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Primordial Prevention of Non Communicable Disease

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Preface

Primordial prevention aims to avoid and attenuate the development of risk factors in the first steps. While usually therapeutic modalities are investigated for the management of non communicable diseases (NCDs), given that only supportive, and not curative, treatment can be provided for such diseases, preventive measures should be highlighted. It is well documented that NCDs origin from early life, progress over time, and become symptomatic in later years of life. Therefore, primordial prevention of NCDs and their risk factors can have extensive, applicable, and cost-effective implications in reducing the burden of such diseases.

Over the past five decades, a growing body of literature has emerged suggesting that beginning preventive interventions from very early life might be an exclusively effective approach to prevent NCDS over the life course. Childhood, especially the "first 1000 days" of life, which are a period of maximal developmental plasticity, can be the best time for implementing preventive interventions. Primordial prevention during this period may thus provide the best possible trajectories of lifelong health, whereas interventions in later years of life may be stymied by established unhealthy behaviors and inadequate physiological responses.

The incidence of NCDs, including cardiovascular diseases, diabetes, chronic respiratory diseases, cancers, mental illnesses, and injuries, is increasing worldwide. They result from a complex interaction between genetics, lifestyle, and environmental factors.

The establishment of healthy lifestyle from early life and modification of unhealthy lifestyle habits may change or delay the incidence of NCD risk factors and outcomes. However, it is noteworthy to consider the role of some epigenetic and genetic factors, as well as environmental exposures and socioeconomic conditions that cause physiological derangements resulting in the development of NCDs. Among the environmental factors, endocrine-disrupting chemicals, including environmental, industrial, nutritional, agricultural, and pharmaceutical chemicals, can alter hormonal activities and might contribute to the progression of some NCDs.

This pattern rests on the notion of sensitive periods of early life, during which modification of lifestyle habits and protection from exposure to some environmental pollutants might have long-lasting impact for NCD prevention. Moreover, the development of NCDs can arise from lifelong accumulation of risk factors; thus sustained interventions to reduce the onset or progression of NCD risk factors are required.

The main focus of this book is on the different aspects related to primordial prevention of NCDs. Given that treatment options have only limited success for the management of NCDs and their global burden, we expect that researchers, health-care providers, as well as health decision-makers would find this book as a useful tool for implementing widespread preventive measures. With involvement of experts from different backgrounds, which contribute with gathering the updates and findings from their own research on how to deal with the complex factors related to primordial prevention of NCDs.

Isfahan, Iran Roya Kelishadi

Contents

Life-Cycle Approach for Prevention of Non Communicable Disease

1

Roya Kelishadi

Abstract

Non communicable diseases (NCDs) become symptomatic in adulthood, but they mainly origin from early life. As NCDs are the major cause of mortality both in developed and developing countries, global actions are necessary for their life course prevention and control. The main preventable risk factors of NCDs include tobacco use, unhealthy diet, and physical inactivity. These risk factors track from childhood to adulthood; it is well documented that healthy lifestyles play an important role for primordial and primary prevention of NCDs. Sedentary lifestyle, especially prolonged screen time, is a main underlying factor for NCDs. Regarding dietary intake, lower consumption of fruits, vegetables and fibers, as well as higher consumption of fatty and salty foods (fast foods, junk food), and carbonated soft drinks are of most usual habits correlated with increased risk of NCDs.

Strategic action areas for the prevention and control of NCDs are health promotion, risk reduction, health systems strengthening for early detection and management of NCD risk factors. Low-cost solutions for reduction the common modifiable risk factors including unhealthy life-cycle are important for guiding policy and priorities of governments and for decreasing the prevalence of NCDs.

Keywords

Life-cycle · Prevention · Non communicable diseases

1.1 Introduction

A combination of physiological, genetic, environmental and behaviours factors are the main underlying factors of non communicable diseases (NCDs). The main goals for management of NCDs are proposed as 25 and 30% relative reduction in the risk of premature mortality from NCDs by 2025 and 2030,respectively [1]. It is documented that healthy lifestyle plays an important role for primordial and primary prevention and control of NCDs [2].

Lifestyle is related to environmental, social or occupational factors. Healthy lifestyle includes personal health, health of others and community health. Main modifiable risk factors of NCDs are tobacco use, unhealthy diet, physical inactivity, and alcohol use [3].

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All aspects of health including physical, mental, and social are considered. Healthy lifestyles including healthy dietary habits and regular physical activities are important for primary care practices and significantly decrease morbidity and mortality rates of many NCDs including metabolic syndrome, cardiovascular diseases (CVDs), type II diabetes, obesity, hypertension, hyperlipidemia, some cancers and chronic respiratory diseases (chronic obstructive pulmonary disease (COPD) and asthma) [4, 5].

The importance of physical activity and healthy intake are understood. However, many people cannot modify their poor lifestyle behaviors to decrease weight and improve chronic conditions [6]. According to WHO reports, physical inactivity and unhealthy eating habits lead to approximately two million deaths per year [7].

Sedentary life, lower consumption of fruits, vegetables and fibers, higher consumption of fatty and salty foods (fast foods, junk food), unhealthy grilled, caloric foods and carbonated soft drinks have been correlated with increased NCDs risk in children and adults [6, 8].

Increase body weight is one of the risk factors of NCDs. According to studies, weight gain plays a role in the pathophysiology of NCDs including diabetes, CVD, hypertension and cancers [9]. In addition, obesity related to enhance mortality, disability and costs of treatment in many communities. Obesity is recognized as the second cause of death worldwide that is preventable cause. Lifestyle behaviors influences weight and lead to obesity [10].

Low-cost solutions for reduction the common modifiable risk factors including unhealthy lifecycle are important for guiding policy and priorities of governments and for decreasing the prevalence of NCDs. However, much work is needed to actually modify lifestyle behaviors on a global level. NCDs prevention and treatment must change from individual and family level to the global population level. Governments must invest in all aspects of prevention strategies including primordial, primary, and secondary [11]. In this regard, life-course strategies should be considered for risky behaviors, risk factors, protective factors, and environmental exposures that would have multiplicative interactions on the development of NCDs.

1.2 Behavioral Risk Factors

1.2.1 Tobacco Use

Tobacco use is one of the important modifiable risk factor of major NCDs including diabetes, cancer, CVD and chronic respiratory diseases. Current smoking and passive smoking increase the risk of NCDs particularly develop and progress of atherosclerosis. Exposure to second-hand smoke at least 30 min for most days of the week or using any number of cigarettes regularly or occasionally lead to NCDs [12]. Passive smoking during childhood associated with the development of asthma in adulthood [13].

Different methods of tobacco consumption including chewing, sucking and smoking are related to incidence of NCDs such as ischemic heart disease, lung cancer, stroke, larynx cancer, COPD, Pulmonary tuberculosis and Buerger's disease. Tobacco chewing with different forms associated with some cancers including oral cavity, esophagus, pharynx, cervix and penis [14–16].

Smoking independently associates with diabetes. Diabetes and smoking increase the risk of death, and diabetes complications including amputations and vision problems [17].

1.2.2 Physical Inactivity

Many studies showed high prevalence of physical inactivity. They have reported sedentary life is pandemic particularly among younger adults. Interest in watching television and spending time on computer, mobile and tablet are increasing that lead to physical inactivity [18]. Another reason for increasing percentage of physical inactivity in developing countries is lack of proper outdoor playgrounds and walking tracks especially for girls and women [19].

Many cross-sectional and intervention studies have investigated the association between

physical inactivity and diseases in different age groups. Findings showed that physical activity could improve the general health and prevent the development of NCDs including obesity, coronary heart disease, type II diabetes mellitus, the age-related diseases dementia and Alzheimer's disease [20]. Regular physical activity can reduce the weight and promotes long term maintenance of weight loss. Findings showed that decrease the body weight more than 7% improve insulin sensitivity and glycemic control [21].

Appropriate levels of physical activity reduce 30% of ischemic heart disease risk, 27% of diabetes risk, and 21–25% of breast and colon cancer risk. Inadequate physical activity is associated with about 3.2 million annually death. Walking or cycling is effective and practical way for increasing physical activity [22].

Moderate to vigorous physical activity should be more than 30 min for more days of week for prevention the incidence of NCDs [19]. Centers for Disease Control and Prevention and the American College of Sport Medicine recommend moderate physical activity of 150 min per week [23].

1.2.3 Unhealthy Dietary Habits

Many individuals, particularly adolescents, have improper dietary habits. They eat more fast foods, junk foods, soft drinks and salt and eat less fruit and vegetable. According to WHO recommendation, fruits and vegetable must be eaten at least three servings per day. This amount is healthy dietary requirement. Nowadays, less than the recommended amount of vegetables, fruits, and dairy foods are consumed by people. Evidence has shown that high intakes of fruits and vegetables reduce the risk of coronary artery disease and stroke [24, 25].

Unfortunately, there is a decrease in fruit and vegetables consumption and an increase in meat and other animal products consumption in all ages. This shift significantly enhance the incidence of NCDs [26].

The amount of salt intake is higher the recommended maximum intake in most low and middle income countries. Decreasing salt intake to approximately 6 gm per day can reduce about 2.5 million deaths annually worldwide. According to studies, 15% reduction of salt intake could prevent 3.1 million deaths over a decade in low and middle income countries [22, 27].

The type of fatty acid intake is effective on health. Saturated and trans fatty acid increase the risk of CVD and have adverse effects on blood lipids. However, polyunsaturated fats can prevent coronary artery disease, ventricular arrhythmias and myocardial infarction [28].

Whole grains consumption with high fiber associate with lower risks of CVD and type II diabetes and facilitate weight control. However, refined starches increase coronary artery disease, type II diabetes and metabolic syndrome [29].

Sugar sweetened beverages (SSB) consist of sugarcane and high fructose corn syrup have negative health outcomes. High calories and glycemic index of SSB lead to obesity, metabolic syndrome and CVD. The amount of SSB intake must be decrease and it is particularly important for public health [30].

1.2.4 Exposure to Environmental Chemicals

Evidence has shown that some environmental chemicals increase risk of obesity. These chemicals are called obesogens. There are approximately 20 chemicals and chemical classes that associate with increased risk of obesity. According to findings, some chemicals including phthalates, bisphenol A, tributyltins, and several pesticides can enhance insulin resistance, type II diabetes and obesity [31].

1.2.5 Socio Demographic Influences

Evidence has shown that racial, life style and socioeconomic status (SES) differences related to different incidence of NCDs. Some certain ethnic groups are at high risk for chronic disorders. Prevalence of NCDs especially obesity in families with high SES is higher than low

SES. Reason for this difference is consumption of high energy density foods including fried meat, high fat animal products and junk foods. They have welfare facilities with less exercise. However, families with low SES eat more plant-based foods with lower energy only for satiety [32, 33].

Recently findings showed that the prevalence of obesity and unhealthy lifestyle in urban areas were higher than rural area. There are some reasons that explain the effects of different geographic regions on NCDs risk. Healthier lifestyle pattern (predominantly fruits, vegetables, grains and legumes and more physical activity) is common in rural families. However, unhealthy lifestyle pattern such as fast food and red meat intake, sedentary behaviour or low PA, and more stress is more common in urban areas [34]. Families in rural regions eat healthy meals at home. While, some family members particularly children and adolescents in cities eat unhealthy meals such as fast foods with their counterparts at restaurants or cafeterias. In addition, breakfast is as the main meal in rural area and eating breakfast is more common in rural regions. However, eating breakfast ignore in urban societies because they have not enough time for school and work preparation [35].

All these items should be incorporated as a life course approach linking conditions from the perinatal environment to the later development of NCDs in adulthood. Individuals and populations should be educated for healthy lifestyle and environment not only by health care providers, but also by public education through schools, campaigns, and media. These works would continue to play a main role, but policy and environmental changes can strengthen these efforts.

1.3 Conclusion

A life cycle approach considering the long- term health outcomes of interactions of biological and social experiences from fetal period to adulthood would be useful in attenuating long term risk of NCDs. Modification of all risk factors is better than each one and comprehensive population services must consider all risk factor for improving health at individual and public levels.

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Epigenetics and Common Non Communicable Disease

2

Mohammad Amin Tabatabaiefar, Roshanak S. Sajjadi, and Sina Narrei

Abstract

Common Non communicable diseases (NCDs), such as cardiovascular disease, cancer, schizophrenia, and diabetes, have become the major cause of death in the world. They result from an interaction between genetics, lifestyle and environmental factors. The prevalence of NCDs are increasing, and researchers hopes to find efficient strategies to predict, prevent and treat them. Given the role of epigenome in the etiology of NCDs, insight into epigenetic mechanisms may offer opportunities to predict, detect, and prevent disease long before its clinical onset.

Epigenetic alterations are exerted through several mechanisms including: chromatin modification, DNA methylation and controlling gene expression by non-coding RNAs (ncRNAs). In this chapter, we will discuss about NCDs, with focus on cancer, diabetes and schizophrenia. Different epigenetic mechanisms, categorized into two main groups DNA methylation and chromatin modifications and non-coding RNAs, will be separately discussed for these NCDs.

Keywords

Epigenetics · Chromatin modifications · DNA methylation · ncRNA · Cancer · Schizophrenia · Diabetes

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Abbreviations

CIMP	Aberrant CpG island methylator phenotype
CLL	Chronic lymphocytic leukemia
COMT	Catechol-O-methyltransferase
DD3	Differential display code 3
DOHaD	Developmental origins of health and disease
ESRD	End stage renal disease

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HATs	Histone acetyltransferases
HCC	Hepatocellular carcinoma
HDACs	Histone deacetyltransferases
IR	Insulin resistance
IRF8	Interferon Regulatory Factor 8
ITGB2	Integrin Subunit Beta 2 (ITGB2)
lncRNAs	Long non-coding RNAs
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
miRNAs	Micro RNA
MWAS	Methylome-wide association study
ncRNA	Non-coding RNA
NR3C1	Nuclear Receptor Subfamily 3 Group C Member 1
NSCLC	Non-small cell lung cancer
PAX4	Paired box 4
PCA3	Prostate cancer 3
PTMs	Post transcriptional modifications
RNAi	RNA interference
SCC	Squamous cell carcinoma
SPI1	Spi-1
T1DM	Type I diabetes Mellitus
T2DM	Type II diabetes Mellitus
TZD	Thiazolidinedione

2.1 Introduction

The key roles of epigenetic modifications in different physiological processes such as chromosomal stability, gene regulation, the establishment of tissue identity and development have been realized [3, 12]. Recent evidence suggests that inefficient epigenetics control is associated with a wide variety of noncommunicable disease (NCDs) such as cancer, diabetes mellitus and schizophrenia and are believed to exert the same major effect as genetic changes in our body [86, 97]. Epigenetic markers transmitted through the parents to the next generation can change during the intrauterine developmental period. These complex epigenetic changes allow the infant to dynamically adapt to the environmental factors during prenatal or postnatal period [69].

Epigenetic refers to gene expression regulation without changes in the structure or content of the gene. Epigenetics modification is done by three main procedures including:

1. Changes in the structure of chromatin by chromatin modulators that depend on ATP. These modulators regulate the accessibility of DNA to the transcriptional machinery through the post transcriptional modifications (PTMs) activities on the tail of histones proteins. PTMs catalytic enzymes have two types: writer and eraser proteins, which separately have acetylation, methylation, phosphorylation, and ubiquitination activities on histones [38].
2. DNA methylation is another type of epigenetic changes regulating the gene expression. Hypo or hyper methylation at different regions of the genome such as promotors of different genes can lead to diseases progression [13].
3. Non coding RNAs, as a group of regulatory genes, have their effect on epigenetic changes specially by regulating the expression of histone modifying complexes or DNA methyltransferases [88].

2.2 The Role of DNA Methylation and Chromatin Modifications in Developing Cancer, Type 2 Diabetes Mellitus and Schizophrenia

The Addition of the methyl group to the 5′ position of the DNA cytosine ring by DNA methyltransferase enzymes has been called DNA methylation process. A small family of enzymes such as DNMT1, DNMT3A, and DNMT3B perform the role. The process needs the CpG dinucleotide sequence context as the signal [32]. In mammalian organisms, the location and level of methylation in CpG areas depend on the developmental state and cellular differentiation processes [96].

2.2.1 Cancer

Cancerous cells can result from mutations in genes responsible for the processes such as controlling the replication, proteotoxic, genotoxic, oxidative stress in our body. Mutations can lead to unlimited proliferations leading to cancer [72, 81].

Cancer genes are generally categorized into three groups: (1) Gatekeeper genes (2) Caretaker genes and (3) Landscaper genes. Gatekeeper genes, which are responsible for the proliferation of cells, have two main subclasses: tumor suppressor genes and proto-oncogenes. Mutation in gatekeeper genes could typically occur either by inactivating hits in both alleles of a gene (tumor suppressors) or activating mutation in only one allele (proto-oncogene) [78]. Caretaker genes have the responsibility to protect genes from structural changes caused by mutations. Thus, they help cells maintain their genome integrity. Mutation in these genes do not directly cause cancer but their aberrant expression can lead to mutation in gatekeeper genes [100]. Finally, the landscaper genes are involved in the regulation of tumor microenvironment. Their mutations will facilitate the stromal microenvironment for cancerous cells [63].

Therefore, mutations could lead to down or up- regulation of gene expression, mislocalization of proteins and accumulation of DNA damages. The resultant inefficient proteins or genomic instability make the cells divert towards promoting caner [92, 106, 107].

On the other hand, epigenetic can control the expression of all the mentioned genes and it may cause tumors growth. Investigations on epigenetic roles in the initiation or progression of cancer have shown that epigenetic modifications and genetic changes can fundamentally effect the progress of malignancies [58]. Stimulation by endogenous and exogenous factors can lead to the change in the fate of cells through altered structure of chromatin, thereby leading to the aberrant expression or repression of some genes that cause cancer [52, 106, 107].

For instance, Polycomb, Trithorax, and Chromatin Remodeling proteins protect the homeostatic chromatin network in the cells. They facilitate the accessibility of regulatory factors and transcriptional machinery to target genes. Deregulation in these genes strongly results in alteration of epigenetic homeostasis that can lead to tumorigenesis [89]. For example, *EZH2* gene mutations result in aberrant histone H3 trimethylation at amino acid position 27 (H3K27me3) that blocks B-cell development in several lymphomas [73].

2.2.1.1 DNA Methylation

In many types of cancers, tumor suppressor genes such as *p16*, *MLH1* and *MSH2* may have aberrant CpG island methylator phenotype (CIMP) that leads to deregulation in their expression [10]. Hypo and hyper methylation have been reported since 40 years ago [9, 45]. Hypermethylation mostly occur in the characteristic landmarks of vertebrate genomes with much higher than average frequencies of the CpG dinucleotide sequence which are called CpG islands [30]. In many cancers, CpG islands in genes responsible for initiation and progression of malignancies undergo methylation changes in different pathways [11, 25]. Our knowledge, however, about methylation changes in cancers is limited. It means that we do not exactly know methylation of which genes or which part of a chromosome are involved in initiating different cancers. We are unable to unequivocally categorize genes into "driver" or "passenger", either [59]. The driver methylation events activate certain genes leading to promoting cell transformation or progressing cancer, and the passenger methylation events are referred to methylation of some genes that are not directly responsible for cancer [70].

2.2.1.2 Chromatin Modifications

Chromatin structure is highly dependent on the internal or external changes. Changes in the chromosome structure could suppress or trigger the expression of some genes when DNA has its unique packed structure [70]. DNA, proteins (e.g., histones, chromatin-modifying factors) and other associated molecules (e.g., RNA species) construct chromatin structure. Nucleosome, as the smallest unit of chromatin, is changed in

structure by covalent modifications in the histone tails resulting in the changes in the access of transcriptional factors to targeted DNA [109]. Epigenetic changes in chromatin structure is related to PTMs of specific enzymes (writer or eraser) which do their activities on histone tails and ultimately decide the fate of the underlying DNA sequences [6], which can be reversible or irreversible [39].

The Addition of the acetyl, methyl, phosphate and ubiquitin groups to the histone tails have different effects on chromatin structure [39]. There are four main proteins for acetylation/deacetylation or methylation/demethylation activities. Histone acetyltransferases (HATs) and histone deacetyltransferases (HDACs) dynamic balance could regulate the chromatin activities in different pathways [68]. Furthermore, outcomes of methylation of histone tails strongly depend on the number of methylation and location of methyl group on histones. For example, overexpression of the EZH2 protein, which is responsible for methylation of a specific amino acid on histone H3, contributes to tumorigenesis and correlates with poor prognosis [73].

Environmental exposures, such as smoking, are considered to methylate the DNA [108]. Recently, Stueve et al. have investigated the role of smoking in changing the signature of DNA methylation in the whole genome. They have found the relationship between hypermethylation of some genes and cigarette consumption in the lung carcinogenesis [104]. Life style is an important solution in preventing cancer. For example, according to the declaration of American Institute for Cancer Research, 45 present of colon cancers are avoidable by changing in life style. Folate, vitamin D, lycopene, selenium and green tea have their own effect on epigenetic changes in different types of cells [14]. For example, vitamin D has a role in reversing the aberrant epigenetic modifications in the prostate cancer [71]. Virus, bacteria or parasites are thought to be involved in cancer progression in about 20% of all cases. Different studies have shown the effect of these exogenous elements in controlling epigenetic changes and directing modifications [67, 79].

2.2.2 Diabetes Mellitus

Diabetes mellitus is one of the most common chronic disorder in the world defined by elevated plasma glucose levels. This disease is associated with a large number of deaths annually. Diabetes has direct side effects on various tissues such as neuropathy, retinopathy, nephropathy and cardiovascular diseases [18].

Diabetes is categorized into two main groups. Type I diabetes (T1DM) caused by a defect in insulin producing pancreatic-β cell due to autoimmune response. T1DM is easily manageable by exogenous regular consumption of insulin. Type II diabetes (T2DM), which constitute 90% of diabetic cases is associated with insulin reduction in pancreatic β-cells and insulin resistance. T2DM develops gradually and patients are generally unaware of disease until consequences appear. Therefore, early detection of T2DM is important for a more effective cure of the disease [18].

The main reasons for developing T2DM are: the progressive insulin resistance and insulin insufficiency [119]. Like the other diseases, a combination of genetic factors [4, 77] and controlling mechanisms, possibly controlled by epigenetic factors, are involved in causing Type 2 diabetes mellitus (T2DM).

Insulin secretion happens in β-Cells of pancreas and 30–60% of their mass is lost in T2DM [119]. β-cells functions can be changed by pathological modifications of epigenome both during developmental stages and adult life [57]. For example, the Paired box 4 (PAX4) gene is hypermethylated in T2DM patients leading to its expression suppression. This gene is necessary for the proliferation and survival of β-cells [114]. In addition to DNA methylation, histone modification, can also lead to deregulation of insulin production [66]. Duodenal homeobox factor 1 (PDX1) has the duty to produce insulin in β-cells when hyperglycemia happens. In the other words, in hyperglycemia, hyperacetylation of histone H4 in the promoter region of the *PDX1* gene leads to recruiting HAT p300 and insulin production [82]. Ironically, in a low level of glucose PDX1 is connected to HDACs, such as HDAC1

and HDAC2, to suppress the insulin production. These findings highlight the importance of epigenetic regulation in the insulin secretion and in development of diabetics. Generally, β-cells efficient function is strongly related to the accurate mechanism of epigenetic changes in three ways: the development of β-cell, reaction to glucose changes and sensitivity to endocrine signals in producing insulin [103].

Insulin resistance, insufficient response to the environmental insulin, is another main point in T2DM and it is related to immunity system. Immunological processes in hyperglycemia condition leads to inflammation which can contribute to the development of insulin deficiency or insulin resistance [60]. Twins studies have shown that high levels of inflammatory factors such as secreted phosphoprotein 1 (SPP1), chemokines and interleukin-1 receptor antagonist (IL-1RA) are in association with hyper DNA methylation of key genes which are responsible for the insulin resistance condition in T2DM patients [84].

2.2.3 Schizophrenia

There is many lines of evidence suggesting that schizophrenia has a strong genetic component, including; heritability with high rates of 80–85%, and identification of several distinct genomic regions, although there remains much to know about the genetic factors causing schizophrenia [5, 75, 105].

Delays in effective treatment of patients have been shown to significantly cause poor prognosis of schizophrenia. Generally, a main goal to psychiatric research is to detect clinical biomarkers that can be used for early diagnosis of schizophrenia and predict the treatment response to do the best for patients [101]. Neurological network formation during development is depended on accurate epigenetic modifications underling the increased or decreased risk of developing schizophrenia later in life [64]. Spi-1 Proto-Oncogene (*SPI1*), Interferon Regulatory Factor 8 (*IRF8*) and Integrin Subunit Beta 2 (*ITGB2*) are the genes responsible for microgliogenesis which show altered DNA methylation in schizophrenia patients [61]. Prenatal exposure to environmental factors can have long lasting effects on gene expression and phenotype. Thus, the early life changes in DNA could lead to aberrant neurological cells function later in life and even in the future generations [64]. There is a link between parental stress or depressive mood and epigenetic changes. For approving this hypothesis Oberlander et al. have done a research on the mothers who had depression during last trimester [85]. They studied DNA methylation signature of the Nuclear Receptor Subfamily 3 Group C Member 1 (*NR3C1*) gene in mothers and offspring. Interestingly, the amount of DNA methylation on the *NR3C1* gene was different and increased DNA methylation levels were observed in the whole blood samples of the adolescent offspring [85]. On the basis of this research, other researchers investigated the epigenetic changes in peripheral tissues, epithelial cells and postmortem brains of schizophrenia patients which showed the epigenetic alterations in the samples of patients [37, 53]. Methylome-wide association study (MWAS) by Aberg and colleagues uncovered and proved the notion of changes in epigenetic mechanisms by the environmental factors in schizophrenia patients. The methylation signature of differentially methylated sites in the blood of schizophrenia patients proved the possibility of environmental effects on epigenetic changes [1].

2.3 The Importance of ncRNAs as Epigenetic Mechanisms

The important role of non-protein coding RNA transcripts in epigenetic gene regulation has been evident [88], although the coding exons of these genes account for only 1.5% of the genome. Percentage of non-protein-coding region correspondingly increases along with the complexity of organisms. In recent years, it has become increasingly apparent that the non-protein-coding portion of the genome have crucial functional importance for the normal development [40, 87].

Non-coding RNA (ncRNA) is mRNA transcribed from DNA but will not be translated into

protein. Rather than being 'junk' DNA, some non-protein coding transcripts may play an important role in regulating the expression of the genes [74]. The flexibility of RNA transcripts and their ability to fold into complex 3D structure enables them to form specific interactions with proteins. The ability of matching with RNA or DNA molecules via base pairing, even with double-stranded DNA, and form networks with DNA, protein complexes and RNA molecules indicate their large potential as an important player with many biological functions [95].

When talking about gene regulation, RNA interference (RNAi) immediately comes to mind (especially in advanced organisms) and it is clear that RNAi-based ncRNAs and some longer ncRNAs have roles in epigenetic processes. Indeed, gene expression can vary due to the role of RNA molecules and their interactions with DNA and/or proteins. Specifically, more emphasis is on the ability of ncRNA transcripts to regulate gene expression and, thus, on their role as epigenetic modifiers [22]. Some of these roles have been known in the past (e.g. X-chromosome inactivation and gene imprinting). In human diseases, particularly cancer, it has been determined that epigenetic and genetic defects in ncRNAs and their processing steps are a common cause of disease [34, 35].

2.3.1 Types of ncRNA and Their Functions

ncRNAs are transcribed from DNA but are not translated into proteins. Many of them have important function and are involved in the processing and regulation of other RNAs such as mRNA, tRNA, and rRNA. Small nuclear RNAs (snRNAs) involved in splicing, RNase P cleaves pre-tRNAs. Other small ncRNAs such as microRNAs (miRNAs) and siRNAs are involved in the regulation of target mRNAs and chromatin. In addition to RNAi mechanism, there are many different ways that ncRNAs can interact with genes to up-regulate or down-regulate expression, silencing translation or methylation. lncRNAs (typically 200 nt) have also been participated in gene regulation. All of these ncRNAs organize a network of processes in epigenetic changes [22]. These could be exploited for the future gene therapy modlaities [27].

Different mechanisms of long and short ncRNAs cause changes in genes expression. Many of these transcripts are necessary for precise targeting of histone modifying complexes and play a role in DNA methylation. Indeed, a definition of epigenetics include the gene silencing or upregulation caused by non-coding RNAs, which occurs in normal biology and affected by epigenetic complexes. It would also cover diversity in gene expression, observed between cells with identical DNA sequence, during differentiation or among developing tissues. It is important to note that when ncRNAs are targeted for repression or overexpression, amplifying changes can occur in the downstream effectors [88].

2.3.2 ncRNAs as Biomarkers in Cancer

Cancer is characterized by a significant heterogeneity within groups of patients diagnosed with the same tumor subtype, and even within different cells of the same tumor mass. This heterogeneity is a consequence of the fact that cancer is a genetic disorder that is caused by the accumulation of different genetic and epigenetic changes. Heterogeneity is a major challenge in choosing the most effective treatment for each patient. Biomarkers can facilitate to overcoming this challenge because they can be used as diagnostic or prognostic indicator of cancer, classifying tumors and determining the stage of the disease [90]. Based on the levels of expression, specific biomarkers can help physicians to predict the response to a specific therapy and also to decide on the optimal dose of a drug for a patient. Besides protein-coding genes and proteins, miRNAs and other ncRNAs are widely investigated for their potential role as biomarkers and targets for therapeutic interventions in human diseases [113].

Although many current biomarkers are based on protein levels, many studies have shown

interest in in the use of miRNAs and other ncRNAs as biological indicators for disease diagnosis, prognosis and prediction to therapeutic responses. miRNAs and lncRNAs (lncRNAs) are stable, even in body liquids such as serum, plasma, urine and saliva, and they show highly dysregulated expression levels in disease. Their expression is tissue or biological stage specific; and can be easily measured by novel molecular methods.[24, 94].

Since cancer is a result of dysregulations in the gene expression networks that maintain normal growth and differentiation cell, most of the genetic components associated with cancer susceptibility have not yet been linked to individual genes, indicating major deficiencies in our understanding of the molecular basis of cancer development [21]. A key development in clarifying the complexity of cancer genetics may be shifting in research from exclusively at the protein- coding region of the genome to role of variation in regulatory elements [21].

2.3.2.1 Cancer Diagnosis

Many researchers try to detect diagnostic miRNA biomarkers that distinguish cancer patients from healthy people and to make early detection. They have commonly established expression profiles to create miRNA signatures of various cancer types. For example, miRNAs signatures have been developed to detect patients with solid tumors such as lung cancer, breast cancer, colorectal cancer, pancreatic cancer, hepatocellular carcinoma (HCC), gastric cancer, prostate cancer and glioblastoma, or hematological malignancies such as acute lymphocytic leukemia, chronic lymphocytic leukemia (CLL), acute myeloid leukemia, chronic myeloid leukemia and follicular lymphoma, diffuse large B-cell lymphoma [16, 36, 43, 106, 107].

The number of reports on lncRNAs in cancer diagnosis is more limited. One of the examples of lncRNAs used as a diagnostic biomarker in cancer is PCA3, previously known as DD3. Its expression has been found to be highly specific in prostate tissue and highly overexpressed in prostate cancer. PCA3 can be detectable in urine and is expressed in early-stage tumors, Therefore, it can be exploited as a diagnostic biomarker in the clinic [15, 91, 117].

2.3.2.2 Tumor Classification

miRNA expression profile can also be used to distinguish different tumor subtypes and to categorize tumors of distinct cellular origin [50]. For instance, in breast cancer, acute myeloid leukemia and gastric cancer, it has been shown that miRNA profile differentiated between different histological and molecular subtypes [111]. For example, in lung cancer, *KRAS* mutation-positive tumors are connected to miR-495 upregulation and EGFR mutation-positive tumors linked to upregulated miR- 21 and miR-25, while miR-155 is particularly upregulated in lung cancer tumors without *KRAS* or *EGFR* mutation [26, 98].

lncRNAs can also be used to distinguish tumors such as pediatric tumors. The presence and overexpression of a 250-kb noncoding transcript has been established in Ewing's family of tumors, but not in other cancer tumor types analyzed [19, 55].

2.3.2.3 Cancer Prognosis

One prominent example of a prognostic lncRNA is metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) that is overexpressed in many solid tumors. It predicts poor prognosis in non-small cell lung cancer (NSCLC) and has been used as a prognostic biomarker for hepatocellular carcinoma (HCC) recurrence after liver transplantation [56, 65, 121].

One important cause of cancer-related death is tumor metastasis, a multi-stage process that refers to diffusion of tumor cells and proliferation at secondary sites. Detection of biomarkers associated with disease progression is very significant as they can be applicable in therapeutic strategies reducing the mortality and morbidity, and enhancing the survival of metastatic cancer patients [31, 83].

miRNAs have been demonstrated to play a role as either metastatic activators or as metastatic repressors in different types of human cancers, such as breast cancer, prostate cancer, testicular germ cell tumors, colon cancer,

pancreatic cancer, nasopharyngeal carcinoma and prostate cancer [83].

Several lncRNAs have also been participated in metastasis. For example, HOTAIR has a specific association with patient prognosis and correlates with metastasis in breast cancer patients, colorectal carcinoma, gastrointestinal stromal tumors and HCC [46, 51, 62].

A unique 26-kb intergenic ncRNA transcript, located on chromosome 2, was found to be overexpressed in a primary Ewing's family of tumors that did not metastasize, while its down regulation was seen in primary tumors that finally metastasized [80].

2.3.2.4 Prediction of Therapeutic Responses

ncRNAs can be used to predict response to therapy and some of them are known to play a role in drug sensitivity and resistance to therapy [43, 123]. An 11 miRNA profile was established in ovarian cancer cell lines, which distinguishes between cisplatin-resistant and cisplatin-sensitive cells. In breast cancer, miR-210 expression levels associated with sensitivity to trastuzumab and miR-125b is predictive of chemoresistance [116, 124].

Notably, two lncRNAs have been correlated with the prediction of chemotherapeutic sensitivity: MALAT1, which has overexpression in a poor responder group of osteosarcoma, and CUDR whose overexpression is correlated with drug resistance in head and neck squamous cell carcinoma (SCC) cell lines [20, 41, 110]. Manipulation of the ncRNAs involved in resistance to therapy may improves the cancer cells response to chemotherapeutic agents [122].

Ameloblastoma of the jaw remains a still difficult to treat odontogenic tumour, with a high recurrence rate. Classically, genetic etiology were known to be partly responsible for its etiology [102]. However, recently the first report of ameloblastoma ncRNA signature was obtained in a total of 95 ameloblastoma cases and a global array transcriptome technology covering >285,000 full-length transcripts was used. Further validation in an independent cohort showed the lncRNAs and small nucleolar RNA (snoRNAs): LINC340, SNORD116–25, SNORA11, SNORA21, SNORA47 and SNORA65 as a distinct ncRNA signature of ameloblastoma. Notably, these ncRNAs were independent of BRAF-V600E and SMO-L412F mutations, histology type or tumour location, but was found to be positively correlated with the tumour size. The study highlights new diagnostic and therapeutic targets for this invasive odontogenic tumour [28].

2.3.3 Diabetes Mellitus and ncRNAs

There are many reports on the function of miRNAs/lncRNAs associated with DM or DM related outcomes. miR-375 was first characterized as pancreatic islet specific miRNA. It controls insulin secretion from pancreatic β-cells [33].

DM results in endothelial deficiency. In a research to identify circulating miRNAs specific to T2DM, miR-126 was found to be down regulated in plasma from T2DM patient compared to healthy controls. This miRNA is critical for endothelial cells function. Also, miR-661, miR-571, miR-770-5p, miR-892b and miR-1303 have been detected as circulating biomarkers for micro vascular complications related to T2DM [115, 120].

Primary classification of T2DM patients with insulin resistance to treatment with insulin sensitizing factors such as Thiazolidinedione's (TZD) illuminates optimal treatment options. miR-320a and miR486 have been identified as biomarkers for response to TZD. Besides, Shah et al. by using next generation sequencing detected 16 miRNAs which are associated with insulin resistance, especially miR-122 [44, 99].

A large number of lncRNAs mapped closer to protein coding genes are related to β-cell function. SENCR is the first circulating lncRNA whose serum expression levels were shown to predict responsiveness to pioglitazone therapy (to improve insulin sensitivity and left ventricular diastolic function) in T2DM patients [29].

CiRS-7, with more than 50 binding sites has high affinity to miR-7. In fact, it is a competing endogenous RNA for miR-7 which plays a role in

inhibition of insulin secretion. Then, Overexpression of CiRS-7 causes the reduction of insulin secretion [118].

GAS5 has a low expression level in patients with HbA1c>5.9 who were not classified as diabetic, because the clinical level for T2DM is HbA1c>6.5. Indeed, GAS5 can be a predictive biomarker for T2DM patient [17].

2.3.4 Schizophrenia and ncRNAs

There are increasing literature showing that miRNA and lncRNA play a major role in the pathophysiology of schizophrenia. Besides, in the CNS, patients with schizophrenia reveal differential expression of non-coding RNA compared with non-psychiatric people [54].

Among the first studies to clarify miRNA expression in patients with schizophrenia, Perkins et al. showed lower levels of the miRNA miR-30B in the prefrontal cortex of patients with schizophrenia. The miR-30B gene is located within region of 22q11.21 that is highly involved in schizophrenia [76]. This chromosome band is the location of several schizophrenia related genes, such as Catechol-O-methyltransferase (*COMT*), and is also involved in DiGeorge syndrome. DiGeorge syndrome patients have deletions across chromosomal band 22q11.2 and have an increased risk of developing a psychotic disorder [49, 112].

Besides, changes in miRNAs expression have been reported through microarray studies in schizophrenia, which demonstrates a wide disruption of miRNA processing machinery. It is important to mentioned that DiGeorge critical region gene 8 (*DGCR8*), a schizophrenia susceptibility region, contains part of the enzyme complex that cleaves the pri-miRNA into pre-miRNA [42]. In agreement of the finding, genetic association studies have confirmed associations between SNPs in pre-miRNA processing gene *DICER1* (rs3742330, rs11621737) and *DGCR8* (rs3757, rs8139591, rs9606248) and the incidence rate of schizophrenia [125].

Many array based studies have indicated dysregulated lncRNA expression profiles in CNS of patients with schizophrenia [48, 93]. Among these investigation there is strong evidence to confirm the involvement of the lncRNA myocardial infarction associated transcript (MIAT) in this disease [8]. Based on these studies, *in vitro* knockdown of the MIAT transcript in neuronal stem cells increases the expression levels of the disrupted in schizophrenia 1 (*DISC1*) splice variant transcripts, and also the neuregulin 1 receptor (*ERRB4*) transcript variants. These expression profile of the *DISC1* and *ERRB4* splice variants are similar to that observed in the post-mortem hippocampus from patients with schizophrenia [8].

Recent bioinformatics study of the chromosome 1p21.3 has suggested that the novel, CNS-expressed lncRNA, EU358092, may also play a role in schizophrenia. Various schizophrenia GWAS SNPs were reported within the EU358092 gene region. Dysregulated expression of EU358092 in SH-SY5Y human neuronal cells in response to psychoactive drugs, proposes its potential effect in molecular pathways related to schizophrenia [47].

2.4 Future Perspectives

The relationship between noncommunicable diseases and epigenetic changes have attracted a lot of attention in recent years. Each of these epigenetic changes, which includes: DNA methylation, chromatin remodeling and effect of ncRNAs can be a major contributor to environmental changes in the development of diseases such as cancer, schizophrenia and diabetes. Considering previous studies, we can hope that better understanding of effective epigenetic factors would prevent and treat these diseases. Evidence about the contribution of ncRNAs in the occurrence and progression of human disorders is increasing, but further research is required to clear the extent of this contribution and the mechanisms by which ncRNAs exert their pathological effects [48].

Future studies are needed to clarify the relationship between environmental factor and changes in DNA methylation, chromatin remodeling and ncRNA functions. Findings about

ncRNAs would help modify the concept of the "central dogma"; RNA is not only an intermediate between DNA and protein, but also performs important regulatory feedback in both transcription and translation levels. Besides the role of ncRNA in classical epigenetics, it is transmitting the message throughout a wide network of dynamic regulation of gene expression [88].

The scientific community and pharmaceutical companies should try harder in this field by using large-scale screening of ncRNA-related drugs, developing knock-in and knockout models for the target ncRNAs. The targeting of ncRNAs and human diseases is still in its infancy, but new important developments are expected in this field [2, 23].

One major challenge will be to clarify all functional ncRNAs that are encoded in the human genome, and novel genomic, epigenomic and bioinformatics approaches will be critical in this way. Procedures based on next generation sequencing, including RNA sequencing, will prepare a more detailed conception of the all human ncRNAs transcriptome. Bioinformatics tools for detection potentially functional ncRNAs will be increasingly important for unraveling the complexity of NCSs [7, 74].

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3 The Role of Environmental Disruptor Chemicals in the Development of Non Communicable Disease

Maryam Zarean and Parinaz Poursafa

Abstract

The increasing prevalence of non communicable diseases (NCDs) poses main challenges to global public health. Various environmental exposures to different chemicals and pollutants might interact with genetic and epigenetic mechanisms resulting in the development of NCDs. Among these environmental exposures, endocrine disrupting chemicals (EDCs) consist of a group of compounds with potential adverse health effects and the interference with the endocrine system. They are mostly used in food constituents, packaging industries and pesticides. Growing number of *in vitro*, *in vivo*, and epidemiological studies documented the link of EDC exposure with obesity, diabetes, and metabolic syndrome, which are the underlying factors for development of NCDs. Prevention of exposure to EDCs and reduction of their production should be underscored in strategies for primordial prevention of NCDs.

Keywords

Endocrine disruptors · Non communicable diseases · Environment · Metabolic disorder · Obesity · Diabetes

3.1 Introduction

Exposure to environmental chemicals, especially in early life, is a notable risk for development of different diseases. Many environmental exposures to various agents might interact with genetic and epigenetic mechanisms, which in turn would affect the normal development [1]. Over the last decade, the scientific perception of the relationship between health and environment has made quick progress, and growing experience exists on the increasing trend of diseases related to environmental pollutants [2]. Studies in the US population revealed that in the past 40 years, non communicable diseases (NCDs) had rapid escalating trend; for instance, breast and prostate cancers have increased by 40% and 57%, respectively. In addition, in the past 30 years, obesity has doubled, and diabetes has tripled in the number of US adults. Since human genome has not changed over this short time-period, undoubtedly the role of environment should be highlighted as the main cause of such increase in NCDs. Environmental endocrine disruptors are probably the underlying

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factor in the rise of many disorders and diseases [3]. Humans are abundantly exposed to chemicals like endocrine-disrupting chemicals (EDCs) in different periods of life with particular concern [1]. EDCs include environmental, industrial, nutritional, agricultural, and pharmaceutical compounds that might alter hormonal activity by either resembling natural hormones or antagonizing their actions and/or homeostasis in organisms and cells [4]. These compounds are the source of progression of some metabolic disorders such as obesity, metabolic syndrome, and diabetes, as well as endometriosis. Synthetic EDCs are commonly categorized into short-lived pollutants considered as persistent organic pollutants (POPs). Short-lived pollutants like phthalates and bisphenol A (BPA) abundantly detected in the environment [1, 5]. It is shown that exposure of girls to low-molecular weight phthalates is positively associated with later changes in indexes of generalized and abdominal obesity. It is indicated that exposure of 6–8-year-old overweight girls to monoethyl phthalate (MEP) (i.e. diethyl phthalate (DEP) metabolite) is associated with their body mass index and waist circumference 1 year later [6]. The targets of classical disrupting chemical are nuclear receptors like estrogen receptors (ER), androgen receptors (AR), thyroid receptors (TR), progesterone receptors (PR), mineralocorticoid receptors (MR), glucocorticoid receptors (GR), and peroxisome proliferator-activated receptors (PPAR). POPs include organochlorine pesticides, industrial byproducts, and flame retardants [7]. NCDs are a global health concern, especially in low and middle-income countries undergoing socio-economic development [8, 9]. In addition to rapid lifestyle changes, environmental exposures are considered as a main underlying cause of such increase. It is reported that ambient and indoor air pollution caused more than six million deaths from chronic respiratory diseases, lung cancer, and cardiovascular diseases in 2012 [10–12]. Over time, humans are often exposed to cumulative extents of these pollutants. Even low levels of exposure to environmental factors in early life might be associated with the development and progress of NCDs can many years later. It is documented that exposure to EDCs in early life can affect the metabolism and might influence mechanisms related to weight control or brain growth, and in turn it can interact with other risk factors resulting in increased risks of obesity, diabetes, cardiovascular disease, and cancer [13]. Increasing body of evidence suggest that EDCs exposure during vital periods of development can be associated with later life reproductive disorders, neurodevelopmental disruptions, thyroid-related diseases, diabetes and obesity, as well as cancers of breast, prostate and endometrium [14]. The rising prevalence of obesity and overweight during the last decades and a number of birth or pregnancy cohort studies suggested the possibility to explore the role of exposure to environmental factors very early in life, at specific critical windows, with growth velocity and obesity in childhood [7]. Obesity is a more serious concern for children and it is a health risk for adults [15, 16]. Moreover, metabolic syndrome (MetS) is a complicated condition consisting of abdominal obesity, insulin resistance, hypertension, dyslipidemia, and hyperglycemia; its prevalence is rapidly growing along with the increasing trend of obesity. Metabolic disorders have been commonly linked to genetic background and changes in lifestyle, and aging. There is now substantial document that environmental pollutants, including EDCs, may be the cause of rapid increase in the incidence of such disorders including MetS [17].

3.2 Overview of EDCs

According to the US Environment Protection Agency (EPA), EDCs are defined as exogenous agents interfering with the production, release, transport, metabolism, binding, action, or omission of natural hormones responsible for the regulation of developmental processes and the maintenance of homeostasis. Moreover, the Endocrine Society defined EDCs as exogenous

chemical that can interfere with any aspect of hormone action. The World Health Organization/ United Nations Environment Program (WHO/ UNEP) defines these chemicals as "an exogenous substance that changes the function(s) of the endocrine system and consequently makes negative impacts in intact organism, or its progeny or population" [17]. EDCs are defined by three criteria based on the decision of the European Food Safety Authority (EFSA) Scientific Committee to use the World Health Organization/ International Programme on Chemical Safety (WHO/IPCS) definition: i) the presence of a negative impact in population or an intact organism; ii) the presence of an endocrine activity; and iii) a demonstrated causal relationship between the negative impact and the endocrine activity [18]. Some pollutants with particular chemical properties that interfere with endocrine systems have been of increasing interest. The information on environmental impact of EDCs is currently incomplete and these compounds are poorly regulated. Preliminary results from epidemiological and clinical studies, and *in vivo* models, have shown that EDCs play a role in different diseases. Therefore, it has become a global public health matter [19]. Recently, most studies examining associations between EDCs and measures like birth weight, birth length, head circumference, gestational age, have revealed notable inverse associations, i.e. lower birth weight, birth length and head circumference for increased endocrine disruptors levels [20].

3.2.1 EDC Categories

EDCs can be categorized according to their sources or their modes of action from a toxicological perspective:

EDCs can be initially classified as:

(i) natural and
(ii) synthetic.

In the second classifications, EDCs can be grouped as:

(i) EDCs affecting reproductive system
(ii) EDCs affecting pancreas
(iii) EDCs affecting thyroid
(iv) EDCs affecting central nervous system
(v) EDCs affecting other systems [1]

From a total of 564 chemicals suggested by various studies or organizations, 147 were shown to be persistent in the environment. In a first assessment, clear evidence of endocrine disrupting activity was noted for 66 out of them [21]. In summary, the most important EDCs are presented as follows:

3.2.1.1 Phthalates

Phthalic acid esters (i.e., phthalates/PAEs) are alkyl aryl or dialkyl esters of phthalic acid and are used to make plastic. Based on a number of studies, human urine and blood were used as biological fluids to evaluate the exposure to these compounds [1]. PAEs are used as plasticizers in many consumer products such as personal care products, floorings, pharmaceuticals, gelling agents, building materials, lubricants, medical devices, food packaging, dispersants and children's toys [22–24]. The major source of PAEs exposure people is diet. Another main source is medical exposure by blood transfusion equipment and blood storage bags during receiving blood transfusion or hemodialysis bags. PAEs are categorized into two distinct groups of low molecular weight (LMW) and high molecular weight (HMW) based on the length of their carbon chain. LMW phthalates, such as diethyl phthalate (DEP), di *n*-butyl phthalate (DnBP), dimethyl phthalate (DMP), and di-iso-butyl phthalate (DiBP) are usually used in the production of personal care products [1, 25–27]. HMW phthalates, such as bis(2-ethylhexyl) phthalate (DEHP), di-iso-decyl phthalate (DiDP), di-iso-nonyl phthalate (DiNP), and butyl benzyl phthalate (BBzP) are mostly used in the production of

medical devices and flexible plastics. Epidemiological studies with cross-sectional designs also suggest relationships between a variety of PAE metabolites, diabetes and insulin resistance [28]. The animal exposed in utero to DEHP include non-sex-specific increases in body weight, visceral fat mass, and circulating leptin, insulin and/or glucose concentrations [29].

3.2.1.2 Bisphenols

Bisphenols are synthetic lipophilic compounds used in the production of epoxy resins and plastics, which contain several related compounds, namely BPA, BPAP, BPAF, BPB, BPE, BPC, BPS, BPF, and BPZ. BPA is the most studied representative of this class [1, 29, 30]. It is used in consumer products like thermal receipts, food can linings, tableware, medical equipment, toys, water supply pipes and food/beverage storage containers [31]. Data from national studies in the US have presented that over 95% of the population have detectable levels of BPA in urine [32]. Water and food intake in children is an important source of exposure to these compounds. According to National Health and Nutrition Examination Survey (NHANES), in children aged 6–19 years, urinary BPA level was linked with increased risk of obesity and albuminuria [33]. The effects of BPA are of critical importance for fetuses, infants, and young children, because they lack mature systems of body detoxification. When they are exposed to the same weight-normalized dose, plasma levels of BPA in newborns were found to be 11 times greater than in adults [34]. Early-life exposure studies suggest significant association between BPA and excess adiposity and an increased risk of being overweight. Multigenerational obesogenic effect has also been stated in this regard [29].

3.2.1.3 Polychlorinated Biphenyls

POPs widely used as industrial solvents and pesticides. Polychlorinated biphenyls (PCBs) are amongst the 12 compounds documented as POPs in the 2001 Stockholm Convention. PCBs are aromatic, synthetic chemicals made by two connected benzene rings with some or all of the hydrogen substituted by chlorine atoms. These compounds are a large group of over 200 chemicals utilized in a range of industrial products, like transformers, hydraulic fluids, lubricants, cable insulation, or fiberglass. They have high environmental resistance to metabolize in organism and tendency to accumulate in lipids which favor their global presence in the environment. Low vapor pressure of PCBs and low water solubility coupled with air, water and sediment transport processes move them from regional contaminated sites to far regions [29, 35]. Oral is the primary route of exposure for this chemical. Over 10 PCBs have been recognized with different obesogenic potential. Notably, a positive relationship between dietary intake of PCBs and prevalence of obesity has been found [36, 37]. PCBs are recognized for their neurotoxic properties, particularly on the developing brain [38]. Some studies have provided convincing evidence for the obesogenic nature of some PCBs; however, the cumulative obesogenic burden of PCBs is still questionable [29].

3.2.1.4 Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons or polyaromatic hydrocarbons (PAHs) are organic compounds that are composed of multiple aromatic rings. PAHs distribute in the environment through sewage, road run-off, smelter industries and fossil fuel sources [35]. They can result from consumption of polluted water and food, contaminated air from occupational settings, inhalation of cigarette smoke, and automobile exhausts. The presence of these compounds in fish and shellfish are a result of contamination of fresh and coastal waters [39]. The coal and biomass burning for heating and cooking result in high indoor levels of PAHs in most developing countries [40]. The increased concern about carcinogen effects of PAH has triggered widespread attention at global level. A study showed that low molecular weight PAHs were present at highest levels and the more abundant compounds were naphthalene, acenapthalene, phenanthrene, and fluorine [35, 41]. As a component in all environmental PAH mixtures, pyrene is not mainly toxic, and only one phase I metabolite (1-hydroxypyrene)

is formed by biotransformation process in eukaryotic organisms. It is a widely used model compound in investigations of PAH metabolism. Moreover, 1-hydroxypyrene is a useful biomarker of human PAH exposure [40].

3.2.1.5 Pesticides

According to WHO, developed countries are consuming 80% of all pesticides. However, due to lack of specific legislation, agricultural workers from developing nations are exposed to higher concentration of pesticides. These compounds persistent organic pollutants are non-bio-degradable, lipid soluble, and EDCs [38]. Pesticides are responsible for several chronic diseases like cancers, diabetes, neurodegenerative disorders, Alzheimer, Parkinson, reproductive disorders, amyotrophic lateral sclerosis (ALS), and birth defects [42]. The finding of Duyzer (2003) indicated the level of 17 pesticides in precipitation exceeded the maximum permissible level for surface water and 22 exceeded the standard for drinking water of 100 ng/L [43]. Dichlorodiphenyltrichloroethane, commonly known as DDT has been used worldwide for pest and vector control. After finding its toxic effects for human, its use was banned in developed countries [38]. Illustrations of pesticides with endocrine disrupting characteristic include the organophosphorus (OPs) and the organochlorines (OCs) pesticides [44]. OPs can result in lower intelligence quotient (IQ) and attention deficit in children. Other pesticides have impact on Parkinson's disease [3]. They are metabolized by xenobiotic metabolizing enzymes and are not persistent in the environment. OCs pesticides are not, however, metabolized by human body. Therefore, such compounds appear to be much more persistent compared to OPs pesticides [44].

3.2.2 Sources and Pathways of Exposure to EDCs

Individuals are exposed to low levels of environmental abundant endocrine disruptors throughout their lives [4]. There are various sources of environmental pollutants [45]. The route and duration of exposure may have considerable influence on how the chemicals are metabolized and whether or not the chemical remains biologically active [46]. Around 1000 compounds have been recognized that meet the criteria of an EDC. These chemicals are utilized in a varied range of consumer products like building materials, food packaging, clothing and upholstery, pesticides, personal care products, cleaning agents, plastics and medical devices, and thermal paper [17]. EDCs are multimedia pollutants that are present in all parts of the environment: inland and seawaters, atmosphere, soils, sediments, and vegetation [35]. Contact with several consumer matters is a major source of exposure to organic pollutants. Such matters include the plastic linings inside food and beverage containers, thermal receipts, soft toys, household materials, dental sealants, flame-retardants in clothing in upholstery as well as water and air pollution from vehicular, industrial and agricultural waste products, with some compounds persisting in the environment well beyond the initial pollution. People living near motorways are at risk of higher exposure to endocrine disruptors (such as benzene and PAHs), which are often components of hazardous air compounds in diesel exhaust. Other probable routes of exposure are through personal care products such as cosmetics, sunscreens, soaps, and many of which contain PAEs [4, 30]. There are other sources of chemicals. For example, pesticides and herbicides, such as DDT and methoxychlor, get into the environment and have adverse consequences. In addition, BPA, are present beverage and food storage containers [45]. The US CDC's National Health and Nutrition Examination Survey (NHANES) evaluates exposures to environmental compounds in the population which has documented widespread exposures to a number of endocrine disruptors. However, a large number of EDCs are not studied and the typical levels of exposure remain to be determined [17].

3.3 EDCs Contributions to Major NCDs

3.3.1 EDCs and Metabolic Diseases

3.3.1.1 Obesity

The worldwide prevalence of obesity has nearly doubled during the past three decades. This increase in the prevalence of childhood obesity and its consequences are no more limited to developed countries, and it has also increased in both developing nations. About one third of US children are obese or overweight, and over 60% of them will become obese adults. Moreover, there is obesity epidemic among infants 6 months of age and younger [17, 47, 48]. In other words, obesity now affects one in every six children and adolescents. Evidence regarding the effect of environmental factors on obesity prevalence is increasingly supported by (i) epidemiological observations and (ii) experimental evidence supportive of global environmental EDCs [29]. The risk of becoming obese may begin during pregnancy, early childhood, or in the first few months of life. Exposure to chemicals proven to cause obesity in animals results in reduced insulin resistance and altered glucose tolerance as well [2]. Obesity has genetic background; however, the recent epidemic cannot be due to mere genetic changes in the population, and thus must result from changes in environmental factors [3]. A subcategory of EDCs called 'obesogens' can distort sensitive metabolic processes if exposure happens during early development, which would result in obesity, type 2 diabetes mellitus, and MetS. These compounds are believed to lead people to weight gain due to changes in metabolic 'set-points', particularly if exposure takes place during sensitive periods of early life. Animal studies showed that important EDCs such as BPA, PAEs, some pesticides (DDT), and PCBs, can lead to weight gain later in life. PAHs, a family of environmental chemicals found in oil, coal and tar deposits, have been shown to prevent lipolysis, and might cause increased fat accumulation in adult mice. Exposure to air pollutants can also lead to excess weight gain later in life [49]. Environmental obesogenic compounds consist of PAEs, non-steroidal estrogens, parabens, organotins, PCBs, and bisphenols which are proven to have an impact on one or more of the following traits: (i) an increase in adipose tissue mass by hyperplasia or hypertrophy, (ii) an induction of dyslipidemia, (iii) a distortion of adipocyte function leading to increased lipid production, (iv) a disruption in metabolic hormone profiles, (v) an increase in preadipocyte differentiation, or (vi) an increase in the fate of mesenchymal stem cells (MSCs) to undergo adipogenic differentiation [29]. Exposure to PCBs remains universal as a result of improper disposal and bioaccumulation in the environment. In some researches, these chemicals have been indicated to accumulate at high levels in adipose tissue and might be a contributing factor in obesity high frequency [49]. BPA, a synthetic estrogen, is broadly used in a wide range of products such as toys, drinking bottles, baby bottles, food containers, medical device, and water pipes. Animal studies have shown that prenatal exposure to BPA is associated with the prevalence of obesity, lipid metabolism, and impaired glucose tolerance [50].

3.3.1.2 Diabetes

Prediabetes, typically defined as blood glucose concentrations higher than normal, is an earlier phase in the hyperglycemic continuum that has been shown to be linked with higher risk of developing diabetes. Prevalence of prediabetes is growing and it is predicted that more than 470 million people will have become prediabetic by 2030. Every year, approximately 5–10% of people with prediabetes become diabetic, while the conversion rate varies with population characteristics and prediabetes meanings [32, 51]. The main environmental factor driving the increased prevalence of type 2 diabetes (T2D) is obesity; 70% of the risk related with T2D is connected to weight gain [17]. For example, according to the data from the NHANES (2001–2008), separately suggested that urinary PAEs metabolites, such as mono-n-butyl phthalate (MBP), monobenzyl phthalate (MBzP), and three DEHP metabolites, including mono(2-ethylhexyl) phthalate (MEHP),

mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono(2-ethyl- 5-oxohexyl) phthalate (MEOHP), are positively associated with diabetes [23]. Moreover, there is accumulating in vitro data supporting a role of BPA in the development of diabetes [52]. A review article presented the role of several environmental exposures on the development of type 2 diabetes; in addition, it proposed the association of exposure to multiple classes of pesticides with risk factors for diabetes and obesity [3].

3.3.1.3 Metabolic Syndrome

The endocrine system involved in the control of metabolism is highly likely to cause EDCs to influence metabolic function. The possible effect of EDCs on the programming of glucose homeostasis during development and, thus, its role in obesity, diabetes, cardiovascular disease, and hypertension has received a lot of attention [2]. MetS is a complex disorder described by abdominal obesity, insulin resistance, hypertension, dyslipidemia, and hyperglycemia; it is a risk factor for cardiovascular disease, T2D, cancers, stroke, and chronic kidney disease. In the medical community, epidemics of metabolic diseases are mostly linked to changes in diet and genetic background, exercise and aging. There is now significant evidence regarding the role of other environmental factors in the rapid growth of MetS [17, 53]. As a matter of fact, various environmental factors are linked to the increase in metabolic diseases like stress, lack of sleep, adenoviruses, childhood antibiotics and exposure to environmental chemicals. Although all of these environmental stressors may play some role in the epidemic of metabolic diseases, we focus here only on the possible role of EDCs. Household air pollution and ambient air pollution from cooking with polluting fuels are estimated to cause 17% and 13% of cardiovascular diseases, respectively [10]. Cardiovascular diseases are still the main cause of mortality with over 80% of them in low-and middle-income countries. It is estimated that by 2030, over 23.6 million people will die from cardiovascular diseases [54].

3.3.2 Effects on the Reproductive Health

EDC harm normal physiological reactions associated to the reproductive system. They decrease the number and quality of sperms as well as increase the risk of prostate, testicular, and breast cancer. Testicular dysgenesis syndrome (TDS), testicular carcinoma, and poor semen quality are main diseases known to be related with some environmental contaminants affecting the endocrine system [42]. Current studies on PAEs are especially focusing on their reproductive toxicity potential. PAEs were recommended to target mostly male reproductive system. Numerous studies have reported that fetal exposures to DEHP instigate TDS-like effects and reduce anogenital distance (AGD) in rodents. According to many reserachers, DEHP malfunctions Leydig and Sertoli cells. Exposure to PAEs, particularly to DEHP, resulted in reduced production of testicular testosterone in rodents, and most reprotoxic effects are thought to be related to their anti-androgenic potential [1]. AGD is an important clinical measure to health effects of EDCs in environmental toxicology and has been identified as one of the endpoints in the US EPA guidelines for reproductive toxicity studies [55]. A recent meta-analysis has also documented the association of exposure to some EDCs with shoortened AGD [56].

3.3.3 EDCs and Cancer

More than 70% of all cancer deaths happen in low and middle-income nations. Mortality from cancer is projected to continue increasing, with an estimated 11.5 million deaths in 2030 [57]. The results of an analysis in animal studies on about 48 EDCs listed under center for disease control and prevention (CDC) have shown close association to mutagenicity, carcinogenicity, and developmental effects. Moreover, a study on infants and children living in agricultural regions using household pesticides showed an increased rate of lymphoma and leukemia. Recently, xenoesterogens have been assumed as the most prob-

able source for developing breast cancer. Increased estrogen level during pregnancy might lead to breast cancer. Some pesticides including DDT, toxaphene, etc. are proposed to give rise to breast tumors [42].

3.3.4 EDCs and Respiratory Diseases

Chronic respiratory diseases (CRDs) are diseases of the airways and the other structures of the lungs including respiratory allergies, asthma, sleep apnea syndrome, occupational lung diseases, chronic obstructive pulmonary disease (COPD), and pulmonary hypertension. The prevalence of these diseases is increasing, mostly among children and elderly people [58]. Exposures during fetal development are crucial and the consequences of these exposures are determined by the stage of development of the respiratory and immune systems when the exposures occur [59]. Researchers reported higher prenatal dialkyl phosphate levels with the occurrence of respiratory symptoms in early childhood during the period (0.5–5 years of age) [44]. Environmental factors related to asthma in childhood include respiratory viral infections, environmental tobacco smoke, aeroallergens, and inflammatory stimuli linked with ambient air pollution and indoor air pollution. Exposure to formaldehyde in early life would also greatly increase the risk of asthma [59].

3.4 Endocrine Disrupting Mechanism of Action

The various contaminants released into the environment create an enormous analytical challenge in quantifying people exposure while the physical properties of some chemicals contribute to their bioaccumulation and persistence in human tissues long after the exposure has ended [60]. The gene networks and target cell activities are managed by hormones and by binding to the responsive elements in the promoter of target genes [35]. EDCs affect human body through various pathways including: i) effect on hormone, nuclear, and nonnuclear receptors, ii) effect on enzymatic pathways, iii) effects on signaling pathways. EDCs were originally thought to exert actions mainly through nuclear hormone receptors. However, recent studies show that the mechanisms of their toxicity are much wider than previously thought. The properties of EDCs make them specifically well suited for activating or antagonizing nuclear hormone receptors. In fact, the nuclear hormone receptors are a super family of transcription factors that play major roles in both physiology and disease. The estrogen receptors (ERα and ERβ) are at the center of endocrine disruption studies. Findings of these studies may provide a model for how other nuclear receptors interact with hormone mimics. Identifying chemicals with estrogenic effect is now a main area of research. Some EDCs act as estrogen mimics. Although other EDCs have estrogenic effect, they are not true estrogens. For instance, BPA was designed as a synthetic estrogen and has been shown to bind to the estrogen receptors, resulting in a cellular signal transduction cascade indicative of an estrogen response. Hence, EDCs do display hormone ranging effects on cellular systems. These chemicals can affect the enzymatic pathways and can disrupt the action of enzymes involved in steroidogenesis, especially in the metabolism of estrogens. Additionally, they can affect cellular signaling pathways. PAEs and BPA are shown to actuate epithelial-to-mesenchymal transition (EMT). These compounds can also up-regulate or down-regulate the genes involved in the regulation of signal transduction [1]. Concern has increased since several EDCs are suspected of disrupting the programming of endocrine signaling pathways during the fetal development period [20]. In order to control exposure to disrupting chemicals, primary prevention and environmental interventions are required with major focus on early development to reduce the incidence of NCDs [59].

3.5 Conclusions

EDCs are commonly present in the environment. Serious measures must be taken to diminish the production of these chemicals as well as exposure to them; regulatory authorities of health and industry must be aware of their toxic effects. Studies in the field of EDCs have increased over the last decades, and increasing knowledge is provided in the areas of environmental toxicology and the risk of NCD development and progress. The growing scientific literature on the long-term effects of exposures adds new dimensions to the importance of preventing the harmful effects of environmental chemicals. Moreover, the novel insights require prospective long-term studies to define early-life exposures to environmental chemicals and provide new emphasis on trans-generational effects of EDCs. Environmental protection activities should be considered in policies and strategies related to primordial prevention of NCDs.

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4 Early Life Nutrition and Non Communicable Disease

Motahar Heidari-Beni

Abstract

The origin of some non communicable disease (NCDs) is in early life. Evidence has shown that early life nutrition is associated with the risk of developing chronic non communicable diseases. Pregnancy and infancy are the most critical stages that influence the risks of NCDs in childhood and adult life. Prenatal maternal undernutrition and low birth weight lead to obesity and increase the risk factors of cardiovascular disease and diabetes later in life. Nutrition is one of the easily modifiable environmental factors that may affect outcome of pregnancy, trajectory of growth, and immune system of the fetus and infant. Healthy eating behaviors associate with prevention of weight disorders in pediatric, non communicable diseases, and deficiencies of micronutrient.

Keywords

Nutrition · Pregnancy · Infancy · Non communicable disease

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4.1 Introduction

Early life nutrition is associated with the risk of developing chronic non communicable diseases (NCDs). Diseases that are non-infectious and non-transmissible are considered as NCDs. According to the World Health Organization (WHO) classification, cardiovascular diseases (CVD), diabetes, chronic respiratory diseases, and malignancy are major disease types of NCDs. The developmental origins of health and disease (DOHaD) hypothesis suggested that nutrition in early life (fetal, neonatal, and infantile periods) and prenatal nutritional environments associated with the risk of developing NCDs in adulthood [1, 2].

Pregnancy and infancy are the most critical stages that influence the risks of NCDs in childhood and adult life. Nutrition is one of the easily modifiable environmental factors that may affect outcome of pregnancy, trajectory of growth, and immune system of the fetus and infant. Nutritional exposures during critical time periods including preconception and the postnatal development correlated to the health of fetus and infant. Thus, nutritional recommendations are important in pregnancy and infancy [3]. Healthy eating behaviors associate with prevention of weight disorders in pediatric, non communicable diseases, and deficiencies of micronutrient [4]. Human studies reported that low birth weight correlated with increased risk of NCDs including type II diabetes,

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obesity, and CVD in later life [5, 6]. Animal studies showed that high fat or low protein maternal diet associated with developing cardio-metabolic disease in offspring [7, 8].

Nutrition during the early months after birth is provided by breastfeeding or formula milk.

Some immune-mediated disorders, obesity and cognitive function disorders are lower in breastfed babies [9, 10].

4.2 Nutrition In Utero and Risk of NCDs in Later Life

Age-associated disease has increased rapidly in developing and developed countries. There is strong correlation between maternal nutrition during pregnancy and increased prevalence of age-associated disease such as CVD, type II diabetes and obesity [11].

Studies showed that offspring of pregnant women during the famine had a low birth weight and were more predisposed to NCDs including CVD, weight disorders, glucose intolerant, hypertension, dyslipidemia, blood coagulation disorders, metabolic and allergic disease in childhood and later life. The time of exposure to the famine associates with the type of disorders in later life. Famine in early gestation increases the risk of CVD, dyslipidemia and obesity. Famine during mid-gestation increases microalbuminurea and renal function disorders. Famine in late-gestation enhances the risk of type II diabetes [12, 13].

Gestational diabetes or maternal obesity has been linked to increased risk of developing the metabolic syndrome and obesity in childhood and later life, premature mortality and coronary heart disease risk in the offspring [14].

Findings showed that Overweight or obese pregnant women had more overweight children than normal weight pregnant women. Body mass index of women at the start of pregnancy is a strong predictor of obesity risk of their offspring in adulthood [15].

Micronutrient deficiencies during infancy and pregnancy are another factor that correlates with healthy outcome in later life. Under-nutrition and vitamin A and zinc deficiencies in infancy associated with deaths of children fewer than 5 years of age. Malnutrition including both under-nutrition and over-nutrition leads to micronutrient deficiencies and NCDs [16].

4.3 Maternal Macronutrient Intake and Its Influence on Appetite and Food Preferences in the Offspring

Appetite and food preferences in the offspring may develop during fetal development. Studies showed that maternal diet during pregnancy was correlated with childhood intake. Protein, fat and carbohydrate intake were assessed during pregnancy and results showed that intake of same nutrients particularly protein and fat of 10 years old children were most strongly related to nutrition in pregnancy. Carbohydrate intake in pregnancy has been related to epigenetic markers changes at birth and childhood [17].

Dutch famine cohort found that the famine during early gestation led to more consumption of high-fat diet by offspring in later life [18].

Evidence has also shown that alterations in the nutritional environment during pregnancy can alter appetite and food preferences in offspring. For example, maternal protein intake reduction can lead to preference for high fat foods in offspring. Maternal under-nutrition can associate with persistent hyperphagia in offspring in later life [19].

4.4 Early Life Nutrition and Allergic Disease

Early life nutrition influences on the developing immune system. Several immune system diseases are inherited. However, genetic factors cannot justify the increase of immune system disorders in recent years. Some maternal nutritional changes including decrease intake of omega 3 polyunsaturated fatty acids, folate and zinc have been correlated with alteration in immune system [20].

A prospective study showed that increased risk of allergies especially eczema in infancy

may be related to highly intake of margarine, vegetable oils and some fruits and vegetables including celery, citrus fruit, and sweet peppers during pregnancy [21].

Other nutrients such as long-chain polyunsaturated fatty acids, prebiotics, probiotics and antioxidants including selenium, zinc, vitamin A, vitamin C, vitamin D and vitamin E have been associated with asthma and allergic disease [22].

Findings showed that antioxidants improved immune system function. According to observational studies, consumption of antioxidant-rich foods including fresh fruit and vegetables and higher antioxidant levels in pregnancy may decrease the risk of wheezing, asthma and eczema in the offspring [23]. However, there are controversial findings [24].

The maternal gut microbial environment is another factor for allergy protection in the offspring. Healthy immune system development needs balance of specific gut microorganisms. Infants with allergic disorders have unhealthy balance of microorganisms in the gut. According to animal studies, gut microorganisms regulate immune system development and decrease allergic disorder, obesity and cardio-metabolic disorders. Soluble prebiotic fiber including oligosaccharides is associated with improvement immune system and metabolic outcome [25].

Omega 3 have anti-inflammatory effects on immune and metabolic outcomes. Some clinical trials showed that fish oil supplementation during pregnancy had immune-modulatory effect and decreased allergic disease outcomes in the offspring. Another, have reported useful effects of omega 3 intake in early life on cardio-metabolic risk factors [26].

Australian cohort study showed significantly association between lower cord blood vitamin D levels and eczema at 1 year of age [27].

4.5 Nutrition in Early Life and Diabetes

One of the most common metabolic diseases is diabetes. Its prevalence is increasing recently. Changes in lifestyle related to urbanization in developing countries lead to increase the risk factors of NCDs including type II diabetes. Genetic and environmental factors are the cause of disease susceptibility. According to human cohorts and experimental animal study, there is association between early life nutritional environment and risk of cardio-metabolic disorders in offspring. Developmental programming is called for this process. It has shown maternal and paternal nutrition play a key role in metabolic programming of the offspring. Potential mechanisms for programming of type II diabetes are not clear. Some components of type II diabetes are correlated to epigenetic dysregulation. Transgenerational transmission of type II diabetes risk is related to eating behavior change and secretion and action of insulin [28].

Human and experimental evidence reported that early life nutrition especially during fetal life and early infancy affect the risk of type II diabetes. Malnourished conditions in fetal life with poor growth in utero (intrauterine growth restriction, IUGR) lead to impaired glucose and energy metabolism including increased peripheral insulin sensitivity, enhanced production of hepatic glucose, decreased insulin sensitivity for muscle protein synthesis and impaired pancreatic development [29].

Several studies showed the U-shaped association between birth weight and type II diabetes. High birth weight (>4000 g) and low birth weight (<2500 g) is associated with an increased type II diabetes risk [30, 31].

The time of solid foods introduction is one of the important nutritional period in infancy. Changes in diet composition including enhance in protein and caloric consumption occur in this period. Findings related to the time of solid foods introduction and weight disorders and glycemic profile in childhood are inconsistent [32]. In addition, there is less studies that investigate the relationship between the time of solid food introduction and glycemic profile in childhood. The difference in the findings is due to various definition of early food introduction; assess outcomes in different stages of childhood and not considering main confounding factors [33].

Study on pregnant women with gestational diabetes mellitus (GDM) showed that prolong breastfeeding was correlated with better glycemic profile and lower A1C levels during childhood. These results highlighted the importance of longer duration of feeding with breast milk for pregnant women with GDM [34].

Breast milk contains high polyunsaturated fatty acids that promote development of brain insulin receptors and lead to lower type II diabetes in later life. Study on Canadian pregnant women with GDM suggested that breastfeeding more than 8 months was associated to lower A1C levels compare to shorter time of breastfeeding [34]. Another study showed that exclusively breastfeeding more than 2 months led to less development of type II diabetes at the age of 10–39 years compare to infants without breastfeeding. The reasons of heterogeneity in findings are various study design and studied populations. Thus, more studies for assessment the role of breastfeeding duration on glycemic profile in childhood and adulthood are needed. In addition, more studies are needed to find new strategies for prevention of childhood obesity in children of pregnant women with GDM [34].

4.6 Nutrition in Early Life and Non-alcoholic Fatty Liver Disease (NAFLD)

According to human study, growth restriction in early life and insufficient nutrient supply for the fetus lead to development of liver disease in later life. Study on women aged 60–79 years showed that there was a relationship between low birth weight and enhanced liver enzymes alanine aminotransferase (ALT), gamma glutamyltransferase (GGT) and hepatic cellular injury [35]. Findings of a case control study reported an association between NAFLD in children and adolescents and IUGR. Low birth weight was associated with high prevalence of nonalcoholic steatohepatitis (NASH). According to evidence, rapid growth pattern after early growth restriction and macronutrient restriction is correlated with NAFLD risk [36].

Animal study showed that restriction of dietary protein during pregnancy and lactation cause to offspring hepatic steatosis and hepatic lipid accumulation in late adulthood. In maternal undernutrition, deposition of hepatic fat happens in fetuses faster than development of offspring adiposity. Thus, it can be concluded that growth restriction, obesity, high fat diets intake, and undernutrition during the critical early life lead to susceptibility and severity of NAFLD [36].

Evidence reports that one way for protection against NAFLD development, progression of NASH and liver fibrosis is early breastfeeding. Longer duration of breastfeeding leads to decrease the risk of obesity and liver disorders in later life [37].

Breast milk is a rich source of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These long chain polyunsaturated fatty acids (PUFSs) can suppress lipogenesis and liver fibrogenesis. Animal study reported that fish oil that rich in PUFAs reduced hepatic steatosis, lipogenesis and increased lipid oxidation [38].

Several peptides including insulin and leptin are present in breast milk. These peptides affect infant growth and body composition. Findings showed that leptin intervention during the neonatal period led to decrease metabolic disorders and progression of hepatic steatosis [39].

Several fruits including red grapes contain naturally resveratrol. Resveratrol has antioxidant and anti-inflammatory effects. It decreases liver steatosis and dyslipidemia and has useful influence on mitochondrial oxidative stress. Intake of fruits in early life can prevent liver disorders in later life [40].

Another item that has anti-inflammatory properties is taurine. It is a sulfonic amino acid. Studies showed that taurine supplementation during pregnancy and lactation can decrease proinflammatory hepatic profile in children. However, more studies are needed to confirm safety of taurine supplementation during pregnancy and lactation [36].

4.7 Early-Life Nutritional Status and Metabolic Syndrome

Metabolic syndrome (MetS) is defined as some CVD risk factors including obesity, dyslipidaemia, hypertension and high blood glucose. Nutrient restriction in the uterus lead to undesirable changes in organ function and enhanced the risk of CVD in later life and adulthood. Low birth weight is one marker for nutritional deficiency in fetal life. It is associated with MetS in adulthood [41]. Findings showed that nutritional deprivation in utero and incidence of disorders in later life differ according to gender. However, most studies did not stratify analysis by gender [42].

Finding of a meta-analysis demonstrated that low birth weight led to 2.4-fold increase in MetS in adulthood. Previously, this association has been shown only in men [43].

4.8 Early Life Nutrition and Cancer Risk

Evidence shows that some cancers such as breast cancer originate in early life. Epidemiological studies reported that environment factors including nutrition in early life associated with breast cancer risk in later life. According to animal studies, both under-nutrition and over-nutrition influence the risk of cancer susceptibility in children. Early life environmental factors can alter epigenome and affect cancer risk. Nutrition in early life as one of the environmental factor leads to persistent epigenetic changes, alteration in mammary gland development and finally increases susceptibility to breast cancer [44].

Animal study showed that low birth weight and protein restriction during pregnancy and lactation associated with increase in the expression of the insulin and estrogen receptor and more incidences of mammary tumors in later life of children. Risk of mammary tumorigenesis enhance in later life by over-nutrition in early life. High fat diets during pregnancy lead to high birth weight and increase mammary tumors in adulthood [45].

According to animal studies, diet high in n-6 PUFA during the peripubertal period led to more incidence of mammary tumor than eating high n-6 PUFA diet during post puberty. It is suggested that nutrition during peripubertal period associate with susceptibility of cancer risk. However, n-3 PUFA intake during peripubertal period decreases mammary tumourgenesis, mammary cell proliferation and increases apoptosis [44].

According to animal studies, some micronutrient intake in early life influences the cancer risk in later life. Finding of some epidemiological studies showed an inverse association between dietary folate intake and cancer risk [46].

However, another study reported that folic acid supplementation more than 400 μg/day increased the risk of breast cancer. Folic acid consumption is increasing because of food fortification, use of supplement and periconceptional folic acid supplementation for the prevention of neural tube defects. Thus, influence of folic acid supplementation in early life on cancer risk in later life must be assessed [47].

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5

Family Based Prevention of Cardiovascular Disease Risk Factors in Children by Lifestyle Change: The PEP Family Heart Study

Peter Schwandt and Gerda-Maria Haas

Abstract

Aim: The 14 years' Prevention Education Program PEP was started 1994 among first graders, their siblings and parents living in the half million city Nuremberg (Germany). The aim of prospective family-based observational study was early detection and lifestyle intervention of traditional cardiovascular risk factors.

Subjects and methods: Out of 3370 families 24,927 adults and 23,740 children participated in the PEP Family Heart study. Anthropometric parameters including blood pressure and fasting lipids were measured. Because these variables change specifically because of natural growth and development in 3–18 years old children we had to calculate age-and gender-specific growth curves using the LMS method. Non-overweight (normal weight) is defined as BMI < 85th percentile (pctl), overweight as BMI 85th to <95th percentile, obesity as BMI ≥ 95th percentile and severe obesity as ≥ 120% of the 95th pctl. Prehypertension is categorized as the ≥90th to <95th pctl or ≥120/80 mm Hg and hypertension as ≥95th pctl on ≥3 occasions.

Main results:

1. Cardiovascular risk (CVD) factor screening in school children predicted CVD risk in parents.
2. The growths curves for auscultatory systolic (SBP) and diastolic (DBP) blood pressure of non-overweight 8713 boys and 8138 girls nearly identical with the percentile curves of all 11,328 boys and 10,723 girls.
3. The shapes of the 10 lipid percentile curves between the 3rd and 97th pctl differ considerably by age and gender.
4. The wais-to-height ratio (WHtR) percentiles as a measure for abdominal adiposity vary substantially by age and gender
5. Among overweight and obese ≥85th pctl the percentile curves of body fat increase steeply until age 10 years and then decrease slowly in boys whereas the BF% percentile curves in girls increase continuously until age 18 years
6. The prevalence of hypertension increased strongly in severe obesity at the 99th pctl, more steeply beyond 120% of the 95th pctl to 59.1% in boys and 56% in girls.
7. The association between hypertension and normal weight, overweight and obesity increased in boys from 0,5, via 2,7 to 4,3 and in girls from 0,4 via 2,1 to 5,9.

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8. Between 2000 and 2007 mean blood pressure decreased from 138.3 ± 18.5 mm Hg to 124.0 ± 13.8 mm Hg in fathers and from 119.1 ± 2.8 mm Hg to 110.4 ± 11.2 mm Hg in mothers.
9. After 1 year weighed dietary protocols demonstrate in 166 fathers a decrease of all six nutrional components like daily energy consumption from 2423 to 2307 Kcal, from 98 g to 91 g fat, from 260 g to 252 g carbohydrates, from 88 g to 84 g protein, cholesterol from 362 mg to 339 mg and alcohol from 19 g to 17 g per day and in 237 mothers from 1915 Kcal to 1830 Kcal, from 79 g to 73 g total fat, from 216 g to 212 g carbohydrates, from 66 g to 64 g protein, from 299 g to 244 mg cholesterol.
10. Sustained intensive individual and family-based lifestyle counseling in daily life in terms of healthy diet, less sedentary behavior and more leisure time physical activity slightly improved the CVD risk factor profiles in parents and their children already after 1 year.

Keywords
PEP Family Heart Study · CVD risk factors · Lifestyle intervention

5.1 Introduction

Cardiovascular diseases (CVD) are the leading causes of mortality and chronic morbidity worldwide, begin early in life and their risk factor profile should be detected in childhood and adolescence for early intervention by lifestyle change [1–3]. A school-based intervention trial in New York describes a decrease in plasma levels of total cholesterol by −8.5 mg/dL and favourable trends in dietary intake and health knowledge after 5 years among 3388 school children [4]. If these findings can be replicated, this will suggest that educational programs to modify coronary risk factors are feasible. Because children have frequent contact with the health care system while their young parents very often have not, the family is an optimal target for early detection of cardiovascular risk factors. The Australian Busselton Population Health Study considered the nuclear family as a point of intervention by modifying risk factors [5]. In six studies, groups receiving lifestyle-based weight loss intervention offering 52 or more hours of contact showed greater improvements in blood pressure than in control groups [6].

Here we report data from the prospective community-based observational PEP Family Heart Study which was performed in the whole family mainly at home by specially trained professionals over 15 years [7]. The two aims of this urban family-based study were *first* to detect cardiometabolic risk factors using easily available, safe, non-invasive and inexpensive traditional measurement procedures and *second* to intervene by regularly controlled sustained lifestyle change in terms of healthy nutritional intake, leisure time physical activity (LTPA) and non-smoking in young adults and their children. This study took great advantage from the Bavarian Cholesterol Screening Project in 220,000 Bavarian residents [8, 9] and from two 6 months' studies on fat modified nutrition and serum lipoproteins in men and women living in closed societies in Landsberg and Oberschönefeld in Bavaria [10–12].

5.2 Subjects and Methods

Subjects From the school years 1993/1994 to 2007/2008 a total of 48,667 volunteers living in 94% of the elementary school districts of Nuremberg (Germany) were enrolled free of charge. The participants consisted of 24,927 adults (55% women) and 23,740 children (12,192 girls) living in 3268 families without known CVD or traditional CVD risk factors. Separate analyses for adults and youths had to be performed because in children and adolescents the anthropometric and laboratory risk variables specifically vary by age and sex because of the natural growth in childhood and adolescence [13]. Informed written consent that included the voluntary participation in the yearly surveys was

obtained from all participants respectively their caregivers. Yearly individual health passports informed each participant about his/her actually ascertained data. Only anonymized complete data sets were scientifically evaluated by the study center. The study fulfilled the criteria of the Declaration of Helsinki and was approved by the ethical committee of the Medical Faculty of the Ludwig Maximilians University of Munich, the Bavarian Ministry of Science and Education and the local authorities in Nuremberg [7].

Healthy Lifestyle Intervention Once a year each participant delivered complete questionnaires reporting his/her sedentary behavior, leisure time physical activity (LTPA), tobacco smoke exposition and dietary protocols recording precisely weighed using special scales the daily nutritional intake over 7 continuous days [14]. The sustained training for weighing dietary components correctly and completing the yearly dietary records and questionnaires together with the yearly provided individual health certificates on the actual risk profiles considerably strengthened motivation and adherence throughout the study. Beyond this health education performed by dieticians and physicians in terms of sustained individual and group counseling at home we provided further advice on healthy lifestyle including additional written material during blood sampling, phone calls, cooking courses, exercise sessions, special seminars and family meetings between the visits at home. According to the AHA recommendations we used four healthy lifestyle factors (current smoking, weight control, LTPA and seven days' dietary records) to determine adherence to healthy lifestyle [1, 15].

Measurements Physical examinations, medical history, questionnaire-guided interviews, healthy lifestyle counseling and seven days' weighed dietary protocols were performed at home by specially trained physicians and certified dieticians, organized by the PEP team residing in the sanitary board of the city of Nuremberg. At each survey, weight and height were measured to the nearest 0.1 cm and 0.1 kg using a calibrated electronic scale SECA (Vogel & Halske, Hamburg, Germany) and a Stadiometer Holtain Ltd (Crymych, UK). Anthropometric measurements were performed at home as previously described [7, 14, 16–22] in terms of BMI, waist circumference (WC), hip circumference (WHR), waist-to-height ratio (WHtR), triceps and sub-scapular skinfold thickness (SFT) using a Holtain skinfold caliper (GPM-caliper, Zurich, Switzerland) on the left body side in triplicate to the nearest 0.1 mm calculating %BF using the age-and sex adjusted Slaughter equations [23]. To obviate inter-observer variation during one survey the same individuals made all anthropometric measurements. Systolic (SBP) and diastolic (DBP) blood pressure were measured twice (calculating the average) in a sitting position after 5 min rest on the left arm supported, cubital fossa at heart level using a validated nonmercury ERKA-Aneroid semi-annually calibrated sphygmomanometer (MTM Munich, Germany) providing 4 appropriate cuff sizes [24]. Fasting blood was collected at Saturdays in November, December and January in central school buildings. Fasting triglycerides (TG), total cholesterol (TC), LDL-C, Non HDLC and HDL-C were measured by enzymatic methods in the central laboratory as described previously [21].

Categorization Non-overweight (normal weight) is defined as BMI < 85th percentile (pctl), overweight as BMI 85th to <95th percentile, obesity as BMI ≥ 95th percentile and severe obesity as ≥ 120% of the 95th pctl [25]. Prehypertension is categorized as the ≥90th to <95th pctl or ≥120/80 mm Hg and hypertension as ≥95th pctl on ≥3 occasions [24].

Statistical Analysis All statistical analyses were performed using actual SPSS (Chicago, Illinois, USA). Bivariate and multivariate analyses were conducted, and multivariate regression analysis was used for age and gender adjustments. Generalized estimating equations (GEE) were used to generate adjusted *p* values that accounted

for correlation among multiple within-family observations, as well as for adjustment for age and gender. Analyses were also stratified by child–parent specified between-subjects gender associations by calculating estimated marginal means [26, 27]. Self-reported physical activities were calculated in metabolic equivalents at task (MET) according to Ainsworth and Ridley using equations for adults and children as previously described [28, 29]. All variables were tested for normal distribution. Statistical tests were two-sided, and p-values less than 0.05 were considered statistically significant, for correlations with $p < 0.01$ and significances for paired differences and regression coefficients respectively odds ratios (OR) with $p < 0.001$. Smoothed age-, gender-and height-specific percentiles for children were constructed using the software package LMS Chart Maker Pro, version 2.3 estimating the skewness parameter L, the median M, and a measure of variation S [30].

5.3 Results

5.3.1 Cardiovascular Risk Factors

5.3.1.1 Family Screening

S*creening* elementary school children for cardiometabolic risk factors may be an efficient case-finding strategy in their parents allowing for early lifestyle intervention in parents and the whole family [16]. We found in 2720 child-parent pairs an age and gender adjusted 2–3 fold higher odds ratio among parents for the same risk factors. This was most pronounced for the silent risk factors dyslipidemia (e.g. for high LDL-C the odds ratio was 2.99, 95%CI 2.36–3.79) and high waist-to-height ratio (OR 2.55. 95%CI 1.80–3.62) but less for hypertension (odds ratio 1.3, 95%CI 0.89–1.90). Within the same gender the associations were even stronger e. g. if the son has low HDL-C the risk for low HDL-C was 1.40 fold (95%CI 0.95–2.05) in fathers and 3.32 fold (95%CI 2.27–4.84) in mothers respectively in daughters with low HDL-C the corresponding risk was 1.6 fold in fathers and 2.1 fold in mothers.

5.3.1.2 Adolescents

Among 3038 German adolescents (1639 males) aged 12–18 years participating in the PEP Family Heart Study we found 412 adolescents with ***central obesity*** defined as elevated WC and/or elevated WHtR [31] who had a three to four times higher risk factor clustering than the 2626 adolescents without central obesity [17]. Central obesity was the only anthropometric variable that significantly predicted increased risk for all seven non-anthropometric CVD risk factors as hypertension (OR 2.5), elevated triglycerides (OR 4.9), LDL-C (OR 2.0), non-HDL-C (OR 2.1), triglyceride/HDL-C ratio ≥3.5 (OR 7.2), low HDL-C (OR 1.6), fasting glucose (OR 1.3), and risk factor clustering (OR 3.8). In addition, the sum of skinfold thickness predicted low HDL-C (OR 2.3; 95% CI 1.2–4.4) and hypertriglyceridemia (OR 3.9; 95% CI 1.2–13.9).

Thus, six simple anthropometric measures can detect seven silent CVD risk factors in adolescents.

In 3024 German ***adolescents*** (1631 males) aged 12–18 years we assessed ***fat patterning*** by measuring with the LMS method [30] age-, gender- and ethnicity-specific percentiles for weight, height, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip-ratio (WHR), waist-to-height ratio (WHtR), % body fat (%BF) as calculated according Slaughter [23], skinfold thickness (SFT) for triceps ($SFT_{triceps}$), subscapular (SFT_{subsc}) subscapular/triceps ($SFT_{subsc/triceps}$) and SFT sum. This study completes our corresponding percentiles in ***children*** [32].

5.3.1.3 Percentage Body Fat

We estimated % BF in 22,113 German youths aged 3–18 years participating in yearly cross-sectional surveys of the PEP Family Heart Study between 1993 and 2007. Percentage body fat was calculated from skinfold thickness (SFT) using Slaughter equations [23].Ten smoothed percentile curves were constructed for % BF using the LMS method [30]. The age- and gender-specific reference curves demonstrate a continuous age-dependent increase of percentage body fat from age 3 to 18 years in girls; whereas in boys, the

percentile curves steeply increase from 5 to 11 years and thereafter slightly decrease [19].

5.3.1.4 Metabolic Syndrome

BMI is not a component of the metabolic syndrome (MetS) according to the International Diabetes Federation (IDF) defining central obesity for children and adolescents as waist circumference (WC) at or above the 90th percentile [33]. Therefore, we aimed to compare BMI with the five components of MetS over ***10 year's follow-up*** (1994–2003) in 2228 (1116 boys) first graders aged 6 years. As shown in Table 5.1 mean values of BMI and waist circumference remained stable over time, while the mean values of blood pressure, triglycerides, HDL-Cholesterol decreased continuously in both genders [34].

5.3.1.5 Elevated Blood Pressure

Throughout 10 years (1994–2003) mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) decreased continuously in 2228 (1116) first graders in boys by −3.8% SBP and −10.2% DBP and in girls by−4.1% SBP and −9.7% DBP [34].

Among 10,841 (5628 males) children and adolescents aged 10 years the prevalence of ***prehypertension*** (85th to <95th percentile) was 14.6%. Prehypertension was significantly associated with cardiovascular risk factors in terms of a more than doubled risk for overweight/obesity and a 1.2–2.5 higher risk of dyslipidemia. Males/females had 1.8/2.0 times higher risk of abdominal obesity and 1.7/1.9 times higher risk of an increased percentage of body fat [35].

Using the LMS (Lamda-Mυ-Sigma) method, we developed ***age-, gender-, and height-adjusted percentile curves for systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the 50th, 85th, 90th, 95th, and 97th percentiles in 22,051 German youths*** (18,917 normal-weight, 1938 overweight, and 1196 obese) aged 3–18 years from yearly cross-sectional surveys of the PEP Family Heart Study Nuremberg [20]. The mean prevalence of hypertension and of obesity is 7.3% and 5.2% among children and 7.2% and 5.8% among adolescents, respectively. The prevalence of hypertension increased with increasing weight (Table 5.2) reaching 59% in boys and 56% in girls with severe obesity The odds ratios between hypertension and overweight were 2.7 in boys and 2.1 in girls increasing to 4.3 (95% CI: 3.5–5.2) in obese boys and to 5.9 (95% (CI): 5.1–7.5) in obese girls (Fig. 5.1). Therefore we calculated separate SBP and DBP percentiles for 1938 overweight and 1196 obese 3–18 years old subjects which provide considerably higher BP values such as 148/91 vs. 136/86 mm Hg for a 17-year-old obese male and 136/91 vs.123/81 mm Hg for a 17 years old obese female, respectively, at the 90th percentile. Similar differences between overall percentiles and obesity percentiles exist for 6 years old obese boys as 112/76 mm Hg respectively 122/84 mm Hg and 6 years old obese girls as 112/76 mm Hg respectively 123/84 mm Hg. Because of these substantial differences we recommended to consider separate percentiles for overweight and obese children and adolescents [20]. Urbina and Falkner criticized this as a wrong conclusion because of the higher risk for target organ damage even at levels below the 95th percentile [36, 37]. Figure 5.2 depicts ***significant associations between elevated blood pressure and measures of body fat distribution.*** Females have the highest risk of hypertension in terms of % body fat ≥ 90th percentile (odds ratio 5.6) and of overweight/obesity (OR 5.4) whereas in males the risk of hypertension is between OR 3.4 and OR 3.8 for all four measures.

5.3.1.6 Dyslipidemia

As demonstrated in 6 years old first graders (Table 5.1) mean values of triglycerides and HDL-Cholesterol decreased continuously over ***10 years*** by −25.9% and −19.8% in 1116 boys respectively 1112 girls by −28.6% and −23.4% [34].

We found significant associations in 5628 males and 5213 females (median age 10 years) between ***prehypertension*** and dyslipidemia in males/females in terms of elevated total cholesterol (OR 1.5/1.4), elevated triglycerides (OR 2.5/2.0), elevated LDL-Cholesterol (OR 1.5/1.1), elevated non HDL-Cholesterol (OR 1.5/1.2). In 839 prehypertensive males respectively 748 females the prevalence of ***elevated total cholesterol*** (≥ 200 mg/dL) was 13.6%/16.3%%, ***elevated LDL-Cholesterol*** (≥130 mg/dL) 11.2%

Table 5.1 Ten years' follow-up of 7 CVD risk variables in 2.228 6-years old males and female first graders participating in the PEP Family Heart Study

Year	Mean age	Median	BMI,kg/m^2	WC, cm	WHtR	SBP, mmHg	DBP, mmHg	TG,mmol/L	HDL-C, mmol/L
1116 boys									
1994	6.4(0.5)	6.0	15.8(2.4)	56.9(5.6)	0.46(0.03)	105.1(10.0)	70.7(8.4)	0.85(0.42)	1.73(0.35)
1995	6.4(0.5)	6.0	15.6(1.7)	56.0(4.8)	0.46(0.04)	104.2(8.7)	67.1∗(7.1)	0.65∗(0.28)	1.55∗(0.40)
1996	6.4(0.5)	6.0	16.0(1.8)	58.0∗(4.7)	0.47(0.03)	104.7(8.9)	70.9(9.0)	0.64∗(0.22)	1.51∗(0.28)
1997	6.6(0.5)	6.0	16.2(2.4)	58.6(6.8))	0.47(0.04)	106.2(9.2)	71.1(6.8)	0.67(0.21)	1.60(0.34)
1998	6.5(0.5)	6.0	16.4(2.3)	58.7∗(5.7)	0.47(0.04)	104.5(10.3)	71.8(7.8)	0.63∗(0.16)	1.57∗(0.26)
1999	6.4(0.5)	6.0	15.8(1.7)	56.8(4.0)	0.47(0.03)	104.0(6.8)	66.2∗(7.1)	0.76∗(0.33)	1.39∗(0.31)
2000	6.4(0.5)	6.0	15.6(1.7)	58.7(5.7)	0.47(0.03)	103.9(8.6)	67.4∗(7.5)	0.67∗(0.25)	1.37∗(0.24)
2001	6.4(0.5)	6.0	16.1(1.8)	56.3(4.7)	0.46(0.03)	101.8∗(7.8)	62.1∗(7.1)	0.61∗(0.26)	1.47∗(0.28)
2002	6.4(0.5)	6.0	16.0(2.1)	56.6(4.8)	0.47(0.03)	102.6∗(6.7)	63.8∗(7.0)	0.62∗(0.23)	1.47∗(0.36)
2003	6.3(0.5)	6.0	15.9(2.4)	56.3(6.1)	0.46(0.04)	101.1∗(7.7)	63.5∗(5.7)	0.63∗(0.23)	1.54∗(0.26)
1112 girls									
1994	6.4(0.5)	6.0	15.6(.4)	55.0(5.4)	0.45(0.03)	105.2(10.0)	71.0(8.5)	0.91(0.41)	1.71(0.35)
1995	6.4(0.5)	6.0	15.7(2.2)	55.4(5.5)	0.45(0.04)	104.1(9.0)	67.1∗(6.9)	0.71∗(0.26)	1.38∗(0.36)
1996	6.3(0.5)	6.0	15.7(1.7)	56.4∗(4.4)	0.46(0.04)	103.5(9.2)	70.0(8.4)	0.73∗(0.30)	1.49∗(0.34)
1997	6.6(0.5)	6.0	16.2∗(2.4)	58.8∗(5.9)	0.48∗(0.05)	104.3(9.4)	71.8(9.7)	0.68∗(0.07)	1.50∗(0.47)
1998	6.4(0.5)	6.0	15.8(1.3)	56.4(3.9)	0.46(0.03)	105.0(9.6)	71.9(7.6)	0.88(0.42)	1.38∗(0.47)
1999	6.4(0.5)	6.0	15.9(2.2)	57.3∗(6.1)	0.47(0.05)	104.0(10.2)	66.0∗(8.6)	0.74∗(0.21)	1.41∗(0.27)
2000	6.4(0.5)	6.0	16.2∗(2.0)	57.1∗(5.8)	0.47(0.04)	104.2(8.2)	67.5∗(7.5)	0.82(0.22)	1.41∗(0.30)
2001	6.3(0.5)	6.0	15.8(1.8)	55.5(4.7)	0.46(0.03)	101.5∗(7.6)	63.7∗(7.0)	0.73∗(0.30)	1.28∗(0.36)
2002	6.3(0.5)	6.0	16.3∗(2.6)	56.9∗(5.5)	0.46(0.04)	102.9(6.9)	64.5∗(6.7)	0.73∗(0.29)	1.40∗(0.29)
2003	6.3(0.5)	6.0	15.9(1.9)	56.1(4.8)	0.46(0.03)	100.9∗(7.6)	64.1∗(7.0)	0.65∗(0.21)	1.31∗(0.21)

*$P < 0.05$ compared with baseline values

Table 5.2 Prevalence of hypertension by BMI percentiles in 11,328 males and 10,723 females aged 3–18 years

	Males (n = 11,238)			Females (n = 10,723)		
BMI	<85th ptl.	85th–95th ptl.	≥95th ptl.	<85th ptl.	85th–95th ptl.	≥95th ptl.
n	8713	1494	1121	8138	1548	1037
%	76.9%	13.2%	9.9%	75.9%	14.4%	9.7%
Normal BP (<90th ptl)	81.1 %	71.3 %	59.5 %	82.1 %	72.2 %	50.7%
Prehypertension (90th–95th ptl.)	13.2 %	18.3%	21.9 %	12.9 %	18.7 %	24.9%
Hypertension (≥95th ptl.)	5.7 %	10.4 %	18.6%	5.0 %	9.1 %	24.4%

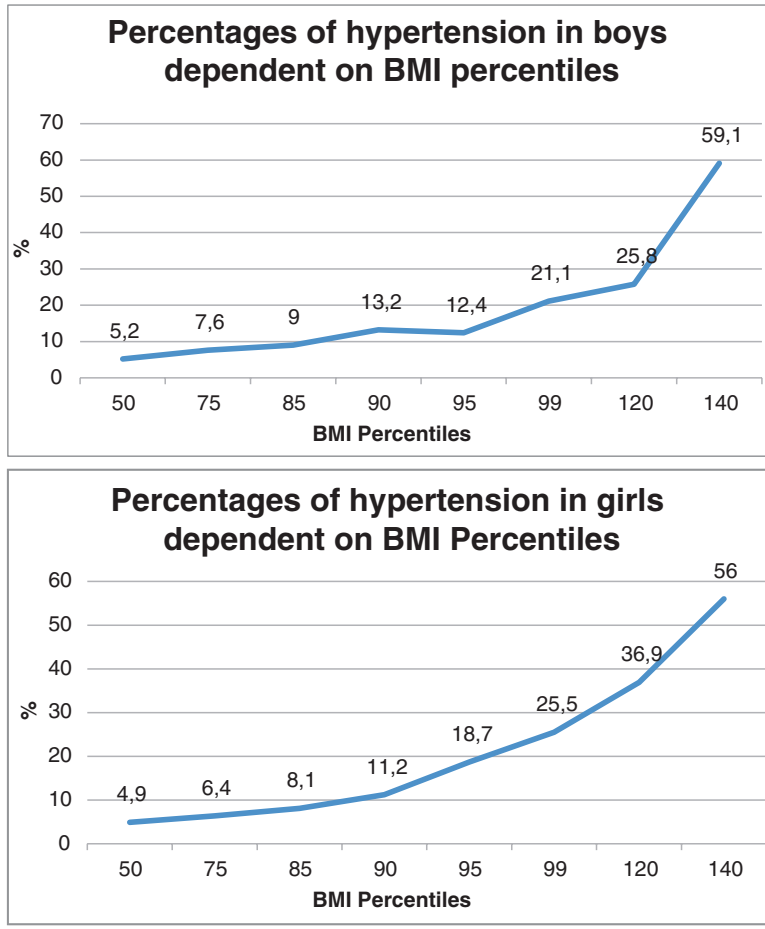

Fig. 5.1 Prevalence of hypertension by BMI percentiles in 11,328 males and 10,723 females aged 3–11 years

respectively 11.8%, ***low HDL-Cholesterol*** (≤35 mg/dL) 2.1% respectively 2.3%, ***elevated non HDL-cholesterol*** (≥145 mg/dL) 11.9% respectively 14.3% and of elevated triglycerides (≥150 mg/dL) 2.4% respectively 2.7%) [35].

5.3.1.7 Overweight and obesity

We estimated ***percentage body fat*** (% BF) in 22,113 German youths aged 3–18 years participating in yearly cross-sectional surveys of the PEP Family Heart Study between 1993 and 2007. Percentage body fat was calculated from skinfold

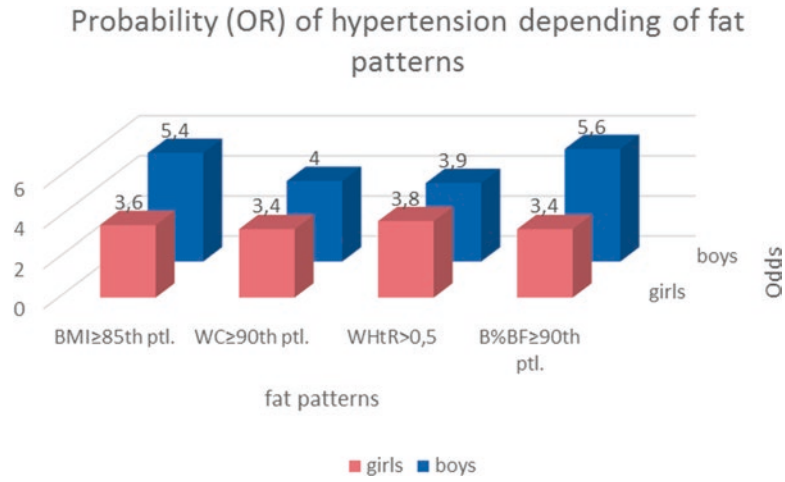

Fig. 5.2 Comparison of the probability of hypertension in different weight groups

thickness (SFT) using Slaughter equations [32]. Ten smoothed percentile curves were constructed for % BF using the LMS method [30]. The age- and gender-specific reference curves demonstrate a continuous age-dependent increase of percentage body fat from age 3 to 18 years in girls; whereas in boys, the percentile curves steeply increase from 5 to 11 years and thereafter slightly decrease [19].

Among 10,841 (5628 males) children and adolescents aged 3–18 years the prevalence of prehypertension was 14.6%. Prehypertension was significantly associated with combined overweight/obesity in terms of ≥85th percentile (odds ratio 2.0 in males, 2.4 in females) and with increased percentage of body fat (OR1.7 in males and 1.9 in females [30].

5.3.1.8 Smoking

Since smokers and (to a lesser extent) passive smokers adhere to an unhealthier diet compared to nonsmokers we randomly selected 419 pairs from 1462 PEP participants living in the same household in 1996. 817 (50.6% females) 27–66 years old subjects with complete data sets were allocated to one of the four groups: Nonsmokers living with a nonsmoker (group I), nonsmokers with a smoker (group II), smokers living with a nonsmoker (group III), and smoker living with smoker (group IV). Daily intake of nutrition was assessed over 7 continuous days as described. The smoking status was verified by plasma cotinin concentration which is a suitable biomarker for quantifying the exposure to tobacco smoke in smokers and passive smokers. Between group I and group IV we found significant decreases for the daily intake of fiber (from 20.1 ± 6.4 to 15.3 ± 4.5 g), linoleic acid (12.4 ± 4.6 to 10.5 ± 3.1 g), ascorbic acid (96.7 ± 49.5 to 73.9 ± 37.0 mg), a-tocopherol (from 11.4 ± 4.1 to 9.3 ± 3.0 mg) and ß-Carotene (3.2 ± 2.7 to 2.0 ± 1.4 mg). The strongest correlations between dietary intake and plasma concentrations was found for ascorbic acid in men (r = 0.40) and for ß-Carotene in men (r = 0.49) and women (r = 0.39) [38].

5.3.1.9 Low Birth Weight

Low birth weight is considered a cardiovascular risk factor. In 843 children and adolescents aged 3–18 years we could not find between birth weight and 9 traditional risk factors for cardiovascular diseases [39]

5.3.1.10 Migrants

As demonstrated in Fig. 5.3 the prevalence of cardiovascular risk factors in adults and their children from three major groups of migrants participating in the PEP Family Heart Study and compared the cardio-metabolic risk profiles between migrants and German participants [40].

In general, in all ethnicities, the mean values of variables studied were significantly higher in male than in female adults and in female than male children and adolescents

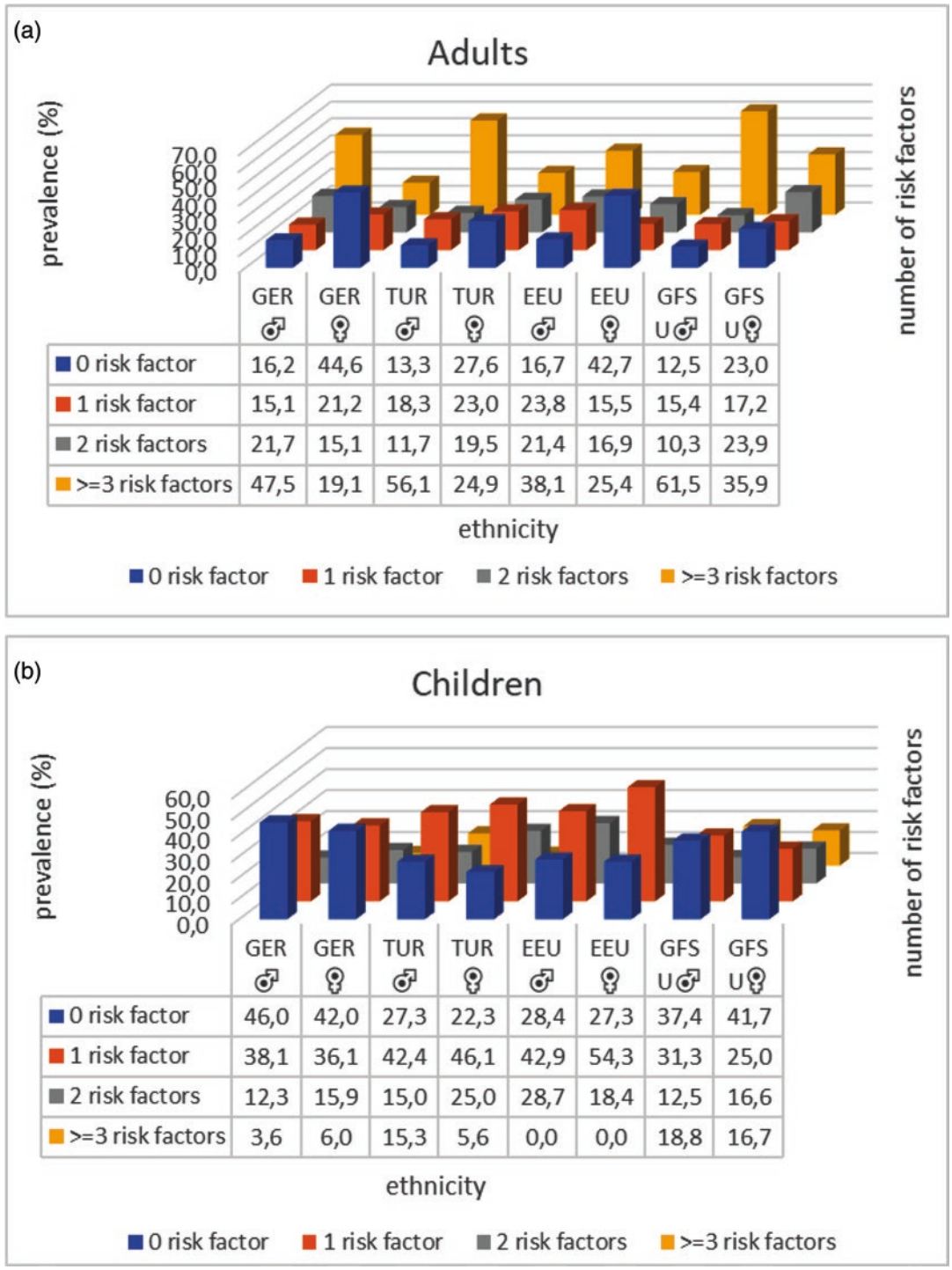

Fig. 5.3 Distribution Cardiovascular risk factor in German residents (GER). migrants from Turkey (TUR). Eastern Europe (EEU) and German emigrants from the former Soviet Union (GFSU) participating in the PEP Family Heart Study [51]

5.3.2 Lifestyle Change

5.3.2.1 Healthy Nutrition

We wanted to learn whether 687 biological child-parent pairs from healthy families would accept sustained advice and repeated control of healthy lifestyle behavior under everyday conditions. We found in this first national effort to implement lifestyle change in healthy free-living families in a primary health care setting that Intra-familial lifestyle behavior and cardiovascular risk factors improved after 1 year of ***sustained lifestyle*** counseling in schoolchildren and their parents [14]. Daily fat consumption as percentage of kcal as percentage fat significantly ($p < 0.05$) decreased by 6% and the ratio polyunsaturated to saturated fat and consequently the P/S ratio increased by 11.7% in all participants. The age and gender adjusted changes in parents (using GEE) after 1 year were predictive in children for reduced energy intake (OR 2.3; 95% CI 1.6–3.1), reduced fat consumption (OR 1.9; 95% CI 1.4–2.6) and a higher P/S ratio (OR 2.6; 95% CI 1.9–3.6). Daily leisure time physical inactivity of parents was associated with low HDL-C (OR 2.0; 95% CI 1.0–4.0) in daughters. Tobacco smoke exposition decreased by 19.3% in all participants whereas alcohol intake in parents decreased by 15% after 1 year.

5.3.2.2 Leisure Time Physical Activity

In 6040 old PEP participants we found significant associations between components of the ***metabolic syndrome*** and leisure time physical activity (***LTPA***) including sedentary behaviour and nutrition [41]. LTPA was higher in boys (26.3 METs) than in girls (15.5 METs) and higher in male (35.8 METs) than in female (21.2 METs) adolescents. We observed a significant ($P < 0.001$) association between low HDL-C and sports less than 30 min/day (OR 2.4; 95% CI 1.2–5.0). Low LTPA was significantly and inversely associated with elevated SBP ($r = -0.446$) and elevated TG ($r = -1.087$). We found the strongest associations of high WC with low sport activity ($r = -0.749$) and with sedentary time ($r = 0.307$), and sedentary time was significantly and inversely associated with high HDL-C ($r = -0.903$). This is consistent with a recent meta-analysis of 14 studies with 20.871 youths showing significant and inverse associations between moderate to vigorous physical activity and HDL-C [42].

5.4 Discussion

Among others the first family studies from Switzerland [43], USA [44], Australia [5] and Germany [7] described that cardiovascular risk factors may be correlated between children and their parents [45]. Considering family functioning is of value in childhood obesity research and including the family in childhood obesity interventions. Twelve cross-sectional and longitudinal studies reported significant associations between family functioning and childhood overweight and obesity in children or adolescents aged 3–17. Poor family functioning was associated with increased risk of obesity and overweight in children and adolescents, and obese children and adolescents were more likely to come from families with poor family functioning [46]

In 2018 the Framingham Heart Study celebrates its 70th anniversary. Daniel Levy, Framingham's director for more than two decades, discussed what the study has revealed about heart disease [47]. "Rates of cigarette smoking have declined and are really quite low at about 10–13% of Framingham participants in the third generation. Rates of uncontrolled high blood pressure are much lower today than they were in the offspring generation or in the original cohort when they were recruited 70 years ago. Uncontrolled lipid levels are much less common today. Average cholesterol levels have declined. We've witnessed in our nation as a whole very steep declines in death rates from heart disease and stroke in the range of 60–70%. This has been true both in men and in women. The one risk factor, though, that has moved in the wrong direction is obesity. We're concerned about the future because of doubling and tripling rates of obesity among our children. That may carry with it increased risks for the development of type 2 diabetes, even at young ages, and elevations in lipid levels. That already is being observed in the

nation as a whole. And that rise in obesity may carry with it greater hypertension and elevations in lipid levels. We may blunt some of the benefits that we've accrued over the course of the last 50 years because of this obesity epidemic." Early work from Framingham opened up the whole field of preventive cardiology by identifying modifiable risk factors for heart disease. The baton was then passed on to clinical trialists to demonstrate that cholesterol, blood pressure, and cigarette smoking can be controlled, and we now know that controlling each of these risk factors can reduce risks for heart disease substantially, both in men and in women

5.4.1 International Comparisons in youths

5.4.1.1 Children

A school-based 5-year intervention trial in two demographically different areas of New York using "Know your body" curriculum including a 24-h recall in the intervention group (n = 22) found favourable trends in blood cholesterol levels −8.5 mg/dL respectively −5.0 mg/dL mg, in dietary intake health knowledge but no effects on BMI, physical fitness or blood pressure [4]. Eight to nine-year old children participating in the Child and Adolescent Trial for Cardiovascular Health (CATCH) had comparable BMI but lower blood pressure, total and HDL-Cholesterol than corresponding PEP children [48]. Though apolipoprotein E-polymorphism seemed to modulate the associations between various indices of obesity and serum lipids we found differences between ***Apo E-phenotype*** in normal weight and overweight children [49].

As shown in Table 5.3 comparisons of ***anthropometric and lipid*** between age-specific reference curves and mean values of 1721 German and 2076 Iranian children aged 6–12 years revealed lower mean values of body mass index, waist circumference and triglycerides and higher values of total cholesterol and HDL-Cholesterol in German than in Iranian children [50]. Furthermore, the comparison of **waist circumference** among 3–19 years' old males and females from 14 countries requires population specific percentiles showing considerable differences (Table 5.4) [18]. Among children from 12 countries the changes of WC at the 90th pctl during growth are considerably different between 6 and 11 years old boys and girls (Table 5.5).

5.4.1.2 Adolescents

Among 3647 German and 2728 Iranian 10–15 years old adolescents the prevalence of the ***metabolic syndrome*** (MetS) according to the unified pediatric definition by the International Diabetes Federation (IDF) from 2007 was four times higher in Iranian (2.1%) than in German (0.5%). Among the 5 MetS-components the prevalence of low HDL-Cholesterol was by far the strongest difference between Iranian vs. German boys (35.9% vs. 7.7%) and girls (41.1% vs.6.6%), followed by hypertriglyceridemia in boys (8.9% vs.1.4%) and girls (12.4% vs. 2.5%) [46]. The

Table 5.3 Comparison of anthropometric and serum lipid variables (mean ± SD) in Iranian and German children

	Iranian Boys	German Boys	Iranian Girls	German Girls
Height (cm)	124.57(11.54)	125.6(11.48)	123.5(10.45)	124.90(11.35)
Weight (kg)	27.08(7.12)	25.51(7.03)	26.8(7.64)	25.29(7.29)
BMI (kg/m^2)	17.35(2.84)	15.89(2.08)	17.28(2.81)	15.93(2.28)
Waist C.(cm)	58.72(8.34)	57.46(6.20)	58.14(8.32)	56.55(6.19)
Hip C.(cm)	68.81(9.8)	65.53(7.30)	69.25(9.12)	66.17(7.78)
WHtR	0.88(0.07)	0.71(0.006)	0.86(0.05)	0.72(0.06)
TC (mg/dL)	153.13(34.30)	172.333(28.86)	149.87(34.78)	176.95(30.48)
LDL-C(mg/dL)	90.02(29.86)	100.5(25.12)	87.60(32.3)	106.44(27.71)
HDL-C(mg/dL)	44.10(12.35)	59.57(13.64)	4.03(12.27)	56.92(14.09)
TG(mg/dL)	93.29(31.53)	60.15(25.04)	94.15(32.43)	67.96(28.08)
TC/HDL-C	3.57(1.23)	3.01(0.81)	3.56(1.16)	3.26(0.92)

Table 5.4 Age- and gender-specific LMS percentiles for waist circumference measured at different sites in children and adolescents aged between 3 and 19 years in 14 countries

Country	Male/Female	Age (year)	Survey	Site	Cutoff[a]	Author
Australia	4277/4162	7–15	1985	II		Eisenmann (2005)
Bulgaria	2952/1758	6–18	2006–2007			Galcheva et al. (2009)
Canada	1540/1524	10.5–18.5	1981	I		Katzmarzyk (2004)
China	1366/1227	6–12	2002–2004	I	85th ptl	Sung et al. (2007)
	7472/7370	6–18	2005–2006	I		Sung et al. (2008)
Germany	1788/1743	3–11	1994–2994	I	90th ptl	Schwandt et al. (2008)
	1633/1389	12–18	1994–2994	I	90th ptl	Haas et al. (2011)
Iran	10,253/10,858	6–18	2003–2004	I	90th ptl	Kelishadi et al. (2007)
Italy	1440/1418	6–14	n.r.	II	2 SD	Zanolli and Morgese (2001)
	443/375	3–11	n.r.	I	90th ptl	Maffeis et al. (2001)
Japan	5851/4762	6–18	1992–1994	III/IV	97th ptl	Inokuchi et al. (2007)
Mexico	415/428	6–10	n.r.	I		Gomez-Diaz et al. (2005)
Netherlands	7482/7018	0–21	1996–1997	I	>1,3/>2,3[b]	Fredriks et al. (2005)
New Zealand	302/278	3–19	n.r.	IV	80th ptl	Taylor et al. (2000)
Spain	701/659	6–15	1996			Moreno et al. (1999)
	140/0	11	1996	I	70th ptl	Moreno et al. (2002)
	1109/1051	13–18.5	2000–2002	I		Moreno et al. (2007)
Turkey	2337/2443	7–17	2005	I		Hatipoglu (2008)
UK	3585/4770	5–17	1988	I		McCarthy et al. (2001)
USA white	742/771	5–18	1992–1994	I	56th/57th ptl[b]	Katzmarzyk (2004)
USA black	519/574	5–18	1992–1994	I	50th/52th ptl[b]	Katzmarzyk (2004)

[a]*I* indicates midpoint between lowest rip and iliac crest, *II* umbilicus, *III* superior border of the iliac crest, *IV* minimal waist, *n.r.* not reported
[b]Male/female

Table 5.5 Comparison of 90th percentile values for waist circumference (cm) among 6 and 11 years old boys and girls from 12 countries. Obtained from drawn curves

	BOYS			GIRLS			
6 years	cm	11 years	cm	6 years	cm	11 years	cm
JAPAN	55.0	UK	67.9	JAPAN	56.0	UK	65.4
UK	57.1	JAPAN	70.0	UK	57.0	JAPAN	66.0
CHINA	60.0	AUSTRALIA	71.3	CHINA	58.0	TURKEY	68.4
TURKEY	61.3	CANADA	71.7	TURKEY	60.1	CANADA	68.7
AUSTRALIA	61.9	TURKEY	72.3	GEMANY	61.8	CHINA	69.0
GERMANY	62.6	CHINA	75.0	AUSTRALIA	62.7	AUSTRALIA	70.4
USA	64.2	IRAN	75.5	IRAN	63.5	GERMANY	74.7
IRAN	65.0	GERMANY	77.1	USA	64.0	IRAN	75.0
CYPRUS	65.6	CYPRUS	78.4	CYPRUS	65.9	MEXICO	75.2
ITALY	67.4	USA	81.1	MEXICO	68.0	CYPRUS	76.6
MEXICO	70.3	MEXICO	87.4	ITALY	73.0	USA	78.3
		ITALY	89.0			ITALY	90.3

pediatric MetS is becoming a substantial health problem at global level [52].

The **BIG Study** is the first study of its kind presenting the prevalence of the components of the Metabolic Syndrome (MetS) in large samples of children and adolescents from European, Asian and South-American ethnicities. A total of 4473 children (mean age 7.7 years; 2218 boys,) and of 6800 adolescents (mean age 12.6 years; 3409 males) participated in the *Belo Horizonte Heart Study from Brazil, The CASPIAN Study from Iran and the PEP Family Heart Study from Germany* according the uniform IDF definition for the MetS components in the pediatric age groups [53]. Based on the data of more than 11,000 youths from three ethnicities, while the prevalence of abdominal adiposity was similar, Iranian and Brazilian youths had considerably higher prevalence of dyslipidemia in terms of low HDL-C and hypertriglyceridemia, i.e., the components of the MetS, than German youths.

Comparing the two parameters (WC and WHtR) of ***abdominal adiposity*** between 11,326 ***Polish*** and 8218 ***German schoolchildren*** aged 7–18 years we found significantly higher mean and percentile values of waist circumference and waist-to-height ratio in German subjects [54].

5.4.1.3 Adults

Among 3055 German and 2925 Turkish 30–79 years old subjects women had significantly higher markers of abdominal obesity than German women, while waist circumference (WC) was similar among males. Blood pressure (BP), concentrations of total, LDL-cholesterol, and apolipoprotein B were significantly higher among Germans, whereas Turks had markedly higher fasting triglycerides and lower HDL-cholesterol. Unlike Germans, the current trend of smoking among Turks correlates with lower WC and lower systolic BP compared to non-smokers [55].

Both systolic blood pressure and low density lipoprotein (LDL) cholesterol show graded associations with cardiovascular disease and together account for two thirds of the population attributable risk of cardiovascular disease. Therefore, combined lowering of LDL cholesterol and blood pressure can potentially have a bigger effect in reducing cardiovascular events than either intervention alone [56] which would be potentiated by reducing obesity and non-smoking.

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6 The Growing Epidemic of Chronic Kidney Disease: Preventive Strategies to Delay the Risk for Progression to ESRD

Farahnak Assadi

Abstract

Hypertension, obesity and metabolic syndromes are leading risk factors for the development of chronic kidney disease (CKD). Considering the high prevalence of hypertension and obesity in children and adolescents and it's risk of progression to cardiovascular disease, CKD should be considered a serious long-term health issue in children with metabolic syndrome. Prevention of CKD requires a professional teamwork consisting of primary care physicians, nephrologists, nutritionist, pharmacist, and social work to identify and manage children at risk of developing CKD in order to provide a highly valuable management strategies. This review focuses on the principles underlying the importance of a team approach for CKD prevention.

Keywords

Chronic kidney disease · Risk factors · Prevention

6.1 Introduction

The prevalence of chronic kidney disease (CKD) is increasing worldwide and is becoming a problem of epidemic proportion. CKD is frequently associated with hypertension, obesity, and metabolic syndrome ant affects approximately 40 per million pediatric population across the globe [1–3]. The consequences of CKD include cardiovascular disease, stoke, and progression of the CKD to end stage renal disease, dialysis therapy, and kidney transplantation, which are serious and costly public health problem [4]. Risk factors for CKD include, history of prematurity, low birth weigh, family history of hypertension, obesity, dyslipidemia, type 2-diabetes mellitus, urinary tract infections, congenital anomalies of kidney and urinary tract, and cardiovascular disease [5–7].

Early identification and proper managements of the risk factors can substantially prevent the CKD progression and reduce the mortality and morbidity [8–11]. In current clinical practice, CKD is typically diagnosed by measuring serum creatinine concentration and estimating creatinine-based glomerular filtration rate (eGFR) [10, 12–19]. However, the eGFR is not reliable and can be affected by a variety of factors in CKD patients, including muscle mass, dietary protein, and exercise that may over or underestimate eGFR in CKD patients [20]. The lag between the initial renal insult and loss of renal

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function as assessed based on eGFR may explain the high mortality and morbidity rates associated with CKD.

Recently, a number of novel biomarkers for CKD detection have been identified and proven effective in predicting CKD before a change in serum creatinine concentrations or eGFR levels. These promising biomarkers include Kidney injury molecule-1 (KIM-1), interleukin-18, Csystin C, liver fatty acid- binding protein (L-FABP) and beta-2 microalbumin [21–28]. Screening urine for microalbumin has also been widely used in high risk population for the early detection of CKD [29].

6.2 Preventive Strategies

CKD is an important cause of morbidly and mortality in children. With the vast majority of CKD children living into adulthood, the primary care physicians serve as leading health care providers in defining the best practices for managing the children's transfer to adult care through a multi disciplinary management team work along with patients and their families, to develop and implement a robust transition education curriculum designed to promote successful self-management.

Preventive strategies should focus on, early recognition of risk factors for CKD development, and management of risk factors such as weight reduction, increase level of physical activities, life style modifications, blood pressure control, and glycemic control in diabetic patients, dietary approach to stop hypertension (DASH) diet, avoidance of over the counter nephrotoxic medications (non-steroidal anti inflammatory agents), and routine daily physical activities [29–32].

An effective and successful prevention strategies should include both patients and primary care providers' education. Increased patient's awareness and education about the seriousness of CKD and it's associated risk of mortality and morbidity is essentially to improve compliance with CKD medications and follow-up clinic visits. Primary care providers should also be educated about the CKD early detection by focusing on identifying risk factors associated with CKD by utilizing eGFR instead of serum creatinine level, and urine microalbumin in their daily routine practice.

Increased patient awareness and communication between the primary is considered the most effective approach in achieving better clinical outcome in CKD. The primary care provider interventions that can slow the progression of CKD include assessing renal function, treating hypertension using angiotensin- converting enzyme (ACE) inhibitors, angiotensin receptor blockade (ARB), maintaining careful glycemic control, ordering a low-protein diet, treating dyslipidemia, managing anemia, and monitoring patients at increased risk of CKD for the development of microalbuminuria [33–37].

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7 Prevention and Control of Childhood Obesity: The Backbone in Prevention of Non Communicable Disease

Roya Kelishadi and Motahar Heidari-Beni

Abstract

Childhood obesity is one of the major public health problems. Childhood obesity mostly remains in adulthood and lead to non communicable diseases like diabetes and cardiovascular diseases at a younger age. Therefore, childhood obesity prevention needs high priority. Several risk factors including genetic factor, unhealthy dietary habits, physical inactivity related to childhood obesity.

Providing suitable strategies and novel interventions should be considered by the entire health care system for prevention and management of obesity.

Keywords

Pediatric Obesity · Prevention · Non communicable diseases

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7.1 Introduction

Infant, childhood and adolescent obesity are increasing in many countries. Obesity as non communicable diseases (NCDs) risk factors threatens public health and associated with decrease life expectancy and quality of life. Childhood obesity mostly remains in adulthood and lead to chronic disorders [1].

The commission on Ending Childhood Obesity (ECHO) has provided recommendations for reducing childhood and adolescent obesity in various contexts worldwide. The main aims of ECHO are decrease the risk of morbidity and mortality due to NCDs, reduce the adverse psychosocial influences of obesity and decrease the risk of the next generation developing obesity [2].

Obesogenic environment including energy imbalance, physical inactivity, spent more times in front of television and sedentary life leads to weight gain and obesity. Single intervention cannot solve the increased prevalence of obesity and all environmental factors and a whole-of-government approach must be considered. Three critical time periods including preconception and pregnancy, infancy and early childhood, and older childhood and adolescence are important in obesity management [2, 3].

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7.2 Factors Related to Childhood Obesity

7.2.1 Dietary Habits

Unhealthy dietary habits including higher intake of caloric foods, sweetened drinks, fast foods, skipping breakfast, eating while watching television and lower daily milk, fruit, and vegetable intake are associated with childhood obesity. Studies showed the correlation between low dairy products consumption and obesity. Low milk intake and higher sugar-sweetened beverages consumption correlated with childhood obesity [4, 5].

There are some mechanisms for explanation these findings. Soft drinks replace milk and low calcium intakes leads to increase the level of 1, 25 $(OH)_2$ D. After that, calcium channels open in the membrane adipocytes and increase cytosolic $[Ca^{2+}]$. Finally, fat synthesis increase and lipolysis decrease in adipocytes. In addition, high intake of fructose, sucrose and fructose corn syrup in beverages are the cause of insulin resistance and obesity [6].

7.2.2 Physical Activity

According to findings, Low levels of physical activity are correlated with higher prevalence of obesity. Watching more than 2 h of television per day increases the risk of childhood obesity and 60 min of moderate to vigorous physical activity per day protect children and adolescents against obesity [7]. A prospective cohort study showed that one predictor of overweight was television to exercise ratio in adolescent and for compensation of 7 h of television per week, 2.5 h of exercise are needed [8].

Lifestyle changes in adulthood are more difficult than childhood. Thus, educational interventions related to healthy eating habits and physical activity (Aerobic, resistance, and combined training) at school is useful for obesity prevention.

Meta-analysis of cross-sectional studies demonstrated a linear relationship between TV watching and childhood obesity. Each 1 h/day increase in TV watching lead to 13% increase the risk of obesity [9].

7.2.3 Sleeping Pattern

Evidence has shown the association between concurrent increase in obesity levels and decrease in nighttime sleep duration among children. Sleep time affect the various aspects of energy balance [10].

A recent meta-analysis found that children with shorter sleep duration had twice the risk of overweight/obesity [11]. Findings showed that duration of nocturnal sleep may be associated with the level of physical activity. Children who have more physical activity may sleep longer at night [12].

Several pathways have been proposed for the effects of sleep on obesity risk. Experimental and human studies suggest the increased exposure to food-rich environments and short sleep affect obesity risk [13–15]. Circadian timing system affects eating behaviors, hormonal release and metabolism, and weight regulation [16–18].

Studies reported that when sleep was restricted, activation increased in the right anterior cingulate cortex, orbitofrontal cortex and ventromedial PFC while participants were presented with food images [19–21]. Thus insufficient sleep may predispose individuals to excessive caloric intake due to rewarding properties of highly palatable foods, impaired responses to energy-dense foods and unhealthy eating behaviors [22]. Consistent with these studies, behavioral findings suggest that sufficient sleep could decrease excessive energy intake by decreasing the rewarding properties of food and enhancing individuals' ability to resist food temptations within the context of our food-rich environment. [15, 23, 24]

7.3 Pathologic Causes of Obesity

7.3.1 Endocrine Causes

Weight gain is observed in some endocrine disorders, such as hypothyroidism, Cushing syndrome, growth hormone deficiency, and pseudo hypoparathyroidis. Cushing syndrome is typically associated with severe obesity; however, all disorders may lead to central pattern of adiposity. Less than 1% of children and adolescents with obesity suffer from endocrine disorders that hypothyroidism is the most common causes of endocrine-related weight gain [25]. Leptin is secreted from adipose tissue and regulate weight and induce satiety. However, there are insulin and leptin resistance in obese individual that contribute to reduce satiety and subsequent weight gain [25, 26].

7.3.2 Psychological Causes

According to findings, there is a correlation between depression and obesity [27, 28]. Depressed people have a 58% higher risk of obesity; the risk for developing depression over time is 55% for persons with obesity [28]. Studies suggest that depressive symptoms are associated with the development of the components of metabolic syndrome such as central obesity [29, 30].

The association between depression and obesity related to inflammatory mechanisms. Obesity has been characterized as a state of chronic inflammation due to elevated pro-inflammatory cytokine levels [27]. Pro-inflammatory cytokines stimulate HPA axis activation that hypercortisolemia promotes adipocyte accumulation, and vice versa [29].

Adiposity seems to induce inflammatory stress responses since that studies suggest that greater central adiposity leads to larger inflammatory responses [31, 32]. Systematic review of nine prospective studies showed the relationship between episodic maternal depression and indicators of child adiposity. Chronic maternal depression was associated with greater risk for child overweight [33].

7.3.3 Genetic Causes

Some gene mutations affect the leptin-melanocortin regulating pathway. MCR4 mutations are common. Gene mutations with several genetic syndromes including Prader-Willi, Bardet-Biedl, and WAGR (Wilms tumor, aniridia, genitourinary anomaly, mental retardation) associated with obesity [34–37].

7.3.4 Prevention and Treatment of Childhood Obesity

Less food consumption and increased physical activity are the main strategies for prevention and treatment of pediatric obesity. Family or school based approaches constitute the main components of programs to reduce pediatric obesity. Pharmacological and surgical treatments can be used when other methods are not beneficial [38].

Prevention is a public health priority worldwide. A Cochrane review showed the effectiveness of child obesity prevention programs for reducing adiposity and BMI in children especially in younger age groups [39].

In children, weight maintenance and healthy behavioral changes are recommended for proper growth. Gradual weight loss is recommended for those who have a more significantly increased BMI [40].

Some approaches recommend by the American Academy of Pediatrics Expert Committee for obesity management including promote healthy lifestyle (physical activity and eating habits), structured weight management, comprehensive multidisciplinary intervention and potential pharmacological and bariatric surgery intervention [41].

7.4 Non-pharmacologic Approaches

7.4.1 Family-Based Interventions

A modest weight loss (5–10%) through family-based interventions which focus on changing

dietary habits, physical activity, and thinking/behavior can lead to improvements in weight-related comorbidities [42]. A Cochrane systematic review showed that healthy lifestyle management reduced of BMI in children younger or older than 12 years after 6 months [43]. Another systematic review showed that comprehensive lifestyle family interventions caused an overall reduction of BMI [44].

Due to larger portions of energy dense foods in restaurants, energy intake is greater when meals are consumed in restaurants compared to homemade meals [45]. In addition, family meals seem to decrease time spent on television watching and improve the quality of the diet [46].

According to 15 randomized controlled trials findings, family-based interventions have positive effects regarding weight loss in overweight children. It showed that family have an important role in changing the lifestyles of overweight children [47].

7.4.2 School-Based Interventions

Prevention studies are more effective than treatment studies. Comprehensive interventions including physical activity and health education in school-based obesity interventions have beneficial effects in weight management [48].

7.4.3 Pharmacologic Approaches

Orlistat, an enteric lipase inhibitor, is allowed in children older than 10 years. Undesired side effects, including gas and oily stools, lead to stop the use of drug [49]. Metformin has been studied for weight loss in adolescents, and one trial showed significant BMI reduction with use of metformin compared with placebo after 6 months. However, some participants experience side effects including nausea, vomiting, and diarrhea. Metformin affect better in weight loss in obese adolescents with insulin resistance and hyperinsulinemia [50].

Some endogenous molecules including leptin, hypothalamic melanocortin 4 receptor, and mitochondrial uncoupling proteins affect body weight and are considered as potential targets for the pharmacological management of obesity [51]. Drugs do not cause permanent changes in life style and dietary habit. Thus, the best way for weigh management is education for improvement quality of life, increase physical activity and healthy dietary pattern.

7.4.4 Bariatric Surgery

Individuals with BMI $\geq$40 kg/m^2 or BMI $\geq$35 kg/m^2 with a significant obesity-related comorbidity are candidate for surgery. Bariatric Surgery improves the metabolic and psychosocial outcomes [52–54].

However, adverse consequences of surgery including those related to the surgical procedure, malabsorption and significant vitamin deficiencies, and weight regain in future, may limit the application of this therapeutic method [52].

Surgery is not allowed in patients with cognitive disabilities interfering with postoperative treatment, pregnant/breast-feeding adolescents or those who decide to become pregnant within the next year, and those who do not fully understand or acknowledge the risks associated with bariatric surgery. However, due to serious complications of surgical procedures, these method apply for the treatment of severely obese adolescents [55].

7.5 Conclusion

Childhood obesity has been identified as a global pandemic. Prevention is the most effective public health approach for increasing the community health. Comprehensive intervention including modification for healthy lifestyle, regular physical activity, decrease screen time and behavioral interventions have been recognized for management of childhood obesity. Anti-obesity drugs are not recommended in younger children. Bariatric surgery is applied for morbidly obese older adolescents but its long term safety effects are limited in this age group.

Family, school and community interventions are important for long term effects on child health. Involvement of government is necessary for developing opportunities for healthy diet and physical activity.

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