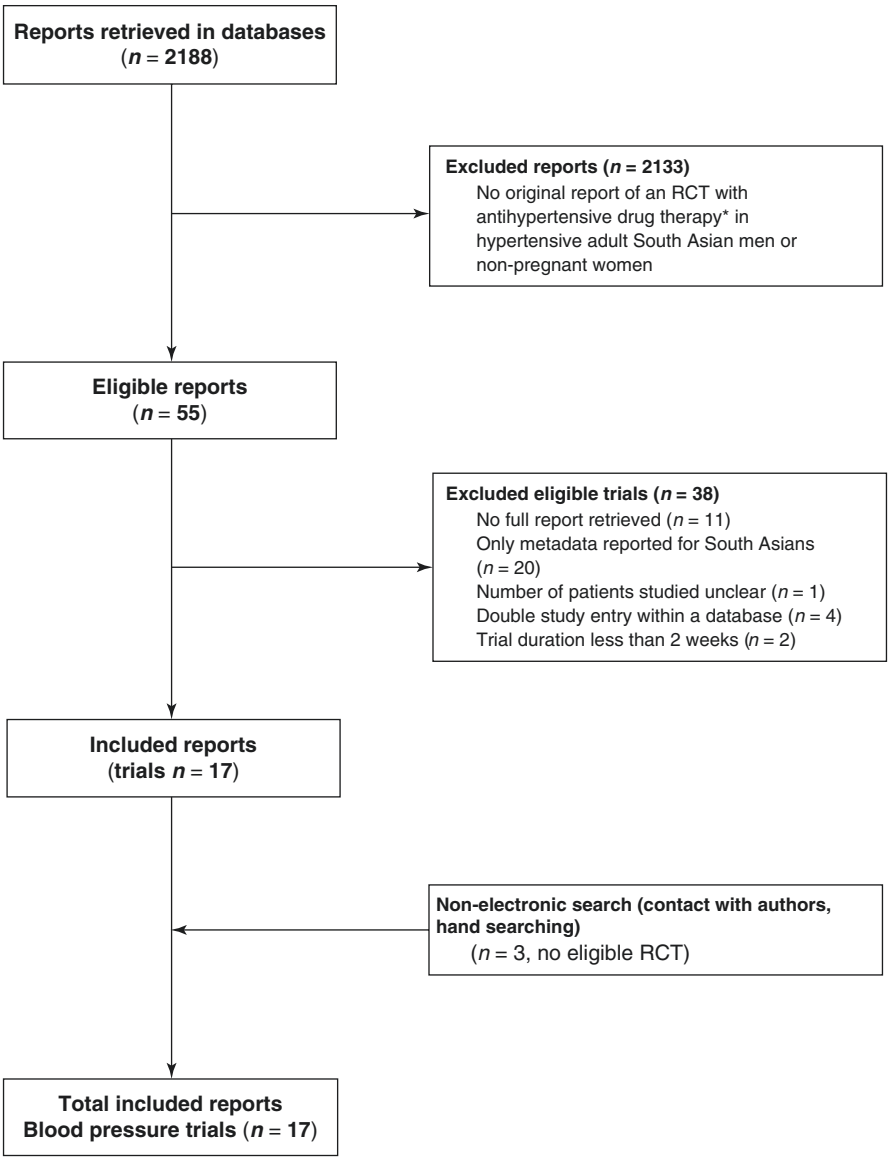

Fig. 20.3 Trial Flow: patients of South Asian ethnicity. *We included randomized controlled trials (RCTs) with single drug therapy versus placebo or versus single drug from another antihypertensive drug class for blood pressure outcomes (at least 2 weeks duration) and with single drug-based or combination therapy for morbidity and mortality outcomes of at least 1-year duration, providing original quantitative data in hypertensive South Asian adult men or non-pregnant women. Excluded reports were not an RCT in South Asian hypertensives or did not use drugs as described in the method section (n = 2133). Eligible trials were mainly excluded because crude data were not or insufficiently reported (n = 20)

Table 20.3 Characteristics of studies in South Asian ethnicity patients: blood pressure outcomes

	Participants of South Asian ethnicity				Drug intervention total daily dose (mg)	Treatment duration	Outcome measure (BP)	Analysis of results	Adverse effects	Jadad score††					
Study, y	N	Country	Age, y	BP, mm Hg						RA	MR	DB	MB	DO	Total
Akat 2010 [90]	80	IND	18–65	n.d.	Telmisartan 40 Enalapril 10	12 w	Cont.	PP	Reported	1	–	–	–	–	1
Ali 2001 [91]	163	IND	Mean 52	DBP 95–115	Losartan 50 Amlodipine 5	8 w	Cont.	PP	Reported	1	–	–	–	1	2
Bhatia 2001 [92]	30	IND	35–65	DBP 90–115	Enalapril 5 Felodipine 5 Prazosin 2	8 w	Cont.	Unclear	Reported	1	–	–	–	–	1
Devi 2011 [93]	161	IND	Mean 50	SBP 140–180 DBP 90–114	Metoprolol 50 Amlodipine 5	8 w	Cont./ dichot.	ITT	Reported	1	–	–	–	1	2
Goyal 2014 [94]	62	IND	Mean 62	SBP 140–179 DBP 90–109	Telmisartan 80 Amlodipine 10	8 w	Cont./ dichot.	PP	Reported	1	–	–	–	–	1
Jalal 2010 [95]	120*	IND	44–63	DBP 90–100	Amlodipine 10 Lisinopril 10	8 w	Cont./ dichot.	Unclear	Reported	1	–	–	–	–	1
Jamali 2008 [96]	80	PAK	20–70	n.d.	Candesartan 16 Atenolol 50	90 d	Cont.	PP	Reported	1	–	–	–	1	2
Joglekar 1998 [97]	122	IND	30–70	SBP 140–180 DBP 90–110	Prazosin 5 Atenolol100	4 w	Cont./ dichot.	PP	Reported	1	1	–	–	1	3
Misra 1998 [98]	110†	IND	30–70	SBP 140–180 DBP 90–110	Prazosin 5 Nifedipine 20	8 w	Cont./ dichot.	PP	Reported	1	1	–	–	1	3

Nadeesha 2009 [99]	120‡	IND	Mean 45	n.d.	Amlodipine 5 Atenolol 25 Enalapril 5 HCT 25	8 w	Cont.	PP	n.d.	1	–	–	–	1	2
Pareek 2008 [100]	300	IND	22–81	SBP 140–159 DBP 90–99	Atenolol 25 CTD 6.25 Amlodipine 2.5	4 w	Cont./ dichot.	PP	Reported	1	1	–	–	1	3
Raja 2016 [101]	100	IND	>25	SBP 140–180 DBP 90–110	Telmisartan 40 Ramipril 5	24 w	Cont.	PP	n.d.	1	–	–	–	–	1
Satia 1995 [102]	65§	IND	45–70	DBP 90–110	Atenolol100 Nifedipine 20	9 m	Cont./ dichot.	Unclear	n.d.	1	–	–	–	–	1
Seedat 1980 [55]	11	RSA	33–61	DBP ≥110	Debrisoquine 20 Mefruside 25	4 w**	Cont./ dichot.	PP	Reported	1	1	1	–	1	4
Shobha 2000 [103]	145	IND	18–65	DBP 95–110	Losartan 50 Enalapril 5	8 w	Cont./ dichot.	PP	Reported	1	–	1	–	1	3
Sumbria 2014 [104]	106‖	IND	Mean 45	SBP ≥140 DBP ≥90	Metoprolol 200 Telmisartan 160	6 m	Cont.	PP	Reported	1	1	–	–	1	3
Sundar 1991 [105]	44	IND	35–60	n.d.	Nifedipine 40 Atenolol 100 Propranolol 80¶ Captopril 100	4 w**	Cont.	PP	Reported	1	–	–	–	–	1

Y (publication) year(s); *N* number of patients randomized. *IND* India; *PAK* Pakistan; *RSA* Republic of South Africa; *(S, D) BP* (systolic, diastolic) blood pressure at inclusion; *n.d.* no data; total daily dose is the maximum dose used; *mg* milligram; *d* day; *w* week; *m* month; *HCT* hydrochlorothiazide; *CTD* chlorthalidone. *Cont./dichot.* blood pressure as continuous/dichotomous outcome. *ITT* intention to treat; *PP* per protocol analysis. *All patients were diagnosed with primary hypertension and microalbuminuria (30–300 mg/24 h), with creatinine clearance >80 mL/min/1.73 m^2; †All patients had an abnormal lipid spectrum; ‡Number of patients in each treatment arm unknown, equal distribution assumed; §52% of the patients had diabetes; ‖In the metoprolol treatment arm, 3.6% had diabetes at baseline versus telmisartan, 2%; ¶Data of beta-adrenergic blockers were averaged in the comparison of drug class versus drug class [35]. **Crossover trial; ††Jadad score, *RA* study was described as randomized; *MR* appropriate method of randomization described; *DB* study was described as double blind; *MB* appropriate method of blinding described, *DO* dropouts with reason

Table 20.4 Systolic, diastolic, and target blood pressure by drug class in South Asian patients

Drug class	Systolic BP mean reduction [CI]	Target SBP (%)	Diastolic BP mean reduction [CI]	Target DBP (%)
Calcium blockers (n = 498)	−19.08 [−22.75; −15.42]	52–88	−11.84 [−13.77, −9.91]	46–82
Diuretics (n = 115)	−13.58 [−24.40; −2.76]	n.d	−9.77 [−16.37; −3.16]	0*
ACE inhibitors (n = 279)	−20.04 [−28.20; −11.88]	n.d.	−11.09 [−15.20; −6.99]	44
Alpha-blockers (n = 119)	−10.41 [−19.48; −1.34]	39–44	−10.06 [−13.78; −6.35]	0–65*
ATII blockers (n = 358)	−23.40 [−29.18; −17.61]	80	−14.86 [−16.40; −13.33]	59–97
Beta-blockers (n = 373)	−21.11 [−26.44; −15.77]	76	−13.99 [−16.71; −11.27]	74–77

Depicted are inverse-variance-weighted means (CI, 95% confidence intervals) of blood pressure reduction (mmHg) per drug type and range of target blood pressure achievement (%) in South Asian hypertensive patients. Evidence from 17 randomized controlled trials of antihypertensive monotherapy [55, 90–105]. Target blood pressure (n = 9 trials) [55, 93–95, 97, 98, 100, 102, 103] was defined by authors, usually SBP < 140 mmHg, DBP <90 mmHg. *Trials typically had an inclusion baseline DBP < 115 mmHg (Table 20.3). In the only trial with baseline DPB >110, no patient reached diastolic treatment goal with diuretics or alpha-blockers [55]. No data were retrieved on centrally acting agents. There was no significant difference in blood pressure lowering effect of different drug types, using comparisons as reported in the trials. Calcium blockers, calcium channel blockers; ACE inhibitors, angiotensin-converting enzyme inhibitors; alpha-blockers, alpha-adrenergic blockers; ATII blockers, angiotensin II receptor blockers; beta-blockers, beta-adrenergic blockers; *n*, number of patients; *n.d.* no data

diuretics and beta-adrenergic blockers were reported to have the well-known metabolic side effects on lipid and glucose metabolism. Non-diuretic, non-beta-adrenergic blocking drugs had a better metabolic profile [97, 99, 102]. There were no separate data provided based on sex.

20.3.2.3 Trials with Morbidity and Mortality Outcomes

We retrieved no trials reporting morbidity and mortality outcomes for hypertensive South Asians.

20.4 Discussion

The WHO Global Monitoring Framework has set a target of a 25% reduction in premature mortality from non-communicable diseases by 2025, including a 25% reduction in the prevalence of hypertension [106]. Hypertension is the main cause of cardiovascular disease and death across populations worldwide [107], and if the targets are met, premature CVD deaths are projected to be reduced to 5.7 million as a result of a 26% reduction for men and a 23% reduction for women [108]. Globally, decreasing the prevalence of hypertension accounted for the largest risk reduction, followed by a reduction in tobacco smoking for men and obesity for women [108].

Since hypertension may differ in age of onset, severity, and response to treatment in different ethnic groups, there is a need for adjusted guidelines to adequately reduce risk factor level in all patient groups.

Antihypertensive drugs were the first cardiovascular therapy for which there was wide recognition of differences in clinical efficacy related to ethno-geographical ancestry [16]. Currently, self-identified African ancestry is the best available predictor of this differential blood pressure lowering response to antihypertensive drugs [16]. This systematic review confirms that patients of African descent as a group respond better to calcium blockers and diuretics, while the response to β-adrenergic blockade and inhibition of the angiotensin-converting enzyme is attenuated [16, 17, 19]. In line with this, trials with morbidity and mortality outcomes indicated that lisinopril- and losartan-based therapy were associated with greater incidence of stroke and sudden death in African ancestry patients.

In contrast, we found no significant differences in the blood pressure lowering response to available antihypertensive drugs in South Asians, but there were limited numbers of studies with small sample sizes available for evaluation. We retrieved no data on the effect of antihypertensive drug treatment on morbidity and mortality outcomes in South Asians. The Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial in intermediate-risk persons without cardiovascular disease (n = 12,705) did include South Asian patients (n = 1854). Blood pressure lowering drugs were given to all patients (of which 35% were hypertensive), through initial combination therapy with a fixed combination of candesartan (16 mg per day) and hydrochlorothiazide (12.5 mg per day), but no separate outcome data were reported for South Asian patients [109].

The existing evidence provides ample evidence of higher risk of premature cardiovascular mortality in South Asian and African ancestry groups [1–22]. However, to better quantify this risk and develop more effective guidelines, we need to improve risk assessment and use risk scores validated for ethnic minorities [110, 111]. To this end, we urgently need European morbidity and mortality outcome data for these ethnic groups, as these are likely to differ from the American and Canadian situation, where far higher treatment and control rates for hypertension are reached [18, 112, 113]. Thus, the risk of premature mortality in South Asian and African ancestry group in Europe is probably underestimated [5]. Although new approaches to estimate risk in these groups have been launched [108, 110], there is still a need for data to support these.

Also, we need data on whether lower thresholds to start treatment and lower therapeutic goal blood pressures need to be applied to these high-risk ethnic groups [109, 113–115]. The Systolic Blood Pressure Intervention Trial (SPRINT) indicated lower cardiovascular morbidity and mortality within 3 years with a systolic goal blood pressure <120 vs. <140 mmHg. However, this difference did not reach statistical significance in African ethnicity patients, with a relatively small sample size and a substantially lower mean age (−5 y) in this subgroup [114]. The International Society for Hypertension in Blacks [116] advises to initiate treatment in patients of African ethnicity from 135 systolic or 85 mmHg diastolic blood pressure, and similar approaches have been suggested in South Asians [15]. The new American Heart

Association guideline states that two or more antihypertensive medications are recommended to achieve a blood pressure less than 130/80 mmHg in most adults with hypertension, especially in black adults with hypertension [113]. Thus, there is increasing support for lower thresholds to treat hypertension in African and South Asian patients.

The strength of this work is that we systematically review the available evidence of the effect of antihypertensive drug treatment on blood pressure, morbidity, and mortality outcomes in hypertensive patients of African and South Asian ethnicity. The aggregated evidence should help reduce premature adverse outcomes in these high-risk population subgroups, but many questions remain.

The cause of the differences in drug responses in African ethnicity persons is largely unknown. Our findings are in accord with the suppressed activity of the renin-angiotensin-aldosterone system in hypertensive patients of African ethnicity, and the high activity of creatine kinase, promoting vasoconstriction and salt retention [8, 16]. As a consequence, patients of African ethnicity are significantly less sensitive to drugs that block the renin-angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) and beta-blockers [16, 17, 19]. Genetic and pharmacokinetic differences did not fully explain these differences [16] but altered cellular functions based on high creatine kinase activity, and enhanced phosphoryl group buffer function has been implied in this group, leading to enhanced ATP-dependent responses including greater contractility, salt retention, and therapy failure [16, 18], as well as lower NO bioavailability [8, 16].

Furthermore, we are not well informed regarding the socio-economic circumstances of trial participants, which may have affected treatment failure [18]. Also, the trials are conducted in the USA, Africa, and India mainly, and data on European ethnic populations are scarce. In addition, trials rarely report outcomes for men and women separately. Finally, there are no available quantitative data on antihypertensive therapy to reduce morbidity and mortality in South Asians, and newer, nondrug techniques for blood pressure lowering in therapy-resistant hypertension such as renal denervation are of unknown efficacy in South Asians, while in African ethnicity patients, there was no significant difference with a sham procedure [117].

In summary, hypertension in persons of African or South Asian ethnicity is associated with high premature morbidity and mortality. Guidelines for cardiovascular risk management are increasingly adjusted to accommodate this higher risk. In addition, emphasis on public health approaches has been suggested with better models of prevention, screening, and delivery of care, with simplified, cheap treatment regimens needed and the use of a registry to treat and follow all hypertensives [118]. Where available, initial low-dose combination therapy might increase adherence and blood pressure lowering efficacy while reducing adverse effects [119]. Policymakers, physicians, and persons of African and South Asian ethnicity should be aware of the need for early screening for hypertension and cardiovascular risk factors and the vigorous preventive and therapeutic measures needed to reduce the high premature cardiovascular mortality in these ethnic groups.

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Cardiovascular Risk Factors in Migrants: Beyond the First Generation

21

Mohamed Bamoshmoosh

21.1 Introduction

Till the first half of the twentieth century, Europe was a source of emigrants to the USA, Canada, Australia and other parts of the world. After World War II, Europe became a net recipient of migrants to fill labour shortages of an expanding economy on a scale that could not be provided locally due to falling birth rates and ageing populations [1]. Europe now is a multi-ethnic, multicultural continent. On January 1, 2016, in the EU, there were 35.1 million foreign-born migrants and 20.7 million migrants from Europe itself [2]. Approximately 20% of all people living in Sweden are first (FG)- or second-generation (SG) immigrants [3–5]. In Luxembourg, 43.2% of the people are foreign residents from over 150 different nationalities [6].

Immigration to Europe changed over time. The first wave was mainly labour immigration followed by family reunification immigration. These migrants constitute the majority of FG immigrants. In the last decades, many European countries discouraged this kind of migration, even with financial incentives for remigration, but this could not be applied to EU citizens because of the legal-free movement within Europe [7].

Other FG immigrants were those who came in Europe as refugees, seeking political asylum, or students [8]. In the last two to three decades, there has been another 'uncontrolled' wave of migrants to Europe due to the conflicts in the south cost of the Mediterranean Sea and to the high unemployment and high demography of sub-Saharan Africa and South-East Asia.

At the same time, the number of FG immigrants' offspring is increasing and, in Belgium, constitutes 8.5% of the total population [8].

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In the scientific literature, FG immigrants' offspring are usually called second- or third-generation immigrants although this is not etymologically correct. It is incorrect to define as immigrants those who were born in the place where they live. In the UK and Ireland, the term 'migrants' is used only for recent arrivals; the more established migrant communities are referred as 'ethnic minority' or 'minority ethnic group' [1].

Usually in the European literature, SG migrants are those who were born in Europe, but with at least one parent foreign-born. The descendants of colonists who were born outside Europe, but of which both parents were native in Europe, when they come back to Europe, they are not seen as migrants, but as natives. There is also an intermediate group, indicated as 1.5-generation migrants, which includes children (aged 18 or younger) born abroad but brought to the host society before adulthood.

In the European medical literature, the term race is being abandoned in favour of ethnicity, which has 'a multi-faceted quality that refers to the group to which people belong, and/or are perceived to belong, as a result of certain shared characteristics, including geographical and ancestral origins, but particularly cultural traditions, religion and languages. The characteristics that define ethnicity are not fixed or easily measured, so ethnicity is imprecise and fluid' [9].

In Europe, research dealing with the health of FG immigrants is lacking, and the analysis of migrant health policies is still in its infancy [1]. Papers that report on the health of SG immigrants are even more rare. An important limit is related to the fact that European countries define migrants in different ways: by country of birth, citizenship, residency or relying on self-identification. For example, in France, where 'all citizens are equal', routine data collection systems refer only to citizenship and country of birth, and do not ask any question about ethnicity or religion. In Germany, no 'ethnic' data are collected officially, in part due to concerns that such information might be misused for discrimination [10]. In the Netherlands, the government addresses the health of migrants and establishes ethnic minorities under the broad umbrella of 'cultural differences' using the concept of 'allochtoon', (i.e. of foreign origin) which includes both categories [1, 10]. Other European countries collect data on self-identified ethnicity, although this comes with additional challenges, such as how to categorise ethnic subgroups [10].

Moreover self-identified ethnicity has other limits, as migrants themselves may be reluctant to reveal information on their migrant status or related variables for fear of discrimination and, in the case of undocumented migrants, even denunciation and deportation [10]. There are also difficulties in collecting information regarding age at migration, health, social and economic circumstances before and after migration and the access to the health-care systems in the new environment [11].

In Europe, other problems are related to the lack in routine data collection on migrant health, either through registry data or regular surveys because of legal and political obstacles. Only few European countries collect large-scale survey data on migrant health and health-care utilisation.

With all these issues, analysing SG migrants' health is, if possible, even more challenging. Moreover SG immigrants cannot be easily identified in administrative

health data [12]. It is difficult to collect information regarding SG migrants' ancestors when there are not probability linkage methods that use computerised probability-matching techniques, such as those developed in particular in Scandinavia, the UK and the Netherlands [13].

Many researches on SG immigrants rely on self-reported ancestor's ethnicity, parents' country of birth and in some cases using typical surnames of ethnic minorities. Finally it is not easy to interpret the results in cases in which SG immigrants are offspring of couples in mixed unions who are constantly increasing over the years. It is not clear how to approach the results of such subjects because of the huge number of potential categories [13].

Thus, there is indeed an interest in studying SG migrants' health. It helps in understanding some topics debated while dealing with FG immigrants' health issues. Does the 'healthy immigrant effect' persist beyond FG immigrants? How does the acculturation process interfere with SG immigrants' health? To what extent do environment, epigenetic and genetic factors influence the development of SG immigrants' diseases? This information could be useful to the health system personnel and to policy-makers to identify optimal approaches to prevention, diagnosis and treatment [14].

These are the assumptions that led us to undertake a research upon the available literature regarding European SG immigrants' cardiovascular diseases.

21.2 Healthy Immigrant Effect

The term 'healthy migrant effect' (HIE) was introduced in 1986 in the USA to explain the low 'adult migrant mortality paradox'. In the USA, it is also called 'Hispanic or Latino mortality paradox'. In Europe, the HIE is known as 'Mediterranean migrants' mortality paradox' [15].

The paradox was related to the fact that FG migrants, despite their often poorer socioeconomic position (SEP), fewer social supports, language barriers, being less likely to interact with the health system and occasionally facing discrimination in the new environment, had a mortality advantage over the host population [1, 11].

HIE can be explained by the fact that a selection process takes place in the country of origin of migrants, with the healthiest and sometimes also the wealthiest individuals being selected. Immigration criteria favour skilled subjects with experience in selected occupations and those with higher levels of education and exclude sometimes through a premigration medical examination those with chronic conditions. With these criteria, immigrants are healthier than the average citizen in both their home and host country. Another explanation for the HIE is that only those who are courageous and ambitious are the ones who leave their country to search for a better life. Others mention cultural factors including traditional diet (reduced smoking and alcohol consumption) and social support that might lead to protective health behaviour. More recently, Vandenheede et al. tried to give a more comprehensive explanation of the HIE with the 'migration as an unusually rapid health transition' hypothesis which claims that immigrants moving from less

industrialised countries to highly industrialised ones pass through an accelerated health transition, from treatable communicable to chronic non-communicable diseases. As soon as migrants arrive in the host country, they benefit from more hygienic environmental conditions and high-quality medical care, leading to a fast decline in communicable disease mortality, which are high upon their arrival. Simultaneously migrants will be confronted with risk factors for chronic disease mortality (cardiovascular (CV) disease being the most common), which however need substantial lag period to develop [8].

The HIE is noticeable in FG immigrants of both non-Western and Western origin and in both men and women. It is noteworthy that there are striking differences in the incidence of CV risk factors and CV events between immigrants from different ethnic backgrounds although in all immigrants the HIE wears off with the length of their stay in the host country [16]. To explain this last phenomenon, the convergence theory is used, which states that the duration of living of migrants in the host country affects their norms and values leading to health behaviours more similar to those of the host population and thus to more similar mortality and morbidity rates [8, 17].

The HIE is likely to be valid for the selective migration to North America and Australia and for the first migration waves to Europe.

However, in case there is an ease to migration that encourages also the less healthy to migrate, the HIE is no more present. This condition has been observed in Irish migrants to Great Britain. The FG Irish migrants had higher mortality rates than those of host population [18].

The HIE cannot also be taken into consideration for the non-selective immigration to Europe due to family reunification or to the massive undocumented migration of the last two to three decades.

Moreover, the first migration waves to Europe came from non-industrialised countries, which were back in their epidemiological transition with a low prevalence of CV risk factors (hypertension, diabetes, obesity, smoking, sedentary life) and CV diseases (myocardial infarction, stroke). In the last decades many, if not all, African and Asian countries are witnessing an accelerated epidemiological transition with high or very high prevalence of CV risk factors and CV events due to higher urbanisation, sedentary life and consumption of more refined and processed foods. This means that migrants now arrive in Europe with an already high burden of established cardiometabolic risk factors that does not allow the achievement of the HIE.

It is also noteworthy that in the last decades, some migrants from countries like Syria, Iraq, Afghanistan and former Yugoslavia have arrived in Europe very stressed due to the military conflicts in their countries with post-traumatic stress disorders, which negatively influence their health.

Portes-Rivas found that the HIE is present in SG migrants only if their ancestors had a relatively high level of socioeconomic achievements. In offspring of the large manual labour flow seeking employment in labour-intensive industries such as agriculture, construction and personal services, the HIE is no more observed [19].

21.3 Salmon Effect

Another explanation to the 'adult migrant mortality paradox' is the 'salmon-bias' hypothesis or 'unhealthy remigration effect'. It predicts that FG migrants return to their roots when they become ill, in order to be cared in a more familiar environment, leaving behind a migrant population with above-average health [20]. Although this hypothesis is intriguing, there are not sufficient data to prove it.

In Sweden, it was estimated that 10% of the immigrants who leave the country do not report their move to the authorities in order to keep an option open for remigration [15]. In Germany in 1981, remigration rates were around 5% for males aged 25–50 and 10% in males aged 50–65 years. These rates decreased to below 4% in both groups from 1990 onwards. In females aged 25–50, remigration decreased from 3% in 1981 to 2% from 1990 onwards and in those aged 50–65 from 6% to about 3% [7].

Recently Norredam et al. found that in a cohort of refugees and family-reunified immigrants, those with low, moderate and high disease scores had a tendency towards fewer emigrations to the country of origin or to any other country compared with migrants without disease. It was also observed that there was a gradient with higher disease severity associated with fewer emigrations. These results do not support the 'remigration bias' hypothesis, but rather suggest the opposite [20].

The salmon effect hypothesis could have been valid for European FG migrants who came from other Western countries. This hypothesis cannot be considered for European migrants from non-Western countries who have in the host country higher quality health services demanding extensive and prolonged care, which, in many if not all cases, have a tax-free access system. It is also difficult to imagine migrants leaving the host country where they have their family and properties [8, 20]. Moreover in the last decades, many non-Western countries from where migrants arrived to Europe are living dramatic political and economic situation, and it is difficult to consider them as places where a migrant who lived a whole life in Europe could return back to.

Anyway the salmon effect cannot be taken into account for SG migrants who in most cases do not have enough contacts in the country of birth of their parents and who consider the country where they were born as their own country.

21.4 Acculturation

Acculturation is a process by which immigrants (minority group) adopt the values, attitudes, beliefs, practices and lifestyle characteristics of the native-born (majority group) [21].

It is not easy to define the acculturation process in medical research because it is a multidimensional construct defined by factors such as engaging in culturally specific behaviours, language proficiency and knowledge of culture, history and identity [22].

In many papers, immigrant's acculturation is evaluated by using as proxy the 'language acculturation', measured by questions about the spoken language at home or with friends, preferred reading language and use of media. Another immigrant's acculturation proxy is immigrant's level of social contacts during leisure time with the host population versus that with people from the culture of origin [23]. Other studies have used surrogate measures for acculturation such as length of stay, family values, shopping preferences, leisure-time physical activity, risky health practices (smoking and alcohol consumption), changes in food habits and dietary practices [24].

Four types of acculturation models have been described: integration, assimilation, traditional and marginalisation.

In the first type, 'integration', an individual or the group, although maintaining the culture of origin, move to join the dominant society to become part of the larger societal framework. In this case immigrants adapt to both cultures and are able to function effectively in both cultures.

In the second type, 'assimilation', an individual or a group accept to lose their cultural identity and acquire that of the dominant group. In this case immigrants are completely absorbed into the dominant culture, and there is little evidence of their culture of origin.

In the third type, 'traditional', an individual or a group have a strong identity and voluntarily decide to keep loyalty to their customs and do not wish to attain cultural characteristics of the dominant group.

In the last type, 'marginalisation', immigrants are neither comfortable in their culture of origin nor to that of the host population; thus, they live at the margin of the society [24].

During the acculturation process, if immigrants are identified as a minority group and not as a part of the whole community, they may be surrounded by discrimination and consistently receive direct and indirect messages that they are not part of the society. In these conditions, chronic stress, which is a persistent and continuous exposure to a source of stress, increases, increasing mental health problems and CV risk factors, in particular hypertension.

Acculturation has a different impact according to the population studied and seems to have both positive and negative influences, implying that it does not lead to a healthier lifestyle per se [6].

In fact in SG non-Western ethnic minorities, women who acculturate tend to take over a wish to be thin, while men take over unhealthy habits such as eating snacks and fast foods and become obese [23].

It is not easy to study the acculturation process in SG immigrants, as it is necessary to consider both their level of acculturation and that of their parents. There is lack of children appropriate acculturation scales, and the few available studies have focused on reading achievements, problem-solving abilities in the school environment and the effect of acculturation on selected health risk behaviours for asthma, drug use and mental health [24].

While studying the acculturation process in young SG subjects, it is necessary to integrate it with all the issues related to adolescence, a period often marked by a rebellion against traditional values generally emphasised by the family and the

desire to engage in behaviours that hasten the acceptance into native-born peer group [25].

Usually SG more than FC immigrants are eager to acculturate and seek to emulate the behaviours of native-born subjects. FG migrants adopt less readily than SG migrants to Western behavioural practices because of their stronger identification with their original values. In most studies, SG migrants have CV risk factor prevalence rates more similar to that of the native-born than that of their parents [26].

Two factors must be considered while dealing with SG immigrants' acculturation. The first one is the 'dietary acculturation', which is when immigrants' families shift from traditional diets of vegetables, meats and whole grains to highly processed, high-fat and high-sugar foods, which are popular, cheap and readily available. This condition is also known as nutritional transition. FG and SG migrants may experience nutritional transition in the host country but in some cases also in their country of origin [27]. The nutritional transition predisposes to obesity alongside the 'obesogenic' environment of the industrialised Western societies and to the stress related of being part of a minority group [17, 28]. Keeping some elements of traditional identity and cultural values may be associated with healthy eating and thus with a protective effect against the development of obesity in childhood. For immigrants who move to a host country where poor dietary habits and sedentary lifestyles prevail, having low levels of acculturation could be protective against chronic diseases later in life. Conversely, increased risk of overweight and obesity may be linked to an energy imbalance through high levels of acculturation and adoption of unhealthy lifestyle habits [24]. Obesity in SG immigrants will be discussed thoroughly later in the text.

The second factor is the 'physical activity acculturation'. Hosper et al. in the LASER (Lifestyle in Amsterdam: Study among Ethnic gRoups) study evaluated the physical activity of first- as well as SG Turkish migrants in relation to their acculturation process. The results of this study showed that acculturated migrants were more physically active during leisure time. This positive association was explained by the fact that acculturated migrants were more exposed to health promotion campaigns, accepted the attitudes and norms towards physical activity of the host population and were better informed about the opportunities for physical activities. Greater cultural and social integrations were associated with increased physical activity during leisure time (odds ratio (OR) 1.85, 95% confidence interval (CI) 1.19–2.85, and 1.77, 95% CI 1.15–2.71, respectively). However, having children, living in a less attractive environment and being engaged in occupational physical activity were barriers for practising physical activity. These barriers were however more present in first than SG immigrants [29].

In another study, Zahner et al. in primary schools in Switzerland found that the participation in extracurricular sport activities or sports club participation (SCP considered as proxy for assimilation) of overweight children and of children with overweight parents was comparable to that of their normal-weight peers. Those who participated significantly less in SCP were children from migrant families (OR 0.31, 95% CI 0.20–0.48) and from inactive parents (OR 0.16, 95% CI 0.05–0.45); all $p < 0.001$. The results of this study showed that the participation in SCP was related

to migrants' integration into the new culture and/or to their adherence to the traditional way of thinking about physical activity and body shape. However, since low income is strongly associated with low leisure-time physical activity and that socioeconomic challenges may limit the ability of immigrants to engage in leisure-time physical activity, the authors invited sports organisations to offer recreational sports at moderate costs and with easy access [30].

Assuming that SG migrants will be more acculturated than FG migrants, it is expected that they will be more likely to adopt the attitudes and norms of the host population.

However, SG migrant morbidity convergence towards the rates of the host population shows that there is not only one single pattern; instead patterns are rather diverse and complex [26].

Hosper et al. in analysing behaviour risk factors in two generation (foreign-born and native-born) of two non-Western immigrant groups (Turkish and Moroccan) in Amsterdam (LASER study) found that there was a converging trend for smoking behaviour in Turkish men (OR 2.15, 95% CI 1.41–3.27) in FG and (OR 1.48, 95% CI 1.05–2.07) in SG; for overweight in Turkish women (OR 2.71, 95% CI 1.98–3.72) in FG and (OR 1.49, 95% CI 1.06–2.10) in SG; for overweight in Moroccan women (OR 2.71, 95% CI 1.80–4.08) in FG and (OR 1.54, 95% CI 1.05–2.25) in SG; and for physical inactivity in Turkish women (OR 1.78, 95% CI 1.21–2.61) in FG and (OR 0.82, 95% CI 0.56–1.17) in SG. The authors however found that there was also a clear reversed trend for smoking in Turkish women (OR 1.11, 95% CI 0.80–1.54) in FG and (OR 1.64, 95% CI 1.20–2.23) in SG and for overweight in Turkish men (OR 1.91, 95% CI 1.22–2.97) in FG and (OR 2.73, 95% CI 1.94–3.84) in SG. Regarding alcohol consumption, the converging trends were even less clear probably because of the religious and cultural norms towards these behaviour in Islamic cultures, which might be of great influence in first as well as SG migrants [26].

21.5 Cardiovascular Mortality

Mortality is a universal indicator for population health [31]. Unfortunately, health information systems in most European countries are generally not designed to identify people by migrant status. An exception in many countries is death registers, which often include indicators of migration [10].

It is well known that there are striking differences in mortality rates between immigrants with different ethnic backgrounds. In England and Wales, East Asian immigrants have the lowest rates for ischemic heart disease, while South Asians the highest. Caribbean immigrants and those with African origin have the highest mortality rates for stroke [32]. Mortality rates depend also on immigrants' country of residence. The same ethnic minority might have different mortality rates according to the country of residence [33].

While over the time a substantial decline has been observed in England and Wales in coronary and stroke death rates for native-born due to favourable long-term changes in population risk factors and treatment, this decline was smaller for

many migrant groups. So for the groups with higher mortality rates than the native population, this remained consistently so over the time, and for those who had lower mortality rates, the disparity increased [34].

Convergence theories speculate that mortality pattern of SG immigrants are more similar to that of the host population than that of their parents because of higher acculturation process, similar exposure to environmental influences and change of genetic heritage due to mixed marriages.

European literature however shows a rather diverse and complex pattern of mortality in SG migrants.

In England and Wales, the mortality of SG Irish, particularly those with both parents born in Ireland, is significantly higher than that of the host population in every social class, for most major causes of death. The excess of death was greater among women than men (standardised mortality ratio 114, 95% CI 106–122, and 111, 95% CI 103–119, for women and men ≥15 years, respectively). These patterns are very similar to those reported for FG Irish. Adjustment for social class, car access and housing tenure does not explain the excess in all mortality causes. Further analysis showed that although socioeconomic disadvantages lessened between generations of Irish people, mortality of the Irish third generation remained high compared to that of the host population (hazard ratio 1.26, 95% CI 1.02–1.56, and 1.49, 95% CI 1.13–1.97, for men and women, respectively). The authors attribute the responsibility for this phenomenon to two reasons: the ease to migration for Irish FG migration that encouraged also the less healthy to migrate and the negative perception of 'Irishness' of second and third Irish generation with consequent unfulfilled expectations and lack of control in these people's environments and lifestyles [18, 35].

On the contrary in Germany FG, Turkish migrants although with lower social status, lower SEP, higher occupational accident rate, higher rates of unemployment and less access to appropriate care have consistently 35–70% lower mortality rates than Germans of the same sex and age group. The data show also that there is no indication of increasing mortality for the second, partly German-born, generation although not fully integrated in the host country. SG Turkish immigrants have strikingly and persistently lower all-cause mortality rates than German population. The authors tried to explain this phenomenon with the fact that Turkish residents might eat a healthier (Mediterranean) diet than Germans, which, by reducing CV mortality, would result in a reduction in overall mortality. Another explanation could be that Turkish immigrants, more than Germans, may perceive a sense of cohesion in their lives, which is 'salutogenic' and protective. However, these data do not consider that for many chronic diseases (psychosomatic, psychiatric and musculoskeletal disorders), morbidity and disability are disproportionately higher than mortality and lower mortality rates in migrants do not necessarily indicate a better health [7].

In Switzerland where health care is regarded to be universal, Tarnutzer et al. found that FG Italians compared to native Swiss (reference group) had an advantage in the mortality risks especially in immigrants who were less acculturated (regional language was used as a proxy for acculturation). In fact, FG Italians, predominantly Italian-speaking men and women, had hazard ratios (HRs) of 0.89, 95% CI

0.88–0.91, and 0.90, 95% CI 0.87–0.92, respectively, while those who adopted the regional language had HRs of 0.93, 95% CI 0.88–0.98, and 0.96, 95% CI 0.88–1.04, respectively. Thus, the mortality advantage in FG Italians was greater in men than women, and with higher acculturation, it diminished in men and lost its significance in women. On the contrary, SG Italians had higher mortality risks: the respective HRs for men and women predominantly Italian-speaking were 1.16, 95% CI 1.03–1.31, and 1.06, 95% CI 0.89–1.26. In SG Italians who adopted the regional language, HRs were 1.10, 95% CI 1.05–1.16, and 0.97, 95% CI 0.89–1.05, respectively. The adoption in SG Italians of the regional language, thus more acculturated, attenuated the excess mortality [15].

Also De Grande et al. in the Brussels-Capital Region, where half of the population is of foreign descent, found similar data. The authors found marked mortality differences according both to the region of origin and to the migration generation. In fact the mortality of FG Maghrebins and Turks (M/T) was lower compared to that of Belgians (for men, mortality rate ratios (MRR) 0.30, 95% CI 0.25–0.61, $p < 0.001$; for women, 0.39, 95% CI 0.20–0.78, $p < 0.01$). On the contrary, 1.5-generation M/T and SG M/T mortality was higher than that of Belgians although not statistically significant. After controlling for education, the mortality risks of SG M/T and Belgians were comparable. In the same paper, the results did not show differences between the mortality risk of FG and 1.5-generation and SG sub-Saharan Africans and Belgians [36].

Similarly Vandenheede et al. in Belgium found that FG immigrants compared to the host population generally had a mortality advantage, which was more marked among non-Western than Western immigrants. In FG immigrants this advantage diminished with the length of stay in the host country. On the contrary in SG immigrants, the picture was gloomier with all-cause mortality as well as CV mortality disadvantages compared to Belgians. This disadvantage was more marked in non-Western than in Western immigrants but disappeared after control for SEP (education, housing status and employment status). The CV mortality rate ratios (MRR), respectively, for SG Western migrant men and women were 1.09, 95% CI 1.00–1.18, and 1.04, 95% CI 0.92–1.19, respectively, and, for SG non-Western migrant men and women, were 1.68, 95% CI 1.32–2.13, and 1.25, 95% CI 0.81–1.92, respectively. However, when settlement pattern and SEP were controlled for, the mortality disadvantage disappeared. MRR, respectively, for SG non-Western migrants men and women were 0.97, 95% CI 0.89–1.05, and 0.89, 95% CI 0.78–1.02, respectively, and, for SG non-Western migrant men and women, were 1.17, 95% CI 0.92–1.48, and 0.84, 95% CI 0.54–1.29, respectively [8].

In a more recent paper, the same Belgian research group analysed young-adult mortality inequalities. The authors found that personal rather than parental education determined the mortality rates, with high all-cause mortality rates among those with primary education and low all-cause mortality among those with higher education. For this reason the authors suggest that investing in education could be a public health strategy worth considering and that public health policies concentrating on adolescent health could benefit by approaching youth in school programmes [31].

21.6 Cardiovascular Disease

CV diseases and cerebrovascular disease are the leading causes of morbidity and mortality worldwide, and the World Health Organization estimates that 80% of this burden lies in low- and middle-income countries from where most immigrants came to Europe.

A recent review, of studies published between 2000 and 2014, suggests that populations such as Surinamese, Finnish, Turkish, Arab and South Asian, in their homeland, have a high prevalence of traditional CV risk factors, which is similar or greater, compared to that of the host country, only few immigrant groups being at lower risk [11]. It is also noteworthy that there are striking differences in the incidence of CV events and CV risk factors between immigrants from different ethnic backgrounds. East Asian immigrants (predominantly of ethnic Chinese) have the lowest burden while South Asians and Africans the highest [16].

Moreover the risk of CV diseases or stroke among FG immigrants, irrespective of their origin and eventually of the HIE, increases with longer duration in the host country with a trend towards convergence to values of their new country especially for SG immigrants [11].

Transmission of health risks between generations is clearly an important public health as well as an etiological issue, which should be studied to know how rapidly new environments affect disease risk [12].

Few European papers addressed the problem of CV diseases in SG immigrants.

In the 1999 Health Survey for England, an intergenerational change in CV risk profile has been found in Caribbean and Irish immigrants, identified by using country of birth and self-reported ethnicity. The national representative, although small-scale data, suggest that UK-born Caribbeans appear to lose the favourable lipid pattern of their parents related to the fact that older Caribbean migrants eat more traditional diets associated with a protective effect for CV disease, with high fresh fruit and vegetable content, while younger Caribbeans have greater energy intake from fat. Moreover, in relation to the general population, SG Caribbean men have higher rates of smoking and women higher rates of obesity. All the aforementioned issues indicate that an increase in CV disease rates in this minority group might be expected [12].

CV disease mortality has been found to be elevated also in Irish offspring although there are no significant differences in the CV risk factors between the Irish and the general population except that Irish men were more likely to smoke and had lower diastolic blood pressure and Irish women were shorter than women in the general population. Short stature in adulthood is an indicator of childhood nutritional status and predictor of CV disease in late adult life. The authors comment that the higher CV disease in UK-born migrants is related also to their persisting social and economic disadvantages [12].

In Sweden, Sundquist and Li studied the rates of first hospitalisation for CV disease or for death from CV disease in FG and SG immigrants using the MigMed database at the Karolinska Institute, which incorporates information on CV disease incidence data on the entire Swedish national population over a period of 15 years, and found a relatively complex, sometimes positive and sometimes negative role of

immigrant status in CV disease rates. The authors explain immigrants' higher or lower CV disease risk by a combination of genetic and environmental effects, which include risk factors for CV disease, low socioeconomic status and stress caused by lack of acculturation and discrimination. Few cases of CV disease were observed in SG immigrant women, and the risk tended to converge to that of the female Swedish population level. Only daughters of Finnish fathers or mothers had a significantly increased risk of developing CV disease. In SG immigrant men, the risks of developing CV disease were similar to those of their FG parents, with only small differences when the risk was calculated based on the sex of the immigrant parent. In particular, six groups of SG men had CV disease risk levels higher than those of their FG parents: men with fathers or mothers born in Denmark, Norway, southern Europe, central European countries, other eastern European countries and Turkey. The increased risk in FG immigrants from Finland declined in SG male immigrants though remained significantly higher than that in the Swedish reference group [4].

van Oeffelen et al. using nationwide registers (7,570,510 unique persons, of whom 944,280, 12.5% minorities) determined the incidence of acute myocardial infarction (AMI) in the Dutch majority population and in 17 minority groups living in the Netherlands. Overall, AMI among SG immigrant subgroups was observed to approach that of the ethnic Dutch, regardless of whether AMI among the same FG immigrant subgroups was lower or higher than the ethnic Dutch population. There were no differences in the intergenerational changes between men and women. In particular, among all European minority groups, except for Italians, the difference in AMI incidence with the majority population did not change or changed unbeneficial over generations. The borderline statistically significant lower incidence in Swiss FG minority in SG converged towards the incidence of the majority population. In minorities from Belgium, Germany and especially Poland, the similar or higher incidence in the FG exceeded that of the majority population in SG immigrants. Minorities from former Dutch colonies (Netherlands Antilles, Suriname) experienced a beneficial change over generations probably because their offspring might have had a stronger social cohesion with the majority population and better language proficiency, which might have improved their ability to adequately use health-care facilities and adhere to prescribed therapy. Among East Asian minorities, Chinese turned from a lower incidence in the FG to a higher incidence in the SG; the opposite occurred in Indonesians. This study was the first one where SG Chinese minorities showed a higher incidence of AMI compared to the majority population. The authors suggested that the healthy behaviours (e.g. traditional dietary patterns) from China might have been lost, while unhealthy behaviours (e.g. physical inactivity and obesity) might have been adopted [37].

21.7 Venous Thromboembolism

Zöller et al. studied ethnic differences in the incidence of venous thrombosis (VT) and pulmonary embolism (PE) in Sweden by using the MigMed2 Database. They found that FG immigrants, both male and female, had usually a lower risk of VT

and/or PE than Swedish-born individuals, although there were some differences according to the country of birth of immigrants. The authors analysed whether the risk for VT and/or PE differed between FG and SG (born since 1932) immigrants. Their hypothesis was that if there were differences in the risk for VT and/or EP between the FG and SG of immigrants, it was likely that environmental factors in the new country have an influence. In case FG and SG had a similar risk, genetic factors were likely to play an important role. The results of the study showed that in SG immigrants there were some differences in the prevalence of VT and/or PE risks. The lower risk for PE in some FG immigrant groups was not replicated in the SG, and in certain SG immigrant groups, the risk of VT/PE was similar to that of Swedish-born individuals. Some SG immigrant groups had reduced risks for VT but not for PE. The authors thus concluded that this complex picture was indicative of a combination of ethnicity-related inherited and acquired venous thromboembolism risk factors that play an important role in the aetiology of VT and/or PE [3].

21.8 Hypertension

Hypertension is by far the most common underlying CV risk factor and is a major health problem globally. Hypertension is highly prevalent in immigrants in particular among population of African descent. Few papers addressed the presence of hypertension in SG immigrants in Europe.

Agyemang et al. [38] in a review of cross-sectional data of papers published from 1980 to 2003 investigated whether ethnic variation in blood pressure (BP) in children of ethnic minorities reflected those of the adult population in the UK and found that, unlike in adults, ethnic variations were small.

African descent boys had generally similar or lower mean systolic (SBP) and diastolic BP (DBP), while African descent girls had lower mean SBP in all papers except one where they had a higher mean DBP. The BP levels reported in children from African decent compared to that of White children was still more unexpected in face of their high BMI. The authors suggested that BP levels changes have a quicker rise at middle age and favour that it may be the effect of environmental (residing countries' national context in terms of opportunities in life, lifestyle factors, stress and social pressure of having a dark skin) or an interaction between genetics and environmental factors rather than only genetic factors per se, because it was hard to imagine genetic factors where the effect is delayed to later adult life. They thus suggested that high BP in African origin population, with appropriate interventions, is a controllable problem.

When children of South Asian origin were combined, there were no significant differences in the mean BP between South Asians and White subjects. Only when South Asian subgroups were separated, some differences came to light. Pakistani boys had higher mean SBP and mean DBP, Pakistani girls higher mean DBP, Indian boys higher mean SBP and Bangladesh girls higher mean DBP. The findings of this last study highlight the importance of studying South Asian subgroups separately rather than mixing them as one homogeneous group.

In the single study where children of Chinese descent were included, Chinese boys and girls had significantly higher age and height-standardised mean DBP despite lower BMI compared to that of the general population.

The authors suggested that these results could be explained by differences in methods of measurement of BP; variation in age, sex and body shape; and weight findings and invite for large-scale epidemiological research that tracks changes of BP from early life to late middle age [38, 39].

These data were confirmed in a more recent paper of Harding et al. in British adolescents in the Medical Research Council Determinants of Adolescent Social Well-being and Health (DASH) school study. In adolescents, the ethnic-specific patterns in BP in adulthood were not observed. Apart from a higher DBP in Indian girls, BP in minority groups was generally lower than that of their White UK counterparts. Unlike African American girls, late puberty in minority groups was not associated with higher BP. The authors suggested that adolescence might be the key time of life at which to minimise ethnic differences in BP [40].

More recently Harding et al. published a paper on ethnic differences in BP, and because BP began in adolescence, they suggested the need for early prevention to avoid adverse CV disease risks in later life. The authors found that among boys, SBP did not differ significantly by ethnicity at 12 years of age but the greater average increase per year for Black Africans compared with Whites led them to have significantly higher SBP at 16 years of age ($p < 0.05$). DBP in boys showed earlier divergences and increasing disparity, with significantly higher DBP than Whites from 12 years of age ($p < 0.05$) for Indians, from 14 years of age for other South Asians ($p < 0.01$) and from 15 years of age for Black Africans ($p < 0.05$).

Among girls, ethnic differences in mean SBP were not significant, but the slopes reflected differential age trends. Between 12 and 16 years of age, SBP increased among Black African and Black Caribbean girls, but hardly changed among White girls. In girls, age-specific differences in DBP were more marked. At 12 years of age, DBP was lower among Black Caribbean ($p < 0.05$) and African ($p < 0.01$) girls than in White girls, but the faster rise led to similar levels by 14 years of age. Indian girls had significantly higher DBP from 13 years of age ($p < 0.05$) and other South Asian girls ($p < 0.05$) from 15 years of age. BMI, height and leg length were independent predictors of BP, with few ethnic-specific effects. Socioeconomic disadvantage had a disproportionate effect on BP for girls in minority groups [41].

21.9 Diabetes

Diabetes is considered to be one of the major public health challenges worldwide. When migrants arrive in the host country, especially those who migrate from less to more economically developed countries, they undergo an important shift in environment and lifestyle. Migrants become more exposed to sedentary activities and energy- dense diets high in salt and fat. In some group of immigrants, especially those from South Asia, the intrauterine environment, small birth weight, high insulin resistance, a diabetes-prone body composition and rapid decline of pancreatic

B-cell function seem to be particularly important contributors to the increased diabetes risk. These are some of the causes of the relatively high diabetes mortality in some migrant groups [42].

Although immigrants' offspring are more exposed than their parents to pressures of 'obesogenic' society, few studies investigated specifically SG diabetes mortality and morbidity.

Li et al. by using the Swedish Hospital Discharge Register between January 1, 1964, and December 31, 2007, found that FG immigrants (recognised by their country of birth) had both increased and decreased risks of hospitalisation for type 2 diabetes mellitus (T2DM). According to the authors, the observed variation in hospitalisation for T2DM was related more to ethnic environmental factors such as obesity, dietary fat intake, smoking and low levels of physical activity than to ethnic genetic factors. In fact the most interesting finding of the study was that the increased and/or decreased risks of hospitalisation for T2DM among certain FG immigrant groups mainly disappeared in SG migrants except for subjects with Finnish or former Yugoslavian parents (i.e. people who had at least one parent from Finland or Yugoslavia). The authors thus invited to do research to identify the ethnic environmental factors that protect or provoke T2DM [5].

Whincup et al. found that the predisposition for T2DM in South Asians appears before adult life. Their data show that compared with Europeans, South Asian subjects (83% SG, mean age 15 years) had higher mean fasting insulin levels (percentage mean difference 17.2%, 95% CI 7.2–26.1%, $p = 0.001$), higher mean fasting glucose (mean difference 0.19 mmol/L, 95% CI 0.08–0.29 mmol/L, $p = 0.0005$) and higher prevalence of impaired fasting glucose (≥6.1 mmol/L) (5.6% vs. 1.5%, OR 3.9, 95% CI 1.4–10.9, $p = 0.004$). The observation of differences in fasting glucose concentration as well as in insulin level and insulin resistance at 13–16 years according to the authors suggests that the emergence of South Asian-European differences in T2DM is well advanced by adolescence. Although South Asian children tended to have slightly higher indices of adiposity than Europeans, the differences in glucose and insulin levels persisted after adjustment for adiposity [43].

Ehtisham et al. in studying healthy South Asian compared to White European adolescents (mean age 15–16 years) found similar differences regarding insulin sensitivity (52.4 vs. 58.9%, $p < 0.05$) in particular in girls. These authors however found also ethnic differences in body fat (girls, 30.6 vs. 26.0%, $p < 0.005$; boys, 20.8 vs. 14.8%, $p < 0.001$) and central fat (waist-to-height ratio in girls, 1.36 vs. 1.25, $p < 0.001$; boys, 1.52 vs. 1.42, $p < 0.001$) suggesting that body fat might contribute to the increased risk of developing T2DM [44].

21.9.1 Type 1 Diabetes Mellitus

Ji et al. in Sweden analysed the ethnic differences in incidence of type 1 diabetes mellitus (T1DM) in SG immigrants (1,050,569 children) and in foreign-born adopted children by Swedes (51,557 children). The result of this study showed a decreased incidence of T1DM in all SG immigrants except in those with Finnish

parents who however had a non-significant increase. Overall standardised incidence ratio (SIR) of T1DM was 0.71, 95% CI 0.68–0.73, for those with only one parent from abroad, and it decreased to 0.57, 95% CI 0.53–0.60, for those with both parents from abroad. SG offspring with one parent from Finland had a SIR of 1.01, 95% CI 0.96–1.06, and those with both parents from Finland a SIR of 1.07, 95% CI 0.97–1.18. Although foreign-born adoptees had a similar environmental, cultural and lifestyle exposures compared with the native Swedes, with the only difference of genetic background, they had a decreased risk for developing T1DM (SIR = 0.33, 95% CI 0.26–0.40) even if it was not significant for all group of adoptees. The authors suggest that ethnic differences of genes might play an important role in the development of T1DM because the incidence of T1DM among SG immigrants and that of foreign-born adoptees is similar to that found in the courtiers of origin of their parents [45].

Hussein et al. using data from the Migration and Health Cohort, which is the result of linkage of a variety of Swedish national health and demographic registers between 1992 and 2009, confirmed the results of Ji et al. that SG children (0–18 years) usually have a decreased risk of T1DM compared to native Swedes (adjusted incidence rate ratios (IRR) of 0.54, 95% CI 0.47–0.63, and 0.71, 95% CI 0.61–0.83, respectively, for offspring of mothers living in Sweden for less than 5 years and for 11 years or more). However, SG children born in Sweden from immigrant mothers form Eastern Africa have a higher risk to develop T1DM, and this depended to the mother's duration of stay in Sweden. In fact offspring of mothers from Eastern Africa living in Sweden for 11 years or more had a doubled risk of T1DM compared to native Swedes (adjusted IRR 2.34, 95% CI 1.30–4.24), while the risk of T1DM of offspring of mothers living in Sweden less than 5 years was similar to that of native Swedish (adjusted IRR 1.03, 95% CI 0.72–1.46). According to the authors, this supports the hypothesis that immigration to Sweden in genetically susceptible individuals contributes to the development of T1DM. This phenomenon could be associated with the exposure to new environmental factors, that, due to the cold climate, increase the time spent indoors and might facilitate the spread of viral infections, alongside with the introduction of certain nutrients, such as cow's milk and gluten [46].

21.10 Obesity

While childhood obesity rates in developed countries are plateauing, in the developing countries, they are progressively increasing, at first in urban areas and lately also in rural areas [47]. Childhood obesity has important public health consequences with serious implications for the sustainability of health-care systems. Obesity is the most important risk factor for hypertension; it is associated with abnormal lipid profiles and predicts the occurrence, before or during early adulthood, of type T2DM, heart disease and a range of other comorbidities. Its consequences extend beyond its health effects such as later socioeconomic status (SES) [48].

Response to environmental 'triggers' of obesity may vary among individuals suggesting that environmental rather than genetic factors are the major drivers for ethnic differences in obesity. Offspring of ethnic minorities who engage in local culture more than their parents are susceptible to the 'obesogenic' environment of the host country. Children growing up in immigrant families with low income and in disadvantaged communities with a prevalence of poor lifestyle habits, including poor diet and physical inactivity, may be at higher risk for developing obesity. Poor family functioning and communication have been found to be strongly associated with childhood obesity especially among migrants [47, 49].

Moreover cultural perceptions regarding overweight and obesity may also play a role in increasing the prevalence of overweight and obesity among immigrants' offspring. In most developing societies and in FG immigrants, having overweight or obese children was and still is synonymous of prestige, good healthy living and beauty.

Immigrants' obesity is used as a proxy for acculturation with twofold greater obesity risk among those with high vs. low acculturation levels. In FG immigrants, obesity is minimised by healthier behaviours in countries of origin and by cultural protections afforded by supportive social networks. However, these beneficial effects weaken with the length of residence in the new host country [49].

There are several papers that analysed obesity patterns in SG immigrants.

In the Netherlands, Fredriks et al. analysed the prevalence of overweight and obesity, defined by the International Obesity Task Force (IOTF) cut-off points, in 14,500 children of Dutch origin, 2904 of Turkish orign and 2855 of Moroccan origin, aged 0–21 years. The category overweight included also that of obesity. This study found high prevalence of overweight and obesity in all children especially in those of Turkish and Moroccan origin. The average overweight (obesity) prevalence across age groups for Turkish boys and girls were 23.4% and 30.2% (5.2% and 7.2%), for Moroccans 15.8% and 24.5% (3.1% and 5.4%), for Dutch living in large cities 12.6% and 16.5% (1.6% and 2.8%) and for the remaining Dutch children 8.7% and 11.3% (0.8% and 1.4%), respectively [50].

Harding et al. by analysing the data of the DASH study found that generation status was an independent correlate of obesity with FGs being far less likely to be obese than SGs (OR adjusted for anthropometry, SES and adolescent behaviours: girls OR 0.62, 95% CI 0.42–0.91; boys OR 0.56, 95% CI 0.40–0.80). In particular, in models adjusted to examine the effect of generational differences within minority groups, Black Caribbean girls and White Other boys, both born in the UK, were more likely to be overweight (OR 1.57, 95% CI 1.12–2.19, and OR 1.49, 95% CI 1.02–2.18, respectively) and obese (OR 1.89, 95% CI 1.17–3.06, and OR 2.80, 95% CI 1.66–4.72, respectively) compared to their White UK peers. This effect of higher risk was not observed in UK-born Black African girls.

The authors found also that apart from Indians, ethnic minorities born in the UK were more susceptible and generally more likely to engage in poor dietary behaviours than their White UK peers. For example, in ethnic minorities born in the UK, skipping breakfast was associated with overweight (OR 1.66, 95% CI 1.38–2.01, and 1.53, 95% CI 1.27–2.84, respectively, for girls and boys) and obesity (OR 1.74,

95% CI 1.30–2.34, and 2.06, 95% CI 1.57–2.7, respectively, for girls and boys). Offspring obesity was also related to parental lifestyle, which was *generally more adverse in* White UK and White Other groups than other ethnic groups. Maternal smoking was associated with overweight (OR 1.28, 95% CI 1.03–1.59, and 1.33, 95% CI 1.07–1.65) and obesity (OR 2.04, 95% CI 1.49–2.79, and 1.63, 95% CI 1.21–2.21), respectively, for girls and boys. Maternal overweight was related to overweight and obesity among girls (OR 1.54, 95% CI 1.13–2.09, and OR 2.01, 95% CI 1.29–3.13, respectively), but only to obesity among boys (OR 2.47, 95% CI 1.63–3.73). The effect of paternal influences varied by gender: paternal overweight associated with obesity among girls (OR 2.32, 95% CI 1.29–4.17) and paternal smoking with overweight among boys (OR 1.38, 95% CI 1.11–1.71). The authors thus conclude that combined adolescent- and parent-focused interventions should be considered in order to reduce obesity in ethnic minorities [48].

Hosper et al. by using the cross-sectional data of the LASER study evaluated the health transition across generation of Turkish and Moroccan men and women. SG women were less often overweight than FG women, while the opposite occurred in men.

The authors considered several potential determinants of overweight: socioeconomic (level of education, position on the labour marker, occupational status), socio-demographic (marital status, having children), acculturation (orientation towards the majority culture versus culture of origin, social contacts), migration-related factors (from where migrants come and the main reason for migration) and religion (importance of religion).

The results of the research showed that women had more significant generational differences in SEP than men, with SG women being more educated than FG women.

SG women were also less often overweight than FG women (21.8% vs. 45%; OR = 0.53, 95% CI 0.19–0.90). Differences in socioeconomic factors seem to partly account for this overweight difference. In fact the association between generational status and overweight weakened when socioeconomic factors were added to the model (OR = 0.77, 95% CI 0.40–1.46). On the contrary, SG men had a reversed pattern; they were more overweight than FG men (32.7% vs. 27.8%; OR = 1.89, 95% CI 1.09–3.24). This association did not change when the potential determinants were added to the model.

The authors suggest that, as indicated also by other studies in developing countries, improving the SEP of women may help in reducing their overweight. Other explanations could be related to the fact that more highly educated parents might be more aware of and monitor the lifestyle of their daughters and that young women and adolescents may be more exposed to the pressure from the society to be thin. It has also been suggested that biological as well as social processes, related to the lifelong effects of better living conditions during growth, may have a relevant role in making women less prone to adiposity. Marital status and having children were associated with overweight in women, but not in men. Less SG women were married and had fewer children. Conversely SG boys with a higher SES, as seen also in studies in developing countries, were more often overweight than boys with a low SES. In this paper, the migration-related factors and religion were not associated

with overweight and could not account for the generational differences. Thus, the authors conclude that socioeconomic factors seem to explain the differences in overweight between generations in women, whereas for SG men, the same determinants did not necessarily imply a healthier lifestyle [29].

In Luxemburg, Alkerwi et al. performed a cross-sectional analysis by comparing the prevalence of CV risk factors between Portuguese immigrants and native Luxembourgers. They found that between these two groups, there were not any statistically significant differences except for overweight/obesity (65.33% vs. 56.15%, $p = 0.012$). In particular Portuguese compared to Luxembourgers were more overweight/obese in unadjusted model (OR = 1.42, 95% CI 1.01–1.99, $p = 0.043$), in age- and gender-adjusted model (OR = 2.08, 95% CI 1.42–3.03, $p < 0.0001$), in SES adjusted model (OR = 1.83, 95% CI 1.16–2.90, $p = 0.01$) and in physical activity adjusted model (OR = 1.91, 95% CI 1.19–3.08, $p = 0.007$). However, this difference was attenuated and statistically disappeared after controlling for dietary factors (OR = 1.57, 95% CI 0.93–2.65, $p = 0.09$) indicating the importance of the dietary practice in the development of overweight and obesity among Portuguese subjects. In light of these findings, the authors examined the relationship between the overweight/obesity status and the acculturation process among FG and SG Portuguese. As proxy variables of acculturation, they used immigration generation status, language proficiency/preference and proportion of life spent in Luxembourg. As expected, mean acculturation score was substantially higher in SG than FG (3.86 ± 0.35 vs. 1.75 ± 0.59, respectively). The overweight/obesity-generation status was also significantly different in the unadjusted model with FG Portuguese being more overweight/obese than SG (OR = 2.68, 95%CI 1.09–6.56, $p = 0.028$). Although there was a tendency of lower risk to overweight/obesity with higher acculturation, none of the acculturation markers, both individually and taken together as a score, were statistically significant after controlling for age and gender probably because the sample of SG Portuguese was small [6].

More recently Martin et al. explored the differences in the prevalence of hypertension and dyslipidaemia among overweight/obese and normal-weight children/adolescents (40921) of three different ethnic groups living in Central Europe (Germany, Austria and Switzerland) based on the country of birth of both parents (Central European, Germany, Austria and Switzerland; South-Eastern European, Turkish; and Southern European, Spain, Portugal, Italy, Greece, Cyprus and Malta).

Turkish obese/overweight children/adolescents had a significantly higher prevalence of hypertension only relative to their Central European (OR 1.14, 95% CI 1.02–1.27, $p = 0.0446$), but not to their Southern European peers (OR 1.19, 95% CI 0.99–1.42, $p = 0.14$). No significant ethnic difference in the prevalence of hypertension was found among normal-weight children/adolescents.

This study showed that there were not any significant differences in the prevalence of dyslipidaemia among the overweight/obese subjects of the three ethnic groups. Central European normal-weight children/adolescents had a higher prevalence of elevated triglycerides than their South-Eastern European and Southern European peers (OR 0.54, 95% CI 0.37–0.77, and OR 0.55, 95% CI 0.32–0.94, respectively) [51].

Some papers analysed differences in metabolic syndrome (MS) prevalence in SG. MS seems to increase with the severity of obesity and identifies individuals at increased risk of developing T2DM. Integral components of MS include abdominal obesity, glucose intolerance, hypertension, reduced HDL cholesterol and increased triglycerides.

Kolsgaard et al. in the Oslo Adiposity Intervention Study found that MS (defined as the presence of at least three abnormal values of waist circumference, BP, fasting triglycerides, fasting glucose and HDL cholesterol) is more frequently present among overweight and obese children and adolescent immigrants (most of them SG with very few 1.5-generation immigrants) than among native Norwegians. This difference was found even after adjustment for age, sex and degree of obesity (20.8 vs. 30.6%; OR = 2.2, 95% CI 1.05–4.77). The prevalence of MS increased with increasing severity of obesity and reached 50% in severely obese immigrants and 30% in severely obese Norwegians ($p = 0.42$). Among the overweight subjects, MS prevalence was 23.5% among immigrants and 19.4% among Norwegians ($p = 0.73$). The authors thus suggest that ethnic minorities may have an increased sensitivity to adiposity and need more aggressive prevention and treatment than their Norwegian counterparts [52].

An increased prevalence of MS [defined according to the WHO criteria: obesity and disturbed glucose metabolism (either elevated R-HOMA levels or impaired fasting glucose or impaired glucose tolerance) and either hypertension or hyperlipidaemia] in overweight and obese immigrant children was found also in Berlin. MS was detected more in Turkish (40.4%) than in German (27.3%) children (OR = 1.62, 95% CI 1.07–2.47) [53].

In the Netherlands, Van Vliet et al. found that there were important interethnic differences in the prevalence of cardiometabolic risk factors in an overweight/obese paediatric cohort. Turkish children showed a higher prevalence of cardiometabolic risk factors relative to their peers of other ethnicities. In particular Turkish as compared to Moroccan children (1.5 or SG immigrants) had higher prevalence of MS (22.8% vs. 12.8%), low HDL cholesterol (37.9% vs. 25.8%), hypertension (29.7% vs. 18.0%) and insulin resistance (54.9% vs. 37.4%; all $p < 0.05$). Turkish children had also higher, but not statistically significant, prevalence of the cardiometabolic risk factors than Dutch native children, except for mean standardised BMI ($p < 0.05$) [54].

It is well known that South Asian adults generally have a higher level of fat per unit of BMI compared with Whites and the relationship between a given degree of adiposity, particularly central adiposity, and CV risk is strong. In an interesting paper, Stanfield et al. found that the characteristic differences in body composition observed between adult South Asians and White European children and adults were already apparent in early infancy suggesting that they are determined via either genetic and/or intrauterine mechanisms, rather than a consequence of behaviours or diet in childhood or at older ages. In fact in early infancy (8 weeks of age), South Asians born in the UK had less fat-free mass (FFM) than White Europeans (0.34 kg

less, 95% CI 0.15–0.52, $p = 0.001$), with a considerably weaker indication of them also having more fat mass (FM) (0.02 kg more, 95% CI 0.14–0.18, $p = 0.789$). These differences persisted even when account was taken of the overall smaller body size of South Asian infants: infant weight (FFM 0.16 kg less, 95% CI 0.25–0.06, $p = 0.002$; FM 0.16 kg more, 95% CI 0.06–0.25, $p = 0.002$) or infant length (FFM 0.20 kg less, 95% CI 0.36–0.04, $p = 0.016$; FM 0.07 kg more, 95% CI 0.09–0.23, $p = 0.391$) [55].

Finally some papers analysed the importance of dietary changes between FG immigrants and their offspring, suggesting that this difference may be responsible for modifying the obesity prevalence in the two groups.

Sharma et al. found that younger UK-born (SG) men had significantly greater intakes of energy and all macronutrients than African Caribbean (AfC)-born men, with similar but smaller differences between women. AfC-born migrants had significantly lower percent of energy from total and saturated fat than younger SG subjects (31.3% vs. 35%, difference in total fat 3.7%, 95% CI 2–5%; 10.9% vs. 12.6%, difference in saturated fat 1.7%, 95% CI 1–2.5%). AfC-born group also ate more fruit (+84 g day 1, 95% CI 36–132 g day 1) and green vegetables (+26 g day 1, 95% CI 3–49 g day 1). Compared with UK national data, AfC subjects consumed some 7% and 5% less energy from total fat and saturated fat, respectively, with over 9% more from carbohydrate. However, there was marked convergence towards the national average in the youngest SG groups. In this study, an interesting paradox illustrating cultural adherence was found. Those eating a traditional diet, although had lower incomes, were choosing to spend more of their income on the more expensive Caribbean foods [56].

Similarly Anderson et al. in a cross-sectional study in Scotland found a generational evolution of diets of South Asian and Italian migrants.

South Asian migrants as soon as they arrive in the host country develop adverse dietary elements, which are however modified in subsequent generations. FG Italians have a cardioprotective diet, but it deteriorates in subsequent generations. The authors suggest that these data predict that British-born South Asian subjects might have lower rates of CV diseases compared to FG South Asian subjects, whereas SG Italians might have CV disease rates converging towards those of the host population [57].

In a review of dietary habits in South Asians, Holmboe et al. found that the picture of dietary change is complex, depending on a variety of factors related to country of origin, urban/rural residence, socioeconomic and cultural factors and situation in host country. However, the main dietary trend after migration is a substantial increase in energy and fat intake, a reduction in carbohydrates, a switch from whole grains and pulses to more refined sources of carbohydrates, resulting in a low intake of fibre, an increase in intake of meat and dairy foods and in some groups also a reduction in vegetable intake. The results of the review suggest that these dietary changes may contribute to the high prevalence of obesity, T2DM and CV diseases in this ethnic minority group in Europe [27].

21.11 Comments

Europe needs migrant labour in many sectors, in particular in the health and social ones to fill low-skilled jobs, such as those providing basic domestic care for sick and elderly people [58]. However, since the 1990s, in several European countries, especially after the recent economic downturn, anti-immigrant parties have made electoral gains with hostile reception for asylum seekers and economic immigrants and a rise in anti-Muslim rhetoric.

While the first waves of immigrants were well accepted, more recent immigrants find difficulties in being integrated and have the feeling that they are refused. This negative perception is now affecting also the first waves of immigrants.

SG immigrants, who were born in Europe, should not be involved in such disputes. Although SG immigrants come from ethnic minority groups, they should be considered an integral part of the society through legal and policy requirements to reduce discrimination and promote equity [33].

A way to achieve this goal is also by taking care of their health. Unfortunately information about the health of migrants in Europe is patchy, and few researches deal with FG as well SG health issues limiting the possibility to monitor and improve their health [58].

The EU has funded several projects designed to improve immigrants' data collection by including minimal additional requirements on existing data collection processes [10, 58]. It is however necessary to move from country of birth, the most commonly available proxy measure for ethnicity, that will not be valid for most descendants of migrants, to other measures of ethnic group, able to track changes across several generations. In the EU, the high costs of fieldwork implementation in a period of budgetary constraints, potential difficulties in accessing ethnic minorities, insufficient researcher's experience and sometimes also lack of interest are some reasons for the overall lack of FG and SG immigrants' health examination surveys. In many ways, these issues are similar to those applied to women until recent times [33, 59, 60].

At the moment, for most EU countries, data on CV diseases among ethnic minority populations are scarce due to incompleteness, variability in the use of ethnic coding and lack of provision within information technology systems. Moreover the lack of consensus on ethnicity indicators in available European data sources limits their use for producing comparable estimates of the burden of CV diseases across ethnic groups and between different European countries [59]. In fact sound data can only be obtained by assessing directly CV risk factors with the adoption of standardised forms to make results comparable.

In Europe, there is a scarcity of immigrants' large-scale research, e.g. cohort studies and trials [33]. Recent papers highlighted the exclusion of ethnic minority groups from European large majority of randomised controlled trials, one consequence of which is the significant lack of information on ethnic disparities in the incidence of CV disease. While the Eighth Joint National Committee guidelines gave specific information on the management approach to hypertension in Black

patients, in the guidelines jointly released by the European Society of Hypertension and the European Society of Cardiology, ethnicity is not covered [61].

Unfortunately Europe has not a law equivalent to that of 1993 US NIH Revitalization Act, which requires investigators to include in their studies ethnic minority populations and women unless there is scientific reason not to do so. In the USA, it is not legally, ethically or scientifically acceptable to exclude ethnic minorities from a research.

Building up databases, including people from minority ethnic groups, is certainly a major and expensive endeavour that will take many years, but it is a way to let European research become equitable, ethical and not institutionally racist. By doing so, it is possible to improve the health and health care not only of ethnic minorities but also of the entire population. In fact research on ethnic group differences and similarities may potentially help advance the understanding of the relationships between risk factors and CV diseases [13, 60].

Overall population health improves if all parts of the population benefit from the health system. It would be deleterious if SG migrants might be subject to direct and indirect discrimination [1]. Not addressing the health needs of FG and SG immigrants, which is against European law, may increase their health inequalities. Indeed ethnic minority health inequalities can be reduced by removing physical, behavioural and cultural barriers to health care, by reducing disparities in the quality of care, by designing public health strategies and with interventions to reduce health risks at the level of communities [62].

Because SG immigrants have a higher prevalence of CV risk factors, in order to narrow inequalities, it is necessary that the minorities with the highest risks of disease improve quicker than the more advantaged ones; otherwise, inequalities will widen or, at best, remain unchanged. However, it is difficult to achieve this goal, and it presents a formidable challenge to public health research and practice [63].

A way to achieve this goal is, for instance, to screen African or South Asian ethnicity subjects at a younger age, to use new approaches to estimate their risk, to start treatment at lower thresholds, to lower BP therapeutic goals, to lower obesity cut-offs and to intensively monitor them to reduce their high premature mortality [64].

Health inequalities should also be addressed by targeting the social determinants of health, which are the circumstances in which people are born, grow, live and work and, in particular, by improving the SEP of ethnic minorities. SEP depends mainly on material conditions like income, on education and on access to valued personal activities (e.g. work) [65].

Vandenheede et al. found that European SG immigrants' mortality disadvantages are due to a lower SEP and urged policy-makers to move beyond targeting only public health and to focus on the different deprivation and integration areas [8].

In fact the diverging trends of SG migrant's health are multifactorial including the background history of their parents, pace of acculturation, family and community resources and economic and cultural characteristics. A high percentage of SG youth who live in the more deprived neighbourhoods have a high dropout rate at school and consequently experience problems in finding a job and in achieving a good social position in society. SG youth have also problems in finding a job not

only because of lack of diplomas but also due to discrimination [36]. An important ingredient of SEP is education, and more often researchers invite public health policies concentrating on adolescent health to invest in education [36].

Another issue related to SEP is that SG immigrants have higher rates of psychological distress and depression, which have been associated with higher risks of heart disease, stroke and all-cause mortality, increased risk of drug use and hazardous and harmful drinking [66].

Understanding the reasons behind the excess of CV risks in FG as well SG immigrants is crucial because, with the ageing of migrant populations, it could help prevent the overburdening of the majority of European health-care systems which offer almost free-of-charge access to emergency medical care [67].

In fact far from being money saving, the underutilisation of primary care services might produce in the long period more rapid disease progression, translating into higher costs.

Finally while the effect of environmental, dietary and lifestyle changes alongside with unhealthy behaviours on the development of intermediate CV risk factors and CV diseases in FG as well SG immigrants is quite well known, the action through which genetic and/or epigenetic factors influence CV risk is not yet completely understood. A clustering of different genetic defects or polymorphisms, and epigenetic changes, which are interaction between genetic heritability and environment, occurring during gestation or in the early period of life, seems to play an important role in influencing the prevalence of CV diseases in SG populations also at an intergenerational level [68].

Although the number of studies covering CV diseases in SG immigrants is low, the fact that a substantial part of literature has been generated in the last two decades indicates a recent increase in attention. However, due to the low number of studies, different outcome measures and sometimes inconclusive results, it is only possible to give a tentatively conclusion.

SG migrants' CV disease mortality and morbidity tend to converge to that of the host population and differ from that of their ancestors. The HIE seems not to persist beyond the FG. The differences existing between SG immigrants with different ethnic origin depend also on how much they were involved in the acculturation process. Further research must however be performed to disaggregate the effects of environment, epigenetic and genetic factors on SG migrants CV risk factors and CV disease morbidity and mortality.

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Hypertension in Pregnancy and Related Health Outcomes in European Ethnic Minorities

22

Alessandra Modesti and Felice Petraglia

22.1 Pregnancy Complications at the Global Level

According to the data provided by the Global Health Observatory of the WHO, every day in 2015, about 830 women died due to complications of pregnancy and child birth. Almost all of these deaths occurred in low-resource settings and are related to pregnancy complications that are inadequately managed because of a lack of access to emergency health care. More precisely, of the 830 daily maternal deaths, 550 occurred in sub-Saharan Africa (SSA) and 180 in Southern Asia (SA), compared to 5 in wealthy nations [1]. In particular the maternal mortality ratios (MMRs) of Sweden, the United Kingdom, and the United States are 4, 12, and 21, respectively, whereas those of Chad, Nigeria, and Congo are 1100, 630, and 540 per 100,000 live births, respectively. The primary causes of death are haemorrhage, hypertension, infections, and indirect causes, mostly due to interaction between pre-existing medical conditions and pregnancy [2]. These high maternal and associated neonatal mortality rates persist despite considerable efforts from the World Health Organization, governments, development partners, and others [3]. Furthermore it is now evident that disparities in pregnancy and child birth are also present among minority groups living in Europe. In wealthy countries, women from minority racial groups have a higher prevalence of a wide range of adverse pregnancy outcomes, including miscarriage [4], stillbirth [5], pre-eclampsia (PE) [6–8], gestational

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hypertension (GH) [9], gestational diabetes mellitus (GDM) [9–11], preterm delivery (PTD) [9, 12], delivery of small-for-gestational-age (SGA) [13, 14] or large-for-gestational-age (LGA) [15, 16] neonates, and elective or emergency Caesarean section (CS) [17]. Apart from the obvious, cultural, and socioeconomic factors and different priorities in health care, additional biological reasons might be responsible for pre-eclampsia syndromes being such a prominent feature of African obstetrics. Hypertension developing in the second half of pregnancy is subdivided according to the presence or absence of co-existing significant proteinuria into pre-eclampsia and gestational hypertension. These two aspects are therefore important for ethnic minorities living in wealthy countries.

22.2 Pre-eclampsia in Ethnic Minorities

22.2.1 Pre-eclampsia

Pre-eclampsia, defined by the International Society for the Study of Hypertension in Pregnancy as blood pressure ≥ 140/90 mmHg and 24-h proteinuria ≥0.3 g, is a multisystem disorder characterized by abnormal vascular response to placentation [18]. The syndrome is characterized by proteinuria and hypertension in a previously normotensive woman after gestational week 20 and occurs with a 2–8% incidence of all pregnancies [19]. Pre-eclampsia is a leading cause of maternal morbidity and mortality globally, accounting for an estimated 50,000 maternal deaths annually [19]. An important determinant of pre-eclampsia is failure of placentation, particularly the physiological transformation of spiral arteries, which leads to a stressed, underperfused placenta [20]. Pre-eclampsia is a recognized clinical entity characterized by new onset of hypertension and proteinuria after 20 weeks' gestation [19, 21, 22]. In SSA the distinction between true pre-eclampsia and pregnancy-induced hypertension is sometimes difficult because proteinuria may not be adequately measured. A further problem is a lack of information on pre-existing hypertension because presentation to the clinic is often late. Data on pre-eclampsia in African Americans (AA) and immigrants from Africa to other high-income countries as compared with other ethnic groups are now available.

In the United States, Black ethnicity is cited as a risk factor for pre-eclampsia [23]. Of four million births recorded in the National Vital Statistics Report, pregnancy-associated hypertension was more common in AA (5.0%) and least frequent in Hispanics (2.9%), and AA women had the highest risk for all the different types of pre-eclampsia when compared with European American women [24]. In a 10-year longitudinal population-based study aimed at investigating ethnic disparity in hypertensive disorders of pregnancy in New York State, AA women had OR 1.67 (1.64 to 1.71) for pre-eclampsia vs. White women [25]. Poor socioeconomic status with lower incomes and level of education, lack of medical insurance, poor utilization of preconception and antenatal services, stress, discrimination, and residential segregation were often reported as possible explanations. However, many of the socioeconomic factors that may contribute to poor obstetric outcomes also apply to

the Hispanic population in the United States, yet several studies have noted that pre-eclampsia, low birth weight, and stillbirth are similar or even better than for White women, the Hispanic paradox [7, 26].

Obstetric outcomes for recent African immigrants in Europe are informative, particularly because these births often take place in countries with good records and universal health-care systems [8]. In the Netherlands, the highest risk for eclampsia and pre-eclampsia was from women from SSA [27, 28]. Cape Verdean and Antillean women were also at higher risk of pre-eclampsia in a report from Rotterdam, the Netherlands [29].

In a large retrospective study in women with singleton pregnancies attending their first routine hospital visit, 80,000 pregnancies that included women of European and Asian ancestry were considered [30]. In Afro-Caribbean women, compared with Caucasians, there was a higher prevalence of miscarriage, stillbirth, pre-eclampsia, gestational hypertension, small-for-gestational age, spontaneous and iatrogenic preterm delivery, and emergency Caesarean section [30]. South Asian racial origin was associated with increased risk for gestational diabetes mellitus, pre-eclampsia, small-for-gestational age, iatrogenic preterm delivery, and Caesarean section, and East Asian race had increased risk for gestational diabetes mellitus and small-for-gestational age [30]. Similarly, in a prospective screening study for hypertensive disorders in women attending for their routine first hospital visit in pregnancy performed in the United Kingdom, Black women were found at increased risk of early pre-eclampsia, both Black and South Asian women being at increased risk for late pre-eclampsia [31]. Predictors of early pre-eclampsia were Black race, chronic hypertension, prior PE, and use of ovulation drugs [31]. Late pre-eclampsia was more common in Black, Indian, and Pakistani women [31]. After a woman has had pre-eclampsia in her first pregnancy, the risk of recurrence is increased, with a relative risk of 15.0 in an authoritative Norwegian study of more than two million women [32]. Other reports support these findings [8].

22.2.2 Genetics of Pre-eclampsia

A genetic component to pre-eclampsia has long been suspected on the basis of a familial recurrence of the syndrome. Daughters of women with pre-eclampsia have more than twice the risk of developing the disease themselves, and sisters of affected women, even if not born from a pre-eclamptic pregnancy, are also at increased risk [33, 34]. Although environmental factors, particularly influences acting in utero, are important, some of the risk is likely to be genetic. Using ancestry informative markers, a case-control study of pre-eclampsia in Latinas, a group with admixture from European, African, and native Americans, showed that African ancestry was associated with pre-eclampsia [35]. Many reports indicate also a paternal contribution to the risk [36].

Some components of the innate and adaptive immune system may participate in the physiopathology of pre-eclampsia [37]. Although it is believed that placental hypoxia plays a relevant role in pre-eclampsia, recent studies suggest that the

presence of hypoxic conditions may not be the key feature in all pre-eclamptic patients. The wall of the uterus is the territorial boundary between two genetically different individuals: the mother and the foetus. The uterine mucosal immune system appears to define this maternal/placental boundary. The decidua must control placentation, because in its absence, the trophoblast infiltrates to a dangerous extent, causing the condition of placenta accreta [38]. The decidua contains an abundant population of specialized natural killer (NK) cells. Placental NK cells, designated as uNK cells, play an important role in the acceptance and rejection of the foetus, as they are in direct contact with the trophoblasts [39]. uNK cells express killer-cell immunoglobulin-like receptors (KIRs) that recognize trophoblast HLA-C ligands [40]. Both KIR and HLA-C are genetically variable, resulting in many possible combinations of maternal KIR and foetal HLA-C ligands [41]. The KIR region is defined by two groups of haplotype: A and B. The KIR A haplotype has seven KIR genes, all encoding inhibitory receptors apart from KIR2DS4. In contrast, the KIR B haplotype contains a variable number of additional KIR, most of which encode activating receptors [42]. All HLA-C allotypes are KIR ligands and can be divided into two groups (carrying either C1 or C2 epitopes) that are distinguished by a dimorphism at position 80 and recognized by different KIRs [43]. A variety of diseases and clinical conditions has been associated with combinations of HLA-C and KIR genes. Case-control studies of pre-eclampsia performed both in pregnant European women [40, 44] and in sub-Saharan African women [45] showed that, when the foetus carries a C2 epitope, maternal KIR AA genotypes are risk factors for pre-eclampsia in both European and sub-Saharan African pregnant women, whereas different KIR B regions confer risk protection from pre-eclampsia in sub-Saharan African [45] and in European women [40, 44]. The KIR2DS1 gene of maternal KIR B haplotypes is protective in European women [40, 44]. The KIR2DS5 and KIR2DL1 genes confer risk and protection to pregnant SSA women [45].

22.2.3 Implications for Birth Weight

Functionally, the risky combination could result in very strong inhibition of uterine NK cells. Triggering of uterine NK cells by HLA-C2 target cells in vitro from women who have a protective KIR B haplotype (in which the activating KIR for HLA-C2, KIR2DS1, is located) results in secretion of cytokines and chemokines that may facilitate trophoblast invasion and vascular transformation limiting the highly invasive placenta while at the same time ensuring the foetus receives sufficient nourishment for normal development through remodelling of the spiral arteries [8]. A failure of the physiological transformation of uterine arteries is a common feature of all the great obstetric syndromes, and this results in a reduced placental supply of oxygen and nutrients, lower birth weights, and the risk of preterm labour and superimposed pre-eclampsia. However, at the same time, maternal and neonatal mortality is not only high under circumstances of reduced foetal nutrition but also when babies are too large for the pelvis. The optimal survival of babies weighing between 2.5 and 3.5 kg seems to be a universal feature of human populations. If

babies become too large, the risk of prolonged obstructed labour, birth asphyxia, and postpartum haemorrhage is increased. Furthermore, these outcomes are much more common in African women with associated features of pregnancy that favour smaller babies: earlier birth (the gestational age is reduced to 38 weeks), the head engages late into the pelvis, and the baby matures earlier than in non-Africans [8]. The small neonatal size in ethnic minority groups is also, at least in part, due to persistent maternal constraints on foetal growth and can probably be regarded as mismatched when exposed to the current obesogenic environment. Thus, there is high mortality in mother and babies not only from pre-eclampsia (associated with low birth weight and still birth) but also at the other end of the normal birth weight spectrum. Both mothers and their babies benefit if the latter have intermediate birth weights and the two extremes of very low and high birth weight are selected against. The balance between these two extremes is partially determined at placentation, when uNK allows trophoblast cells to access sufficient maternal oxygen and nutrients without starving the baby (defective trophoblast invasion) or risking uterine rupture (excessive trophoblast invasion). In an African population, because of the greater risk of cephalopelvic disproportion, there is even greater selection for reduced foetal size with associated pre-eclampsia; this effect is consistent with the higher frequency of maternal KIR AA/paternal C2 combinations in SSA. In Europeans, opposing KIR/HLA-C combinations are associated with the extremes of birth weight: a paternal C2 epitope is associated with both extremes, but in pre-eclampsia and low birth weight (less than fifth centile), the risk is with maternal KIR AA genotypes, whereas in high birth weight, the association is with maternal KIR2DS1. Thus, there is a balance between the KIR A and KIR B haplotypes in both populations, but they differ in the regions of the KIR B haplotype that correlate with protection from pre-eclampsia. tB regions and KIR2DS1 are infrequent in Africans compared with Europeans, but the opposite is true for cB regions containing KIR2DS5. During the out-of-Africa migrations, it is possible that only individuals having tB with KIR2DS1 moved away from SSA. The higher Caesarean section rates seen in high-income countries in women of African ancestry may reflect not just delivery of women with pre-eclampsia but also an increased frequency of obstructed labour [46]. Furthermore, shoulder dystocia has also been reported to occur more commonly in African American women [47].

Thus, different KIR B regions protect sub-Saharan Africans and Europeans from pre-eclampsia, whereas in both populations, the KIR AA genotype is a risk factor for the syndrome. These results emphasize the importance of undertaking genetic studies of pregnancy disorders in African populations with the potential to provide biological insights not available from studies restricted to European populations.

22.3 Gestational Diabetes Mellitus in Ethnic Minorities

One consistent finding from studies from the Netherlands [48], Switzerland [49], and Norway [50] was that women originating from African and Middle Eastern countries tended to enter their pregnancies with higher BMI levels than the majority

population in each country. All studies found, on the other hand, that pregnant women of South and East Asian descent overall were leaner than the European population. For instance, Asian/Asian British and Chinese/other had significantly higher OR for lean (BMI < 18.5) vs. ideal weight compared with White British women [51]. However, these figures need to be interpreted considering studies showing substantial differences in the amount of body fat relative to BMI across ethnic groups, especially in Asians [52, 53]. South Asians appear to be more insulin resistant than Europeans for the same level of BMI [54].

Pregnancy can be considered as a diabetogenic and inflammatory state due to the higher levels of maternal insulin resistance, hyperlipidaemia, and fat deposition. These normal alterations are aggravated by maternal adiposity. The insulin resistance in pregnancy increases about 50–60% during pregnancy, irrespective of the prepregnant level. Thus, overweight and obese women start their pregnancy more insulin resistant compared with normal weight women and become highly insulin resistant in the second half of their pregnancy. This is also the case for pregnant women from East and South Asia, as they are found to be more insulin resistant compared with Western Europeans for the same level of BMI. Pancreatic B cells must compensate for the pregnancy-induced insulin resistance with increased insulin secretion. If not, hyperglycaemia may occur. South Asian women are reported to be less able to increase their B-cell function mutual to the pregnancy-induced insulin resistance compared with Western Europeans [55]. Reduced B-cell insulin response, in the setting of insulin resistance, is also seen among Asians outside pregnancy [56].

Gestational diabetes mellitus is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [57, 58]. The different methodologies, diagnostic criteria, and screening practices make comparison of prevalence figures between populations a challenge [59, 60]. In line with the trends for obesity and T2DM, increasing rates of GDM and undiagnosed T2DM in pregnant women attending antenatal care are observed in most parts of the world. A 2–3 higher OR for GDM was observed in women of South Asian origin [30, 50, 61–63]. The grouping of the ethnic minority population varies between studies, but also Black African [61], East Asian and Afro-Caribbean [30], and Middle Eastern [50] women had significantly higher OR for GDM.

The increasing trend for GDM globally, and the relatively higher susceptibility of many ethnic minority women in Europe today, is worrisome. GDM may reflect either a pre-existing, an undiagnosed T2DM, or a pregnancy-induced glucose-intolerant state with a high risk of future T2DM [64]. T2DM may be prevented or postponed in women after a pregnancy complicated by (GDM) and most clinical guidelines recommend a sustained screening program [65]. The time when the pregnancy GDM developed, obesity, insulin needs influence the gradual reduction in B-cell function and progression into T2DM [66]. Ethnicity is another parameter influencing the progression of the disease though the relation is complex and seems to differ between studies [67, 68]. Recurrence rates of GDM in subsequent pregnancies vary between 30 and 84%, with higher rates in minority groups compared with White populations and among those who do not develop GDM in a second pregnancy, had a reduced risk of T2DM [69].

A GDM pregnancy implies a substantially increased risk of future T2DM, although ethnic differences in conversion rates may exist. GDM may also imply a slight predisposition to later CVD. Regarding the neonates of women descending from Asian and African countries, the birth weights are generally lower than in the majority population. The small neonatal size in ethnic minority groups is most likely, at least in part, due to persistent maternal constraints on foetal growth and can probably be regarded as mismatched when exposed to the current obesogenic environment. Evidence is mounting that low birth weight increases the risk of later obesity, T2DM, and CVD. Furthermore, neonates exposed to maternal obesity and GDM may carry an increased risk of the same conditions linked to foetal overgrowth.

New public health initiatives need to focus more on early life interventions as interventions in adulthood have shown limited results. As breastfeeding may be associated with a decreased risk of obesity and adult disease both for the mother and baby, current efforts to promote breastfeeding should be strengthened, not least for ethnic minority groups.

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Ethnic Differences in Left Ventricular Remodelling in Athletes: Implications for Preparticipation Visit

23

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23.1 Physical Activity and Cardiovascular Disease

People who regularly engage in physical activity are at lower risk of cardiovascular disease than others, and the more one exercises, the better the outcome [1]. Habitual exercise is associated with an overall reduction in the risk of sudden death (SCD) and diminishes the risk of SCD during vigorous exertion [2]. It has however been demonstrated that the risk of SCD transiently increases during exercise, but the overall benefit of exercise on the risk of cardiovascular disease remains convincing. SCD incidence increases sharply with advancing age. A 10-year analysis of all-cause mortality in the National Collegiate Athletic Association (NCAA) indicates that the highest annual risk of SCD is in athletes who are men (2.65/100,000) and black (4.65/100,000) and play in the Division I men's basketball (19.2/100,000) [3]. In middle-aged and elderly people, sudden cardiac death often occurs in the context of coronary heart disease. Apart from ischaemic heart disease, SCD may be caused by cardiomyopathies (heart muscle anomalies) or end-stage valvular or hypertensive heart disease. In very rare instances, SCD is caused by a genetic arrhythmogenic heart disease. The preparticipation examination (PPE) is the practice of screening athletes prior to athletic activity to identify medical conditions that may place the athlete at increased risk for adverse events during athletic participation. Notwithstanding the public media dissemination of an adverse event may divert the attention of the general population away from the benefits of exercise as a potent

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intervention for the primary and secondary prevention of heart disease, the number of participants in sport activities increased constantly in recent decades. During the 2010–2011 academic year, more than 7.6 million high school students in the USA took part in organized interscholastic sports, compared with 7.1 million in 2005–2006 [4]. Similarly, an additional 444,077 National Collegiate Athletic Association student–athletes participated in intercollegiate athletics in 2010–2011, compared with 393,509 in 2005–2006 [4]. Furthermore, growing population, an ageing subpopulation of "baby boomers", and a culture enamoured with sports are also contributing to the recent increase in the number of masters athletes [4]. In particular over the past four decades, there has been an explosion in the number of elite black athletes participating in competitive sports at national and international levels in both Europe and the USA, and the prevalence of black athletes participating regularly in the English Premier League (soccer) is high [5, 6]. Most notably, the PPE was reported to represent the sole source of medical evaluation for 30–88% of children and adolescents annually [7, 8]. It is therefore clear that this occasion is nowadays an important opportunity to identify conditions that, although not necessarily related to or requiring restriction from athletic participation, nonetheless call for additional follow-up [9]. Some authors [9] have advocated this practice to evaluate the general health of the athlete and to provide an opening to discuss high-risk behaviours, preventive care measures, and nonathletic concerns.

Different screening models (with or without ECG) offer their respective benefits and limitations, but the absence of clear outcome-based evidence precludes any universal or mandated policy for all athletes [10]. It is also clear that some athlete groups are at substantially higher risk of SCD than others, suggesting that a "one-size-fits-all" approach is not appropriate. Evidence supports that differential risk for SCD in young athletes is influenced by ethnicity in addition to age, sex, sport, and level of play, important consideration when identifying optimal screening strategies.

23.2 Exercise-Related Left Ventricular Remodelling in Athletes with Different Ethnicities

Regular and intensive physical exercise induces several morphological and functional heart modifications [11, 12], characterizing the so-called athlete's heart [13]. This ventricular adaptive remodelling is adequate, reversible, and characterized by a normal systolic and diastolic function [14, 15]. It has been widely demonstrated that cardiovascular adaptation to sports training is influenced by many factors including body size, age, gender, lifestyle, load training, and ethnicity of the athlete [16]. Ethnicity is considered an important determinant of the electrical, structural, and functional remodelling of the athlete's heart [17]. Although most of knowledge on cardiac adaptation to exercise largely derives from echocardiographic evaluation in white adult athletes, the exponential increase in the number of multi-ethnic athletes competing at high level highlights the necessity to define ethnic-specific patterns of myocardial adaptation to exercise. Key differences in ECG and

echocardiographic characteristics have been reported in individuals of black ethnicity. As early as the 1950s, T-wave changes on the ECG were reported in over 10% of adult black males, and recent studies have demonstrated a higher prevalence of marked repolarisation changes and voltage criteria for LVH when compared with white subjects of all ages [18]. In a collaborative study between the UK and France where repolarisation abnormalities in white athletes were compared with black athletes and black sedentary controls, the prevalence of T-wave inversion was 23% in male black athletes, 10% in black sedentary controls, and just 4% in male white athletes [19]. Echocardiographic data show significant differences in black athlete's wall thickness (WT) compared to white athletes, and this pattern already appears in prepubertal age, which is notoriously associated with important structural modifications. Echocardiographic studies in hypertensive subjects have shown a significantly greater left ventricular mass index and magnitude of relative LVH in black individuals compared with white individuals matched for age and gender with similar blood pressures. Based on these data, it has been postulated that exercise-associated changes in preload and afterload may result in greater physiological cardiac adaptation in black athletes. In a UK study that compared 300 asymptomatic, normotensive male black and white athletes, echocardiographic data demonstrated no difference in LVEDD between groups (53.0 ± 4.4 mm vs. 53.6 ± 4.1 mm, ns), but mean maximal LVWT was greater in the black athletes (11.3 ± 1.6 mm vs. 10.0 ± 1.5 mm; $p < 0.001$) irrespective of sporting discipline [20]. More precisely LVWT was ≥13 mm in 18% and 4% in male black and male white athletes, respectively; LVWT was ≥15 mm in 3% male black athletes, whereas among white athletes, none had LVWT ≥ 15 mm. Of note, male black athletes with substantial LVH ≥ 15 mm did not exhibit non-dilated LV cavity, enlarged left atrium, abnormal indices of LV diastolic function, or LV outflow tract obstruction [20]. There is growing pressure to identify talented athletes at increasingly younger ages, and data have demonstrated that the physiological adaptation of cardiac dimensions associated with athlete's heart have already started to occur in post-pubertal adolescents. In a study comparing 219 male black athletes with 1440 male white athletes, greater LVWT in black adolescent athletes compared with their white counterparts (10.4 ± 1.6 mm vs. 9.4 ± 1.2 mm, $p < 0.001$) was observed [18, 21]. Maximal LVWT was >12 mm in 11% of black adolescent athletes and only 0.4% of white adolescent athletes ($p < 0.001$) [21]. A recent study, carried out by our Sport Medicine research group, enrolled white and black adolescent elite soccer players (aged 17 years old), trained with the same load and having the same lifestyle. Our study showed comparable chamber diameters and volume values in both ethnic groups, whereas a statistically significant augmentation of interventricular septum (IVS) and posterior wall (PW) thickness was found in black players compared to white players (IVS, 10.04 ± 0.14 and 9.35 ± 0.10 mm, $p < 0.001$; PW, 9.70 ± 0.20 and 9.19 ± 0.10 mm, $p < 0.05$, respectively), despite blood pressure response to exercise was comparable in both groups.

The exercise-related left ventricular remodelling is already present during prepubertal age and has a more pronounced effect on adolescent black athletes. Ethnicity is an important determinant of cardiovascular adaptation to physical training. Since

blood pressure response to exercise does not seem to be influenced by ethnicity [22], genetic factors seem to play a central role on exercise-related ventricular remodelling.

23.3 The Diagnosis of Hypertrophic Cardiomyopathy in Ethnic Minorities

Participation in intensive physical exercise is associated with increased left ventricular (LV) dimensions [23]. The upper limits of LV wall thickness are established in Caucasian (white) athletes [24] and serve an important role in differentiating physiologic LV hypertrophy (LVH) from hypertrophic cardiomyopathy (HCM) [25]. In an adult, HCM is defined by a wall thickness ≥ 15 mm in one or more LV myocardial segments—as measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging) or computed tomography—which is not explained solely by loading conditions [25]. A common challenge encountered in clinical practice is to make a differential diagnosis between hypertensive heart disease and HCM associated with systemic hypertension. In the presence of hypertension, a wall thickness ≥ 20 mm is now considered as clinical features that assist in the differential diagnosis for black subjects [25]. However, the diagnosis of hypertrophic cardiomyopathy is also challenging in athletes where the differentiation between physiologic LVH and HCM is crucial [3]. Diagnostic errors have potentially grave consequences, and a false-positive diagnosis of HCM might cause unnecessary disqualification from competitive sport.

The screening protocol proposed by the AHA/ACC for preparticipation screening in competitive athletes consists of a 14-point history questionnaire [26] and physical examination (including a brachial artery blood pressure at rest, cardiac auscultation, and recognition of the physical stigmata of Marfan syndrome) as a potentially effective method to detect cardiovascular disease in athletes. Although mandatory screening with an electrocardiogram (ECG) is not recommended, the AHA/ACC support electrocardiographic screening where physician interest and local resources are in place to achieve sufficient quality control. According to a recent prospective, multicentre trial of cardiovascular screening at 35 National Collegiate Athletic Association institutions investigating a cohort of 5258 athletes from 17 intercollegiate sports [27], most subjects with serious cardiac conditions would have been missed if ECG were not included in the cardiovascular evaluation. The study revealed a trend for African-Americans to have more abnormal ECGs compared with Caucasian athletes (4.8% vs. 3.4%; $p = 0.069$). ECG is currently recommended at the first clinic visit in all individuals with known or suspected HCM [25]. In a single-centre prospective study [28], pathological Q waves, T-wave inversion, or ST-segment depression was most helpful in distinguishing adolescents with hypertrophic cardiomyopathy (HCM) from normal athletes [28]. However, both ESC and Seattle criteria were reported to have a false-negative rate >10% for the HCM cohort [28–30]. The potential impact of ethnicity on ECG changes in young trained athletes was early revealed by Magalski et al. [31] in a large cohort of

1959 collegiate football players (of whom 67% were black) where a substantially larger proportion of abnormal ECGs in black compared with white athletes (30% vs. 13%) was observed.

Anterior (V1–V4) T-wave inversion on an athlete's 12-lead electrocardiogram (ECG) is indeed observed also in healthy athletes, with a reported prevalence of 2–7% in the general population of Caucasian (white) athletes [19, 32, 33] and 12–13% in African/Caribbean (black) athletes [19, 20]. J-point amplitude and distribution of T-wave inversion across the precordial leads were reported to provide information to differentiate athlete's heart from HCM regardless of ethnicity [34]. However, according to current guidelines, the diagnosis of hypertrophic cardiomyopathy (HCM) rests on the detection of increased LV wall thickness by any imaging modality being based on a purely morphological disease definition, that is, the presence of increased left ventricular (LV) wall thickness, and echocardiography is central to the diagnosis and monitoring of HCM [25].

Ethnicity (through a combination of genetic, endocrine, and other still unknown mechanisms) may be also responsible in black athletes (and mostly in those from West Africa or Caribbean) for a disproportionate cardiac remodelling, characterized by a greater LV wall thickening (but equivalent cavity size), than in white athletes [35]. In a series of 300 nationally ranked normotensive black male athletes (mean age 20.5 years), a significant minority (3%) of black athletes (but none of the white athletes) had substantial LVH (≥15 mm), which could have been consistent with morphologically mild HCM [20]. Upright exercise testing in athletes with LVH failed to identify abnormalities in BP responses to exercise. Black athletes participating in sprinting, boxing, and basketball exhibited a significantly greater magnitude of LVH compared with black athletes in other sporting disciplines. None of the long-distance black runners, who were all East African, exhibited LVH. Conclusions derived from LV wall thickness might have resulted in a diagnosis of HCM and disqualification from competitive sport in the nine black athletes (3%) with LVH ≥15 mm. However, none of the nine athletes exhibited other morphologic features suggestive of HCM. Specifically, none exhibited a non-dilated LV cavity, enlarged left atrium >50 mm, LV obstruction, or evidence of impaired myocardial relaxation. In the absence of cardiac symptoms or a family history of HCM, an LV wall thickness ≥15 mm in black athletes may represent physiologic LVH when the LV cavity is enlarged and diastolic indexes are normal [20, 36]. In the majority of cases, HCM is inherited as an autosomal dominant genetic trait with a 50% risk of transmission to offspring [37]. Some HCM cases are explained by de novo mutations, but apparently sporadic cases can arise because of incomplete penetrance in a parent and, less commonly, autosomal recessive inheritance.

23.4 Ethnicity and Genetic Testing

With improved automation of sequencing, and aspects of the interpretation process, the costs associated with genetic testing, and specifically whole genome sequencing, have significantly declined. Cardiomyopathy gene panels have grown in size

and scope, and it has now become commonplace to evaluate 50 to 120 genes in a single test, depending on the specific cardiomyopathy subtype and accompanying cardiac arrhythmias. In patients fulfilling HCM diagnostic criteria, sequencing of sarcomere protein genes identifies a disease-causing mutation in up to 60% of cases [37]. The likelihood of finding a causal mutation is highest in patients with familial disease and lowest in older patients and individuals with non-classical features. Testing of broad gene panels and overly inclusive interpretation of variants may lead to erroneous conclusions about pleiotropic effects of genetic variation [38, 39] and overestimates of double/compound mutations [40] and the population prevalence of the disease [41]. The challenges of variant interpretations in Mendelian disorders are particularly well illustrated by inherited cardiomyopathies: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC). These largely autosomal dominant disorders are relatively common, genetically heterogeneous, and medically important; consequently, cardiomyopathy genes are featured prominently in the American College of Medical Genetics and Genomics list of proposed genes to be routinely analysed in all exome or genome sequencing [42]. Although clinical genetic testing in cardiomyopathy has been available for more than a decade, the number of genes reported as disease-causing has increased dramatically in recent years, often without robust evidence.

The principal challenge of genetic testing is to separate truly pathogenic variants from the historically underappreciated amount of background variant noise in the genome. The provision of false genetic information to a patient, such as when a patient is incorrectly informed that one of his or her variants is causal when in fact it is benign, can have far-reaching adverse consequences within the family. Misclassification of a benign variant as pathogenic may lead to stress and economic burden consequent to an incorrect diagnosis; overestimation of the benefits of implantation of a cardioverter–defibrillator to prevent sudden cardiac death. Likewise relatives who do not have the non-causal variant may receive false reassurance that further surveillance is unnecessary. Health disparities may arise from genomic misdiagnosis. More precisely, disparities may result from errors that are related neither to access to care nor to posited “physiological differences” but, rather, to the historical dearth of control populations that include persons of diverse racial and ethnic backgrounds. For instance, rare variants originally classified as pathogenic in European white individuals have been reclassified as benign after examination revealed high frequencies in African populations [43]. The variants would not have been linked to HCM if databases of controls had contained more genetic information from blacks. The variants’ occurrence in blacks ranged from 2.9 to 27%, while their frequency in whites ranged from 0.02 to 2.9% [43]. Furthermore seven patients, five blacks and two of unspecified ancestry, with benign variants had been previously misclassified as pathogenic in genetic reports [43].

Newer and larger database from the Exome Aggregation Consortium (ExAC) contains information about genetic variants from thousands of African-American, Latino, East Asian, and South Asian individuals [44]. The analysis of data from 7855 individuals referred for clinical diagnostic testing for inherited

cardiomyopathies, along with 60,706 ExAC reference samples, exemplifies the many challenges of variant interpretations in genetically heterogeneous disorders [44]. The pathogenicity of disease genes originally identified through family linkage is resoundingly validated, for example, the majority of sarcomere genes in HCM. However, for several more recently reported HCM genes (TNNC1, MYOZ2, ACTN2, ANKRD1) [45–47], there was no significant excess of rare genetic variation in these HCM cases [44]. Likewise, MYBPC3, MYH6, and SCN5A which have all been reported to be major contributors to DCM [39, 48] showed little or no excess burden despite adequate numbers and power [44].

23.5 Characteristics of Hypertrophic Cardiomyopathy in Ethnic Minorities

A combination of sport activity [19, 20] and hypertension [49, 50] creates diagnostic challenges with respect to the differentiation of morphologically mild HCM from other causes of LVH in ethnic groups [20, 51]. The issue is confounded by the high prevalence of hypertension in the black population [52, 53]. Furthermore, reports from the USA reveal that deaths from HCM are more prevalent among black athletes [54]. The influence of African/Afro-Caribbean (black) ethnicity on the clinical profile and outcomes in hypertrophic cardiomyopathy (HCM) was recently investigated in the UK [55]. HCM was diagnosed on the basis of LVH ≥15 mm in any myocardial segment on echocardiography and/or cardiac MRI, in the absence of another condition capable of producing the same magnitude of LVH [56]. Among patients with a history of hypertension (41.9%), HCM was diagnosed in the presence of severe LVH ≥20 mm [56]. In cases of mild (<15 mm) LVH (14.1%), HCM was diagnosed in the context of supportive features, including [1] an established pathogenic gene mutation, [2] a family history of HCM or sudden cardiac death (SCD) in a first-degree relative, [3] LVH confined to the apical segments, and [4] presentation with cardiac arrest in the presence of mild asymmetric septal hypertrophy and unobstructed coronary arteries [56]. Pathogenic mutations were defined according to joint consensus recommendations [57]. Almost all black patients (98.2%) exhibited an abnormal ECG, with a high prevalence of T-wave inversion (91.4%), which was frequently deep and involved the lateral leads. In contrast, almost 10% of white patients revealed a normal ECG [55]. One-third of black patients exhibited apical or concentric patterns of hypertrophy compared with only 12% of white patients. In the context of hypertension, concentric LVH may be mistaken for hypertensive heart disease, while apical hypertrophy may go undetected on conventional echocardiography and the associated marked repolarisation changes falsely attributed to a “left ventricular strain pattern” [55]. The observation that patients with a history of hypertension (mainly black) were diagnosed with HCM, on average, 15 years later than normotensive patients supports this theory. The electrical and structural differences between black and white patients with HCM persisted even after excluding individuals who may be considered to have hypertensive heart disease, suggesting that such differences are a genuine reflection of the impact

of ethnicity on the HCM phenotype [55]. In this regard, a diagnosis of HCM should be entertained in all black patients with a history of hypertension who exhibit marked LVH and T-wave inversion in the lateral leads despite good BP control [58]. Patients with a history of hypertension were diagnosed more than a decade later than normotensive patients, and the higher prevalence of hypertension in the black cohort may have resulted in more black patients with HCM arriving later in the healthcare system with established disease [55]. Ethnicity was not a determinant of the composite primary outcome of death, cardiac arrest, or appropriate ICD therapy, and findings do not indicate a more malignant course of HCM in black patients. Conversely, multivariable analysis identified non-sustained ventricular tachycardia and hypertension as independent predictors of the primary outcome, irrespective of ethnicity, gender, or age [55]. Therefore HCM in black patients was associated with a similar prognosis as white patients. However, a history of hypertension had an adverse impact on mortality, regardless of ethnicity [55].

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