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Roya Kelishadi *Editor*

Healthy Lifestyle

From Pediatrics to Geriatrics

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Roya Kelishadi
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Healthy Lifestyle

From Pediatrics to Geriatrics

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Chapter 1
Unhealthy Lifestyle Behaviors During Pregnancy and Offspring Health Risks at Birth and Early Childhood

Xin'nan Zong and Bo Xi

Abstract Pregnancy is a special stage linked to various biopsychosocial changes. Lifestyle behaviors during pregnancy may change along social, mental and physical changes in a woman's body. This chapter focused on the potential impact of several common unhealthy lifestyle behaviors (e.g., physical inactivity and sedentary behaviors, alcohol use, exposure to tobacco smoke, unhealthy diet, sleep disturbances, psychosocial/mental stress) on offspring health risks at birth and early childhood. In fact, adherence to healthy lifestyle behaviors, the majority of adverse health consequences may be avoidable for newborn babies and young children. Further, healthy lifestyle interventions during pregnancy are expected to promote the health of mothers and their offspring from the earliest moment in life.

Keywords Growth restriction · Low birth weight · Cesarean · Stillbirth · Birth defects · Fetal alcohol syndrome · Attention-deficit hyperactivity disorder · Asthma · Allergy

Introduction

Pregnancy is a special stage linked to various biopsychosocial changes. Lifestyle behaviors during pregnancy may change along social, mental and physical changes in a woman's body. Several unhealthy lifestyle behaviors, including physical inactivity, sedentary behavior, alcohol use, exposure to tobacco smoke, unhealthy diet pattern, sleep disturbance, and psychosocial/mental stress, may occur during pregnancy that may have potential substantial impacts on offspring health risks at birth and early childhood. In addition, these unhealthy lifestyle behaviors may have more complicated interaction effect.

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From the perspective of life course epidemiology, biological studies of early life experiences have focused largely on prenatal or infant life, and have led to some clear understanding that periods of rapid organ system development during pregnancy and childhood are critical to later adult health [1]. A recent systematic review demonstrated the effect of periconceptional maternal lifestyle on clinical biomarkers and features of placental development and function during pregnancy [2]. A synthesis of existing empirical evidence posits that obesity epidemic in childhood may be the consequence of non-genetic evolutionary processes altering the interplay between maternal energy resources (e.g., adiposity and body mass), maternal patterns of physical activity, and the ensuing metabolic sequelae of pregnancy that may affect subsequent fetal outcomes [3]. A population-based birth cohort showed cardiovascular risk factors (micro- and macro-vascular) tracked from mother to child, regardless of the course of pregnancy [4]. From the perspective of Developmental Origins of Health and Disease (DOHaD) theory, coronary heart disease and type 2 diabetes may originate in early life through two widespread biological phenomena, namely compensatory growth and developmental plasticity [5]. Therefore, the deep understanding for associations between unhealthy lifestyle behaviors during pregnancy and offspring health risks at birth and early childhood may be very helpful to improve maternal well-being and prevent offspring adverse consequences.

This chapter focused on the potential impact of several common unhealthy lifestyle behaviors during pregnancy on offspring health risks at birth and early childhood, and provided more evidence for discussing, developing and revising interventions and recommendations.

Physical Inactivity and Sedentary Behaviors During Pregnancy

Physical inactivity and sedentary behaviors have been shown a substantial increase during pregnancy and are a cause of obstetric co-morbidity [6]. Compared with trained (e.g., exercise and sport) and physical activity, physical inactivity and sedentary behavior represent lower body movement and energy expenditure level that may cause adverse health outcomes [7].

Regular physical activity has been proven to result in remarkable benefits for both mother (including improved cardiovascular function, increased mood stability, limited pregnancy weight gain, decreased musculoskeletal discomfort, reduced incidence of muscle cramps and lower limb oedema, attenuation of gestational diabetes mellitus and gestational hypertension) and offspring (including improved stress tolerance, advanced neurobehavioral maturation, decreased fat mass) [8]. Another meta-analysis of 14 randomized controlled trials also concluded that structured physical exercise programs during pregnancy seemed to be safe for newborns, mainly favoring a lower birth weight within normal range [9]. Physical activity during pregnancy was

therefore recommended in some national guidelines and international guidelines [10, 11].

Increased time in sedentary behaviors during pregnancy may have potential impact on pregnancy outcomes for both mother (e.g., high levels of C-reactive protein and LDL Cholesterol) and child (e.g., larger abdominal circumference and higher birth weight) [12]. A systematic review and meta-analysis of 12 randomized controlled trials showed that in comparison of being more sedentary, aerobic exercise for about 30–60 min per time three to seven times per week during pregnancy was linked to a reduction in the incidence of preterm birth in overweight and obese pregnant women [13], as well as further aerobic exercise for 35–90 min per time three to four times per week may be safely performed by normal-weight women with singleton, uncomplicated gestations [14].

Alcohol Use During Pregnancy

Alcohol use during pregnancy is common in many countries. Alcohol use during pregnancy is the direct cause of fetal alcohol syndrome (FAS) that was linked to gross motor deficits (e.g., balance, coordination and ball skills) [15]. It was estimated that one in every 67 women who consumed alcohol during pregnancy would deliver a child with FAS which translates to about 119 thousand children born with FAS around the world every year [16]. A population-based cohort showed that a fourfold increased risk of birth defects classified as alcohol-related birth defects was observed after heavy prenatal alcohol exposure in the first trimester [17]. A longitudinal study confirmed high sustained prenatal alcohol exposure was associated with deficits in weight and length at birth, and deficits in psychomotor and mental performance at 6 to 12 months of age and even low-to-moderate prenatal alcohol exposure continued across gestation was linked to certain deficits [18]. Maternal alcohol consumption during pregnancy may be associated with a markedly increased risk of acute myeloid leukemia as well as neurodevelopment and cognition in childhood [19–21]. Prohibition and abstinence of alcohol consumption should be screened periodically for all pregnant women and women of child-bearing age [22, 23]. More effective interventions targeting alcohol use during pregnancy are urgently needed.

Exposure to Tobacco Smoke During Pregnancy

Attention-deficit hyperactivity disorder (ADHD) may be associated with prenatal exposure to cigarettes (OR = 2.1; 95% CI: 1.1–4.1) and prenatal exposure to alcohol (OR = 2.5; 95% CI: 1.1–5.5) during pregnancy [24]. Exposure to tobacco smoke in utero was suspected to be linked to childhood ADHD and ADHD symptoms [25]. Current systematic review showed that exposure to cigarettes, alcohol or illicit drugs during pregnancy might play a role in the development of neuroblastoma in

children [26]. A systematic review and meta-analysis including 18 studies further showed that secondhand smoke exposure, and particularly passive fetal exposure to maternal smoking during pregnancy, significantly increased the health risk of invasive meningococcal disease in childhood [27].

Maternal smoke exposure during pregnancy was connected with reduced fetal anthropometric measurements after the first trimester, particularly reduced head size and femur length [28]. Exposure to environmental tobacco smoke for non-smoking pregnant women may lead to reduces of mean birth weight by 33 g or more, and increases of the health risk of birth weight below 2500 g by 22% [29]. Exposure secondhand smoke for pregnant women were may be associated with the health risk of stillbirth (OR = 1.23; 95% CI: 1.09–1.38) and congenital malformation (OR = 1.13; 95% CI: 1.01–1.26) [30]. A systematic review and meta-analysis further strengthened the evidence that pregnant women should not smoke, and all women of reproductive age should be warned that exposure to nicotine and smoke products increases the health risks of stillbirth, neonatal death, and perinatal death [31].

Current evidence from systematic review and meta-analysis showed prenatal exposure to maternal smoking may play an important role on the induction of wheezing and asthma in children, particularly in the first years of life [32, 33]. In addition, childhood obesity may be also associated with prenatal exposure to environmental tobacco smoke [34].

Unhealthy Diet During Pregnancy

A mother's diet patterns during pregnancy may have potential influence on both herself and her child's short- and long-term health. A systematic review and meta-analysis from 25 observational studies showed that unhealthy dietary patterns during pregnancy, which was characterized by high intakes of refined grains, processed meat, and high saturated fat or sugar foods, were connected with lower birth weight (mean difference: −40 g; 95% CI: −61 to −20 g) and higher risk of preterm birth (OR = 1.17; 95% CI: 0.99–1.39) [35]. On the contrary, another systematic review and meta-analysis including 21 studies showed that dietary patterns with a higher intake of fruits, vegetables, legumes, whole grains and fish were linked to a decreased likelihood of adverse pregnancy and birth outcomes, such as pre-eclampsia (OR = 0.78; 95% CI: 0.70–0.86), gestational diabetes (OR = 0.78; 95% CI: 0.56–0.99), and preterm birth (OR = 0.75; 95% CI: 0.57–0.93) [36]. A synthesis of current findings also revealed the positive association between unhealthy diet patterns (such as food low in fruits, vegetables, fish and unsaturated fats and high in fat, sweets and salt) and maternal antenatal depressive and stress symptoms that may increase ultimately the risk of adverse health consequences in the offspring [37, 38].

According to a synthesis of current findings, a strong level of evidence supported the association between disordered eating during pregnancy and depressive and anxiety symptoms during pregnancy [39]. Further, eating disorders were linked to anxiety and depression and also have negative consequences for both mothers and

fetuses (e.g., cesarean, miscarriages, and premature births) [40]. Health education of healthy diet patterns during pregnancy should be strengthened to make dietary structure more reasonable, and to further reduce the occurrence of adverse pregnancy and birth consequences.

Sleep Disturbances During Pregnancy

Sleep disturbances are frequent during pregnancy, which were usually considered to be connected with adverse maternal and fetal outcomes. A systematic review and meta-analysis of 10 observational studies showed that short sleep duration and poor sleep quality may be linked to an increased risk of preterm birth [41]. Another systematic review and meta-analysis of 65 studies showed that sleep disturbances (e.g., obstructive sleep apnea, snoring, extreme sleep duration and poor sleep quality) were associated with an increased risk for preeclampsia (OR = 2.77; 95% CI: 1.81–4.24), gestational diabetes (OR: 1.96; 95% CI: 1.62–2.38), cesarean delivery (OR = 1.99; 95% CI: 1.70–2.33), depression (OR = 3.98; 95% CI: 2.74–5.77) and preterm birth (OR = 1.95; 95% CI: 1.55–2.45) [42]. Maternal sleep-disordered breathing during pregnancy may be associated with increased risks of adverse intrapartum and perinatal consequences, such as low birth weight, intrauterine growth restriction, preterm birth, cesarean delivery, low Apgar score, as well as gestational diabetes, pregnancy-related hypertension and preeclampsia [43–45]. Furthermore, a systematic review and meta-analysis showed poor sleep quality may be also linked to perinatal mood disturbances [46] that may increase ultimately the risk of adverse health consequences in the offspring. Therefore, expectant mothers should be advised to practice healthy sleep measures.

Psychosocial/Mental Stress During Pregnancy

Prenatal maternal stress may influence offspring's atopic risk through sustained cortisol secretion resulting from activation of the hypothalamic-pituitary axis. A systematic review and meta-analysis including 30 studies (enrolling > 6 million participants) showed prenatal maternal psychosocial stress may be linked to increased risks of allergy and asthma in the offspring [47]. A South African birth cohort reported the association between maternal antenatal and/or postnatal psychosocial risk factors (including psychological distress, depression, alcohol abuse and intimate partner violence) and infant lower respiratory tract infection [48]. Another large prospective birth cohort study of 7,814 mother–child pairs showed prenatal maternal depression symptoms were associated with unhealthy diet, and both depression and unhealthy diet were also each independently associated with abnormal child development [49].

In addition, a systematic review also displayed there may be a direct association between maternal prenatal stress and later obesity in the offspring [50]. Efforts should be made to improve maternal well-being to decrease the risk of offspring adverse health consequences.

Perspective

Epidemiological studies have indicated that exposure to some common adverse lifestyle behaviors during pregnancy (such as physical inactivity/sedentary behavior, alcohol use, exposure to tobacco smoke, unhealthy diet pattern, sleep disturbance, and psychosocial/mental stress) may be linked to adverse health consequences in the offspring. In fact, the above-mentioned adverse lifestyle behaviors during pregnancy are avoidable risk factors for offspring adverse health outcomes at birth and early childhood. Evidence that long-term health is shaped by the environment in early life calls for prenatal interventions to reduce the burden of chronic disease, however, society should not blame the mothers, by contrast, clearly should support mothers to secure future public health [51, 52].

The above-mentioned unhealthy lifestyle behaviors are prevalent during pregnancy that may result in severe health consequences in the offspring if they cannot be prevented and controlled effectively. Adherence to healthy lifestyle behaviors during pregnancy, such as regular aerobic physical activity, quitting smoking and being away from secondhand smoke, abstain alcohol use, healthy diet pattern (such as characterized by high intakes of vegetables, fruits, whole grains, low-fat dairy, and lean protein foods), appropriate sheep duration and good sleep quality, and positive and healthy psychosocial/mental status, may reduce the risk of intrauterine growth restriction, preterm birth, low or high birth weight, cesarean, stillbirth, neonatal or perinatal death, fetal alcohol syndrome/alcohol-related birth defects, acute myeloid leukemia, attention-deficit hyperactivity disorder, asthma, allergy, lower respiratory tract infection, and obesity at birth and early childhood (Fig. 1.1).

A woman who is healthy in the preconception period and during pregnancy is more likely to have a successful pregnancy and a healthy child. Healthy lifestyle interventions during pregnancy are expected to improve the overall health status of mothers and their offspring from the earliest moment in life. Future research should continue to examine in depth physiological consequences of maternal unhealthy lifestyle behaviors by adjusting major confounding factors and the robustness of healthy lifestyle behavior interventions based on current literature evidence. Finally, we call for heightened awareness of adverse lifestyle behaviors in the preconception period and during pregnancy, and continued efforts should be made to promote both maternal health and child health.

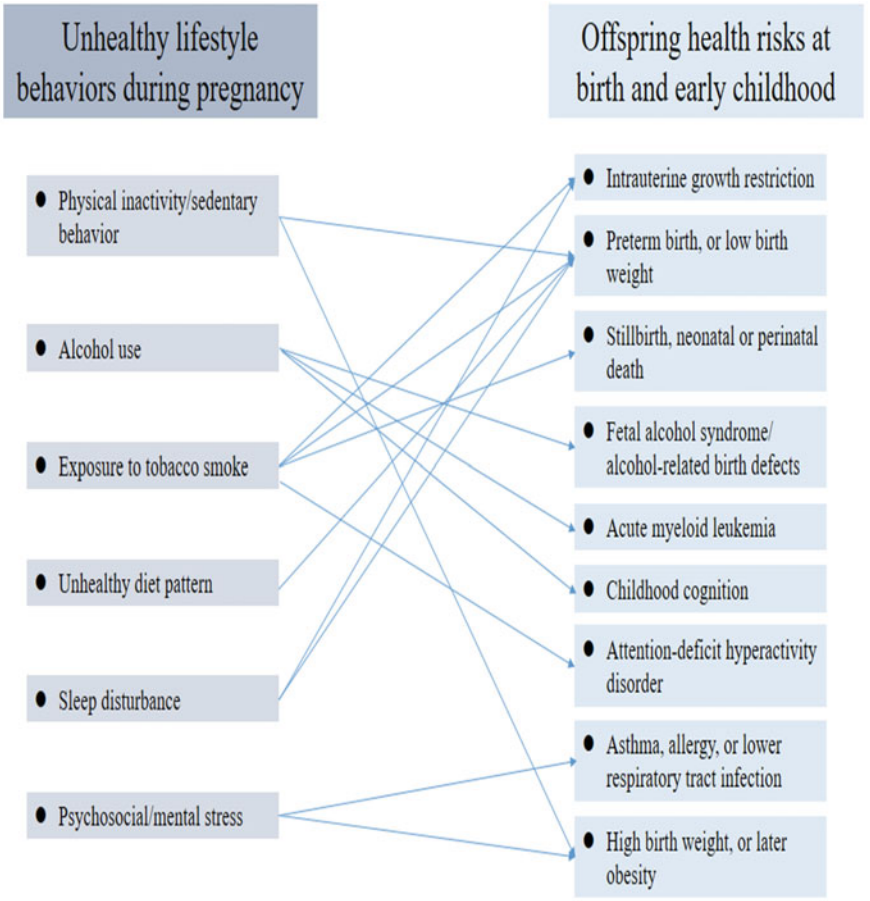

Fig. 1.1 Association between unhealthy lifestyle behaviors during pregnancy and offspring health risks at birth and early childhood

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Chapter 2
The Role of Healthy Lifestyle in the Primordial Prevention of Metabolic Syndrome Throughout Lifetime: What We Know and What We Need to Know

Farahnak Assadi, Mojgan Mazaheri, and Roya Kelishadi

Disease is an abnormal state of the body which primarily and independently produces a disturbance in the normal functions of the body. It may be an abnormality of temperature or from structure. Symptoms are a manifestation of some abnormal state in the body. It may be harmful as a colic pain or harmless as flushing of cheeks in peripneumonia. Avicenna

Abstract The incidence of metabolic syndrome including obesity, elevated blood pressure, dyslipidemia, and elevated blood glucose, has reached epidemic proportions in both pediatric and adult populations worldwide. The cost of treatment of metabolic-related diseases is a major concern to health care community. Suboptimal lifestyle behaviors, including poor nutrition, physical inactivity, and smoking habits as well as environmental exposures leading causes of preventable metabolic-related diseases. The process of metabolic syndrome begins in childhood and tracks for decades, leading to hypertension, cardiovascular events, diabetes mellitus, chronic kidney disease, stroke and sudden death during adulthood. Population-based and clinical studies have shown that healthy lifestyle from early childhood including healthy maternal diet, reducing salt intake, avoiding tobacco use, regular physical exercise, reducing the exposure to endocrine disruptor, as well as diet rich in vegetables and fruits and low in animal fats can prevent or retard the progression of metabolic syndrome later in life. Cost effective analyses suggest that public policy, community

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efforts and lifestyle modifications are likely to be cost-effective comparing with pharmacological treatment of risk factors. Early primordial prevention strategies of metabolic syndrome will provide great value in developing a healthier society and improved quality of life in older age. This article summarizes the rational and available data that support a healthy lifestyle approach to primordial prevention throughout life course and emphasis on the development of healthy lifestyle behaviors to reduce the risk of metabolic syndrome and its adverse heath consequences.

Graphical Abstract

Keywords Behavioral intervention · Dyslipidemia · Hypertension · Obesity · Primordial prevention · Physical inactivity · Tabaco use

Introduction

Currently, we are experiencing an epidemic of metabolic syndrome characterized by increasing rates of obesity, hypertension (HTN), type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and kidney disease (CKD) in both children and adult populations worldwide [1]. The burden of metabolic-related syndromes is paralleled by the enormous cost for delivering care.

The preclinical substrates for metabolic syndrome begin in childhood and are influenced over time by epigenetic and environmental exposures [2].

Prevention of the development of risk factors in the first place (primordial), and interventions to modify adverse events of risk factors (prevention) highlight the importance of preventing the development of metabolic syndrome [3–5].

We do have preventive measures that are relatively simple and quite effective. Unfortunately, the clinical delivery for preventing or slowing progression of metabolic syndrome is sadly inadequate or often not adequately implemented.

Clinical trial evidence clearly indicates that primordial preventions are effective and provide important information that it will work in communities [6]. According to the concept of "fetal programming" maternal suboptimal lifestyle habits that disrupt fetal growth and development in utero can program the fetus to express metabolic syndrome in later life. The National Children's Study also supports the value of primordial prevention beginning early in life by examining the effects of environment and genetics on the growth, development, and health of American children [7]. This study includes the cohort of children from before birth to 21 years of age and contributes to an understanding of the role that various factors have on health and disease. Further evidence comes from studies demonstrating a direct relationship between risk factors for CVD in childhood and increased carotid vascular changes in adulthood [8–11].

Metabolic syndrome affects a considerable number of people worldwide and the prevalence is on the rise in many Western countries as well as in many under developed societies [12–14].

The diagnostic criteria of metabolic syndrome has been recently harmonized according to a joint interim statement provided by the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity collectively, provided a harmonized definition of metabolic syndrome [15]. According to this joint statement, a diagnosis of the metabolic syndrome is established when 3 of the 5 risk factors including BMI > 30 kg m^2 (≥95th percentile in children) or enlarged waist circumference with population–specific and country-specific criteria, elevated blood pressure, fasting blood sugar (≥100 mg/dL), hypertriglycerides (≥150 mg/dL), elevated blood pressure > 125/85 mmHg (>90th percentile for children), and high density lipoprotein cholesterol (HDL-C) (<40 mg/dL in men and < 50 mg/dL in women) are present (Table 2.1) [15].

Subsequent to the established criteria by this joint statement, waist to height ratio has been found to be a better predictor of cardiometabolic syndrome than body mass index (BMI) and waist circumference [16].

Table 2.1 Diagnostic criteria for metabolic syndrome in children, adolescents, and adults

BMI	>30 kg/m^2 or ≥ 95th percentile in children
Triglyceride (TG)	>150 mg/dL
Low-density lipoprotein cholesterol (LDL-C)	>200 mg/dL
High-density lipoprotein (HDL-C)	<40 mg/dL in men; <50 mg/dL in women
Blood pressure	>130/85 mmHg or ≥90th percentile in children
Fasting blood sugar	>100 mg/dL

Pathogenesis

Mechanisms underlying the development of metabolic syndrome are not fully understood. It is suggested that insulin resistance plays a major role in the pathogenesis of metabolic syndrome [17, 18]. In obesity, increased free fatty acids can result in increase secretion of cytokines including tumor necrosis factor-α (TNG- α), interleukins 1β, and interleukin-6 leading to insulin resistance [19].

The insulin resistance via several different mechanisms plays a key role to the development of metabolic syndrome and can result in development of hypertension (HTN), T2DM, and dyslipidemia [20].

Major Risk Factors for Adverse Health Behaviors Associated with Metabolic Syndrome

Risk factors including obesity, cigarette smoking, dyslipidemia (high levels of low-density cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol) and elevated blood pressure, physical inactivity has shown to predict increased carotid-intima-media thickness in adults (Table 2.1) [9, 21–24]. The US Preventive Health Services Task Force has recently introduced a set of lifestyle objectives including nutrition, weight status, physical activity, and tobacco use for optimizing the health of American people [25]. The Healthy People 2020 aims to address some of these risk factors in clinical and community-based prevention in several programs despite of substantial differences and disparities in the delivery of preventive services [26]. In addition, obese children and youth with T2DM, have significantly greater carotid-intima-media thickness than their leaner counterparts [27–29]. Overweight, obesity and elevated blood pressure is prevalent in children and adolescent. These children are at risk for a number of metabolic syndrome including HTN, T2DM, CVD and CKD later in life.

Key Primordial Prevention Strategies for Metabolic Syndrome

The first and most important initiative for prevention of metabolic syndrome is to develop and improve public awareness about the seriousness of the problem. The second initiative is to improve prioritization of education programs that would meet the needs of patient care. Additional initiative is to include standardization of tools and procedures for education design to implement the population-based strategies for primordial prevention of metabolic syndrome (Table 2.2).

The population-based strategies to reduce risk factors in childhood to incident clinical metabolic syndrome in adult life should include comprehensive school-based programs to increase physical activity, improve nutrition, and prevent tobacco use.

Table 2.2 Recommended primordial prevention for metabolic syndrome

Diet/Nutrition	
Education	Educational campaigns to promote consumption of specific healthful foods and limiting salt and saturated fat consumption
Labeling	Detailed nutrition facts on packaged foods and beverages
Schools	Educational curricula for improving both school foods and beverages
Workplaces	Comprehensive worksite wellness programs focused on nutrition, physical activity, and tobacco cessation
Goal	Weight loss via healthy dietary intervention and physical activity
Physical activity	
Education	Encourage use of stairs vs. elevators and regular daily walking
Schools	Effective interventions on improving physical activity during school hours
Workplaces	Comprehensive worksite wellness programs with nutrition, physical activity, and tobacco cessation
Tobacco use	
Education	Increase public awareness of the tobacco-related health hazards
Labeling	Cigarette packages warning
Schools and workplaces	Community restriction on smoking in public places

Preventive intervention must begin from before birth to throughout life course to maintain appropriate weight, blood pressure, lipids, glucose, eat healthful foods and beverages, avoid smoking and do regular exercise [30, 31]. Therefore, rational and accepted evidence that support a life course community-based approach to primordial prevention must include the following categories:

Nutrition/Diet

The effects of dietary habits with development of metabolic syndrome begins from prenatal period and maternal diet has long-term impact on the components of metabolic syndrome in the offspring [32].

Early life nutrition is also important in this regard, for instance breast-feeding is documented to have beneficial effects in preventing metabolic syndrome [33].

Whereas excessive caloric intake and physical inactivity are likely important factors driving the obesity-related HTN, CKD, and CVD epidemic, it is important to consider additional mechanisms. Evidence suggest that sugar, particularly excessive fructose intake, has a critical role in the epidemic of cardiorenal diseases. Comprehensive interventions to promote healthy eating for school and day care meals and beverages are highly recommended. It is recommended to improve food labeling and to increase awareness especially about calories, sodium, fat and added sugar (Table 2.2). Diets rich in fruits, vegetables and whole grains, low fat dairy products as well

Table 2.3 Recommended Mediterranean diet in the primordial prevention of metabolic syndrome

Recommended	
Olive oil	Consume ≥50 g (~4 tablespoon/day)
Nuts	Consume ≥3 serving/week
Vegetables and fruits	Consume ≥4 serving/day
Sea food	Consume ≥3 serving/week
White meal (Poultries)	Consume ≥3 serving/week
Legumes	Consume ≥4 serving/week
Discouraged	
Avoid carbonated drinks containing fructose, corn syrup or added artificial sweeteners	–
Salt	Limit sodium intake to ≤1.5 g/day

as nuts and legumes are proven to be cardioprotective not only because of their low amount of sodium but also because they contain large amounts of potassium [27]. The American Heart Association recommends limiting consumption of red meat, sodium intake <1500 mg/day and refined sugar [34–40] (Table 2.3]. Increased added refined sugars especially fructose should be avoided for their possible link in the development of metabolic syndrome [41] as well as HTN and CVD [19, 20].

Increased added sugar consumption has also been linked to dyslipidemia [37]. Dietary intervention targeting polyunsaturated fat consumption is an effective mean to decrease the risk of CVD. Diets containing saturated and trans fats must be avoided, as they are known to increase the level of LDL-C and the incidence of CVD [38, 39] (Table 2.3).

Physical Activity

Routine physical activity (30–40 min sessions, 3–4/week) of moderate-intensity exercise is considered an important life style factor for primordial prevention of metabolic syndrome [37]. Both aerobic and anaerobic exercises can lower blood pressure and reduce body fat [42–45].

Initiatives should be undertaken to promote physical activity to ensure schools adopt and implement high-quality physical education and physical fitness programs throughout the school day in combination with dietary guidelines.

Blood Pressure

One cannot underestimate the importance of HTN across the breadth of clinical medicine. HTN affects 20% of the population and the risk of developing HTN

increases with age to such an extent that the lifetime (cumulative) risk for middle-aged individuals is 90%. The consequences of HTN include coronary artery disease, stroke, heart failure, and CKD.

Primary HTN is closely directly correlated with the body weight, body fat and insulin resistance. High body mass index (BMI), history of prematurity, low birth weight, and smoking are among risk factors associated with HTN [46].

Recently, the assessment and management of HTN has focused on accurate blood pressure measurements, appropriate nonpharmacological (lifestyle) strategies for prevention and control, how to attain target blood pressures that will reduce the risk of complications and minimize adverse effects, and how to assess and manage resistant HTN. Each of these topics is dealt with in this theme issue. The treatment of HTN should include behavioral modification such as sodium reduction. Weight loss in overweight and obese individuals and appropriate diet are also recommended.

With the marked rises in the prevalence of obesity and HTN in childhood, blood pressure screening programs for all school-age children and adolescents are warranted. Efforts to achieve lifestyle changes in diet, physical activity, and weight managements are the first step in the treatment of mild HTN, in the absence of CKD or CVD [47]. Dietary Approach to Stop HTN (DASH) have shown benefits in blood pressure lowering from diets rich in vegetables, fruits, grains, low fat dairy products, and reduced salt intake [48]. DASH diet effects on lowering blood pressure and CVD risk reductions are comparable to antihypertensive medications used in stage-1 HTN (Table 2.4). Significant decrease in both systolic and diastolic blood pressure may occur. Reduction in systolic blood pressure by 10 mmHg and in diastolic blood pressure by 5 mmHg has been reported in patients with mild HTN consuming DASH diet (Table 2.4). DASH diet also reduce CVD incidence by 15% and stroke by 27% in hypertensive patients [49, 50].

Table 2.4 Effects of lifestyle intervention on blood pressure

Modification	Approximate SBP reduction (mmHg)
Weight loss (10 kg)	5–10
Adopt DASH eating plan	8–14
Dietary sodium reduction	2–8
Physical activity	4–9
Smoking cessation	2–4

SBP systolic blood pressure; *DASH* dietary approached to stop hypertension
Modified from: Moore et al. [51] and Doring et al. [52]

Body Mass Index

Overweight and obesity are known to increase risk of metabolic syndrome including HTN, dyslipidemia, hyperinsulinemia and impaired glucose metabolism [39]. The US National Heart, Lung and Blood Institute has defined the following BMI (weight (kg)/height (m^2) for adults:

- Underweight < 18.5 kg/m^2
- Normal weight 18.5 to 24.9 kg/m^2
- Overweight > 30 kg/m^2.

For Children, Centers for Disease Prevention and Control growth charts has defined overweight as BMI between 85th and <95th percentile and obese as ≥95th percentile. Obesity management programs should be implemented in all schools by reducing calories and promoting physical activity. Calorie-dense snacks between meals must also be eliminated.

Smoking

Tobacco smoking has been shown to increase the risk of CVD and has been considered a metabolic risk factor [53]. Smoking prevention interventions in school-age children and adolescent can be effective by implementing comprehensive smoke-free clean air environment in schools and public buildings.

Endocrine Disrupting Chemicals (EDC)

Growing body of evidence exists on the role of environmental exposures in the development of metabolic syndrome and its consequences. EDCs include environmental, industrial, nutritional, agricultural, and pharmaceutical chemicals that might change hormonal activity by simulating natural hormones or antagonizing their actions and homeostasis in cells [54, 55].

Exposure to these chemicals contribute to the progression of some metabolic disorders including obesity, metabolic syndrome, and diabetes [56].

Given that these effects begin from prenatal period [57] and continues from childhood to adulthood [58] healthy lifestyle habits regarding environmental protection, and reducing the exposure to pollutant chemicals would help in prevention of metabolic syndrome and its components.

Type-2 Diabetes Mellitus

T2DM is associated with increased risk of HTN, CVD and CKD. The incidence of T2DM is also closely related to the increase in prevalence of obesity in children and adults [59, 60]. Lifestyle modifications and blood glucose screening programs should be implemented for diabetes prevention especially in the high-risk pediatric and adult populations. Lowering and maintaining HbA1c to <6.5% is highly recommended.

The community leaders, policy makers, and health care providers must implement the primordial preventive strategies that promote a healthy diet, increased physical activity, and cessation of tobacco use at the community level. Lower socioeconomic status is an established risk factor for metabolic syndrome. Obesity, physical inactivity, smoking, HTN and T2DM are disproportionately prevalent in the low socioeconomic populations [61]. Disparities often follow ethnic, racial and low socioeconomic status. To address these disparities, policy makers must provide opportunities to disadvantage members of their populations to have free access for preventive screenings and health promotion programs.

Summary

The prevalence of clinical metabolic syndrome including obesity, HTN, dyslipidemia, and elevated fasting blood sugar has increased significantly worldwide and in all age groups. The cost of treatment of metabolic-related diseases is a major burden on families, communities and public health. Most of these metabolic-related diseases are preventable. Initiatives should be undertaken to make healthcare providers, policy makers and the general population more aware of seriousness of metabolic-related syndrome and its risk for the development of HTN, CKD, CVD, and stroke. Primary physicians remain the cornerstone for the primordial prevention to improve metabolic heath. This review provided a range of population-based preventive strategies to promote healthy lifestyle by improving diet, increasing activity, and reducing smoking habits and exposure to environmental chemicals. Establishment of healthy lifestyle from childhood is much easier and more effective than attempts to lifestyle change, and families and health policy makers should consider this.

> There are no incurable diseases - only the lack of will. There are no worthless herbs - only the lack of knowledge. Avicenna

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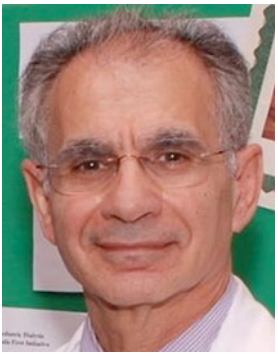

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Chapter 3
Lifestyle Genomic interactions in Health and Disease

Reza Nedaeinia, Sima Jafarpour, Saied Safabakhsh, Maryam Ranjbar, Parnian Poursafa, Pauline Perez, and Rasoul Salehi

When you do not know the nature of the malady, leave it to nature; do not strive to hasten matters. For either nature will bring about the cure or it will itself reveal clearly what the malady really is. Avicenna (ca. 970–1037)

Abstract There has been increasing interest in how lifestyle may have an impact on genomics. Nutrition, physical activity and other environmental factors are determinants of health and disease in any defined population, primarily through interaction with components of the genome and proteome. It is proposed that practical and reciprocal interactions exist between nutrients and the human genome. The struc-

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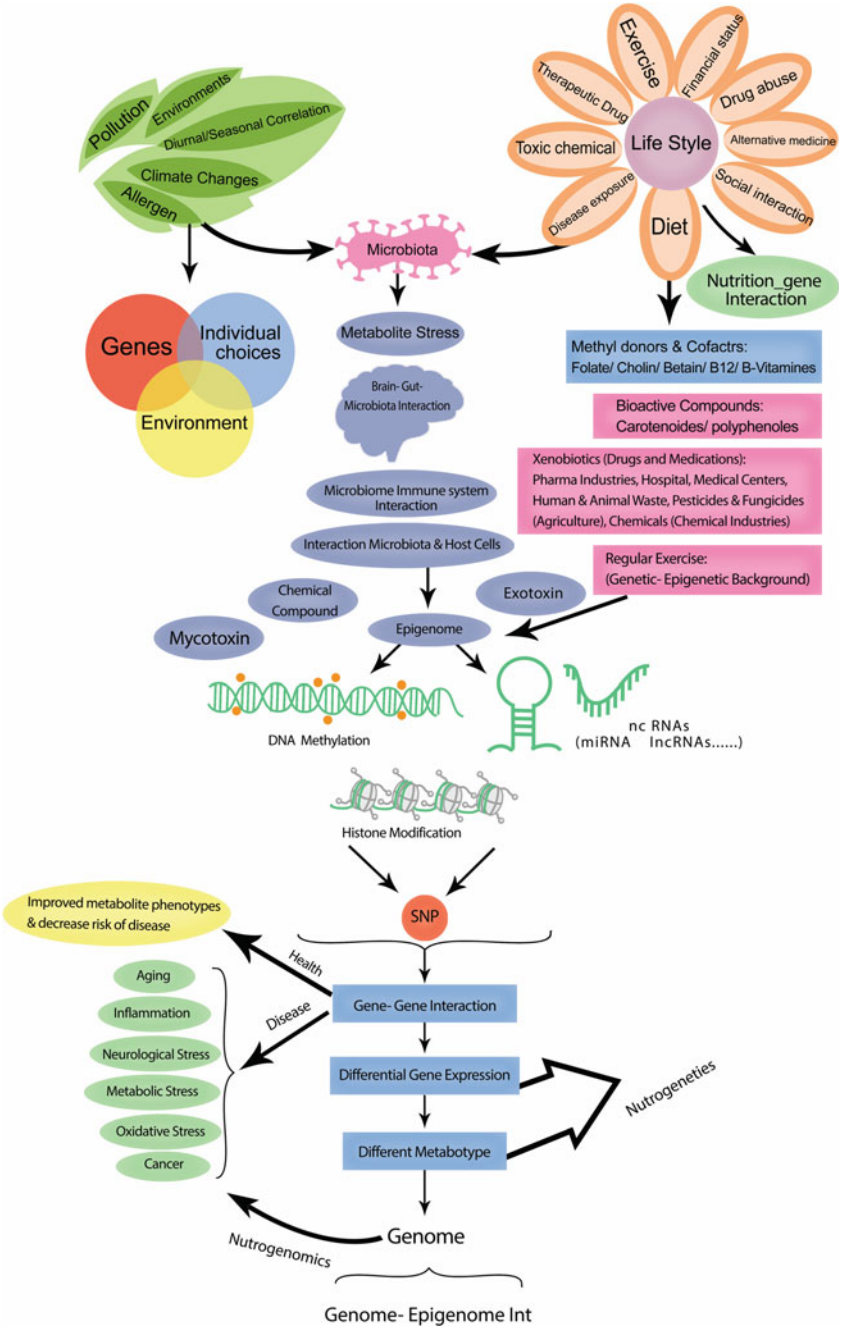
tural complex and functional coordination is in a continuously evolving dynamic state. Nutrigenomics is the study of effect of foods and food components on the expression of the genome. It may also be defined as the effect of genetic diversity on nutrition by linking gene expression or genetic diversity to nutrient uptake, metabolism, or biological effects. Current scientific evidence supports the idea of trans-generational epigenetic influence on gene expressions. Epigenetic effectors like methylation, acetylation, non-coding RNAs, including microRNAs and long noncoding RNAs, are influenced by dietary components. Despite the fact that methylation is an enzymatic reaction, the availability of methyl donor moiety from diet through nutrients, play a pivotal role. Extra-cellular vesicles contain a specific cohort of epigenetic effectors that are ingested along with various foodstuffs and would safely travel through the gastrointestinal tract. They are then absorbed into systemic circulation and delivered to specific end organs with appropriate receptor. Our body is also influenced by an extensive extra-genomic array of our gut microbiome. An individuals' microbiome is an important determinant of energy extraction from various foodstuffs and also influences energy homeostasis which is the main effector of metabolic disorder development. Another important aspect of lifestyle is physical activity and its impact on molecular pathways contributing to the optimal health or disease state. In this chapter we plan to present a comprehensive overview of lifestyle genomics in health and disease.

Graphical Abstract



Keywords Life style · Epigenetic effectors · Gut microbiome · microRNAs · Nutrigenomics · Nutrigenetics

Introduction

Over the past twenty years, clear explanation of various genomic aspects of lifestyle and gene interactions with nutrients has come to be the focus of scientific research. Past studies had focused on the interaction between human genes and diet, which regulates cell nutrients and organ systems. An increase in the prevalence of non-communicable diseases (NCDs) such as hyperlipidemia, obesity, osteoporosis, coronary heart disease, diabetes and cancer was observed in Western societies and other countries. These studies are fundamentally aimed at providing a better quality of life by preventing chronic diseases such as metabolic syndrome, obesity, diabetes and cardiovascular disorders. Moreover, recent studies have focused on understanding the basis of feeding behavior in terms of neural and molecular pathways, and the influence of many nutritional elements that through influence of genetic factors regulate the various metabolic pathways.

Archibald Garrod was the first to describe the notion of nutrient-gene interactions in the early twentieth century [1]. The old term of "nutrient-gene interactions" has changed to the new term of "Nutritional Genomics" with the human genome project completion in the Omics area. The final goal of Nutritional Genomics is to develop strategies to deliver personalized nutrition for enhancing health and preventing chronic disease states [2]. Personalized genomic medicine is a new approach in which detects different genetic variations that increases the risk of developing a specific disease. In another word, personalized genomic profiles provide a tool for the detection of individual risk factors for developing a particular disease with the aim at risk reduction measures to prevent disease. These measures also include environmental exposures, vitamin use, diet, or other lifestyle changes. The primary assumption of this approach is that each person can use his/her genomic profiles for the reduction of NCDs, or improvement of general health and wellbeing of the individual [3].

Our understanding of genetic factors related to human health has led scientific research to personalized genomics in categories such as oxidative stress for skin health and aging profile, oxidative stress profile, obesity susceptibility profile, cardio genomic profile, osteopenia susceptibility profile, detoxigenomic profile, tissue repair screen, alcohol metabolism screen, immunogenomic profile which will help experts in their respective fields [3]. Genetic testing focuses on distinctive aspects to design a personalized diet plan. These aspects include determining the number of vitamins and minerals one needs, examining genes involved in controlling appetite, cravings for sweets, obesity predisposition, how nutrients are metabolized, and genes related to the body's response to compounds such as lactose, gluten and, caffeine. For example, by examining the genetic variations of individuals, diets can be modified so that a more effective path is designed based on the individual's genetics and achieve

maximum effects. Knowledge of individual's genetic differences will allow nutritionists and geneticists and other team members to design the individual's nutritional program for ideal body weight with a lasting outcome. Furthermore, it is possible that an individual's genetic predisposition would allow us to identify the individual's dietary needs for vitamins and flavors. Moreover, genetic testing can provide information on susceptibility to depression and mental health problems, food and drug allergies in different ethnic groups, ability and capacity for endurance and strength exercises. Our primary goal is to present an overview of recent studies on various dimensions of lifestyle genomics in health and disease. This provides a platform for highlighting new developments in lifestyle-gene interactions and understanding their impact on health and disease.

We will review how genetics will influence a person's response to lifestyle factors, including diet and nutrition, healthy natural products, physical activity, sleep, and lifestyle factors in the expression of genes, proteins, and metabolites [4].

The aim of this chapter is to summarize the current knowledge of how lifestyle can impact on genomics to help reduce development of common and chronic diseases, while facilitating the development of personalized medicine to improve the quality of life of an individual. It will help understanding the relationship between nutrition and genetics, the effects of genetic differences in functional foods or nutraceuticals responses, and the effect of nutrition on gene expression in preventing or controlling the disease.

Functional Foods and Nutraceuticals

Food is a natural and essential need of human beings and the quality of food has a significant impact on people's health. Food has a different value for humans for centuries, and using food as medicine to treat diseases has a long history. Nutraceutical is a hybrid term derived from "nutrients" and "pharmaceuticals". This term was first introduced by Stephen L. Defelice in 1989 to define a medical value for foods and nutritional supplements [5, 6]. Nutraceuticals can deliver a concentrated form of a foods' bioactive substances to treat or prevent diseases. There is currently an unlimited and constantly increasing list of nutraceuticals [7]. Nutraceutical compounds such as antioxidants, probiotics, and vitamins derived from animals, plants, microorganisms, and their health-promoting effects are continuously being discovered in scientific studies [8]. Recently, nutraceuticals have attracted much attention among health researchers and nutritionists [9, 10]. On the other side, the term "functional food" was introduced for the first time in 1984. Functional foods are similar to their traditional counterparts and are defined as foods or dietary components that have physiological benefits beyond their nutritional values [11, 12]. Functional foods have three categories: basic, processed, and enhanced. The last two categories consist of foods with additive bioactive compounds with the latter being richer in these components. Basic foods, on the other hand, are unmodified and only contain natural bioactive substances (such as carrots that contain beta-carotene). Examples of the foods

containing additive bioactive substances include milk and orange juice, to which omega-3 fatty acids (FA) and calcium are added during processing, respectively. In the last category, despite foods containing natural bioactive components, the level of bioactive constituents are modified by breeding or genetic manipulation (for example, tomatoes with increased lycopene level) [13]. It seems that there is no clear boundary between the definitions of nutraceuticals and functional foods, and because of this, these two words are often used interchangeably [13, 14]. Both nutraceuticals and functional foods have health benefits that reduce the risk of various diseases. Unlike functional foods however, nutraceuticals as purified foods are used in different forms (tablet, capsule, powder) in medicine and are not part of a regular diet. This seems to be the only difference between the two concepts [15, 16].

Functional Foods, Nutraceuticals, and Human Diseases

Diet components have significant effect on humans' health and quality of life. The disease-preventive and health-protective effects of functional foods and nutraceuticals have been reported in many scientific studies [17–19]. Most nutraceuticals which are derived from fruits and vegetables have anti-inflammatory and anti-oxidant properties. These compounds are useful in preventing chronic diseases such as cancer [20], gastrointestinal diseases [21], metabolic syndrome [22], diabetes [23], and cardiovascular diseases [24]. For example, functional foods take part in a remarkable role in the efficient management of inflammatory bowel disease (IBD) and improve their symptoms by modulating anti-inflammatory signaling pathways. Likewise, vegetarian diets containing polyphenols, probiotics, amino acids, and omega 3 can regulate many inflammatory cytokines (e.g., IL-1, IL-10, IL-6, and TNF-α) in IBD [25].

Diabetes Mellitus

Numerous studies have shown that nutraceuticals/functional foods have anti-diabetic effects [26, 27]. Functional foods' bioactive compounds can prevent carbohydrate absorption in diabetic patients after a meal. Alpha-amylase and α-glucosidase are two principal enzymes that hydrolyze complex carbohydrates to glucose and eventually cause postprandial hyperglycemia [28, 29]. Many polyphenols and phenolic compounds are suitable inhibitors of α-glucosidase and α-amylase enzymes [30, 31]. The increased levels of sorbitol in people with diabetes can cause nephropathy, retinopathy, neuropathy, etc. [32]. In hyperglycemic states, the aldose reductase enzyme produces sorbitol via the polyol pathway, therefore, inhibiting this enzyme is one of the therapeutic approaches in patients with hyperglycemia [33]. Some nutraceuticals can block aldose reductase in diabetic patients. Products such as calabash nutmeg, bitter leaf, Ethiopian pepper, and ginger have also shown vigorous

Table 3.1 The anti-diabetic properties of functional foods and nutraceuticals

Functional foods/ nutraceuticals	Anti-diabetic mechanism
Flavonols [37]	α-glycosidase inhibitors
Flavonoids [38–40]	α-glycosidase inhibitors
Caffeic & Chlorogenic acids [41]	α-glycosidase inhibitors
Xanthones [42]	α-glycosidase inhibitors
Sacrcoviolins isolated from the edible mushroom [43]	α-glycosidase inhibitors
Daidzein & Myricetin [32]	α-amylase inhibitors
Catechin derivatives [32]	α-amylase inhibitors
Berberine from *Tinospora cordifolia* [32, 44]	Disaccharidases inhibitors
Catharanthine,Vindoline, Vindolinine, Arecoline [45]	Hypoglycemic activity
β-carbolines (Norharmane, pinoline) [44]	The stimulator of insulin secretion
Triterpenoids isolated from bitter melon [46]	Anti-hyperglycemic
Hispidin, Hispolon isolated from the ethanol extract of *Phellinus merrillii* [32]	Aldose reductase inhibitors
Phenolic acids in coffee beans (caffeic acid, chlorogenic acid, gallic acid, and caffeoylquinic acid, and *p*-coumaric acids) [47]	Aldose reductase inhibitors
Paulownia coreana seeds [48]	Aldose reductase inhibitors

antidiabetic activity [34–36]. The antidiabetic properties of functional foods and nutraceuticals are summarized in Table 3.1.

Cardiovascular Diseases

Cardiovascular disease (CVD) has multifactorial pathogenesis and various risk factors. For example, diet has a remarkable role in the development and progression of CVDs [49]. The active components of nutraceuticals and functional foods can decrease the risk of CVDs through different mechanisms. Cholesterol-lowering substances like Soy proteins, Flavonoid (in dark chocolate), Lycopene (in tomato), and Monacolin K (in red yeast rice) can reduce plasma LDL cholesterol level [50]. The phytosterols of functional foods also have cholesterol–lowering effects through inhibition of intestinal cholesterol absorption and increasing the expression of LDL receptors on liver cells, resulting in increased hepatic absorption of plasma LDL [51]. Epidemiological and clinical evidence suggest that the consumption of nuts, seeds, seafoods, coffee, tea, vegetables, and fruits can reduce the complications of CVDs through different mechanisms inducing antioxidant pathways, modulating endothelial cells' function, preventing platelet aggregation, and decreasing plasma triglycerides and lowering systemic blood pressure [52].

Cancer

Dietary patterns play an essential role in fighting against cancer development. Studies suggest that nutraceuticals and functional foods have preventive or even therapeutic effects on development of various cancers [53, 54]. The consumption of some dietary products or bioactive substances may reduce the risk of many cancers. For example, vegetables, fruits, and soy reduce the risk of breast cancer (BC) through different mechanisms such as cellular apoptosis and reducing angiogenesis, metastasis, and the proliferation of tumor cells [55, 56]. Many studies have reported the anti-cancer role of soy in BC patients [57]. Soy contains a considerable amount of isoflavones, and its consumption has been linked with better survival in BC patients [58]. Furthermore, a meta-analysis study reported that the consumption of soy after BC diagnosis was associated with reduced mortality and improved survival in BC, particularly ER/PR positive, postmenopausal, and ER-negative patients [59]. Epidemiological studies have reported factors such as ethnic diversity, reproductive status, the amount of consumed soy, length of exposure, and the expression status of receptors on tumor cells can influence the impact of soy on BC progression and prognosis, explaining the heterogeneity of results in these studies [57, 60]. Many spice-derived nutraceuticals like curcumin, bergapten, canthaxanthin, Allyl isothiocyanate, and capsaicin have proapoptotic and anti-proliferative effects against cancer cells [61]. For example, many studies have reported the anticancer properties of curcumin in prostate, breast, lung, and digestive system cancers [62]. Curcumin, a polyphenol present in turmeric, has promoted its anti-inflammatory effects in BC by downregulating NF-κB-induced genes [63]. Anti-apoptotic proteins such as Bcl-2 and survivin have also been shown to be inhibited by curcumin in human multiple myeloma cells [64]. Curcumin also reduced NF-κB expression in human lung cancer cell lines by inhibiting the activity of JAK2 and subsequently suppressing the JAK2/STAT3 signaling pathway [65]. Epigenetic manipulation is a new therapeutic approach towards treatment of cancer [66]. A growing body of evidence suggests that bioactive dietary components can induce epigenetic modifications and restore average epigenetic marks in cancer cells. Therefore, they can be beneficial in the prevention and treatment of cancer [67, 68]. In this regard, it has been reported that curcumin can restore the expression of glutathione S-transferase pi 1 by reversing the hypermethylation of its promoter in MCF-7 BC cell line [69]. Curcumin also reduced the expression of DNMT1 in acute myeloid leukemia (AML) cell lines, which promoted the reactivation of the p15 tumor suppressor gene and induced apoptosis in tumor cells [70]. Furthermore, Genistein (a soy-derived isoflavone) and Epigallocatechin gallate (EGCG, an ingredient of green tea) inhibited histone deacetylases and DNA methyltransferases. They restored the expression of some tumor-suppressor genes in human cervical cancer cells [71, 72].

Chrononutrition

In simple terms, chorononutrion is the study of how nutrition relates to the internal clock or the circadian rhythm which in turn controls the physiological, emotional and supra-tentorial functions in human body. Circadian system controls several physiological and behavioral psychology such as feeding behavior and metabolism of energy. Scientific studies have demonstrated that the circadian clock system essentially includes several clock genes. Several genes monitor the biological clock as markers of the peripheral clock, such as CLOCK (positive regulators), BMAL1, CRY1, CRY2, PER1, PER2, and PER3 (negative regulators) [73]. In Non–Hodgkin's Lymphoma (NHL) for the effect of the circadian system on immunological cancers, a study focused on CRY2, a core circadian gene in NHL. CRY2 analysis of a single nucleotide polymorphisms (SNP) that three SNP areas were distinctly correlated with increased risk for development of NHL [73]. The different components of metabolic syndrome (MetS) are correlated with several SNP areas, and some of these SNPs have been used to change the reaction of an individual to lifestyle treatment methods. Therefore, genetic variants may also influence the degree to which a person reacts to diet and/or exercise changes. The second expression of the microarray was demonstrated by silencing the gene in vitro and explaining the effect on downstream genes that play roles in immune and hematological systems that can induce disease processes [74]. The expression level of nine circadian clock genes of cancer and healthy tissues was assessed in Head and Neck Squamous Cell Carcinoma (HNSCC) to investigate the relationship between CLOCK genes variations and HNSCC [75]. The findings demonstrated a substantial reduction in the expression levels of the genes of CRY1-2, PER1-3, CKIε, and BMAL1 in cancer cells. Each gene's down-regulated expression has been associated with various tumor functions. Such findings suggest a role in HNSCC etiology for the circadian clock genes [76]. The expression of the nine circadian genes in hepatocellular carcinoma has demonstrated a decrease in expression levels of PER1, PER2, PER3 and CRY2 [77]. Reduced expression is caused by methylation of promoters or by any other factors excluding mutations [73]. The daily pattern of eating controlled by circadian clocks, including food intake and metabolism, plays a key role in people's health. Circadian clocks play an important role in driving the rhythmic expression of multiple circadian transcriptomes in eukaryotes with differentiated tissue and organisms to regulate physiological, behavioral and biochemical functions. A core set of clock genes generate a circadian expression of genes in interaction with feedback loops that regulate rhythmic transcriptions. In mammals, the mechanism of the circadian clock consists of two key transcription factors of CLOCK and BMAL1, forming a heterodimer which in turn activates the expression of transcriptional repressors, Cryptochromes (Cry1 and Cry2) and Periods (Per1 and Per2). Evidence indicates that function of CLOCK: BMAL1 advances beyond transcriptional activation. For example, while the histone acetyltransferase activity of CLOCK has been reported, modifications of CLOCK target gene chromatin have been described at the genome-wide level [78–82]. The important thing is that drosophila clock can generate ectopic circadian clocks. This

indicates that CLOCK can help the establishment of a circadian program similar to developmental programs regulated by Pax6 [83]. It is well known that midnight snacks can cause obesity. This is due to chromatin remodeling by the glucocorticoid receptors and nucleosome remodeling promoting at target lineage-specific genes [84, 85]. Furthermore, it is well established that eating only one meal a day may causes obesity. This dietary pattern also changes the liver clock. The rhythmicity of hepatic lipid metabolism of sporadic meals can induce variations from the norm in the hepatic circadian clock thereby increasing the blood cholesterol levels [86]. The principal cause of hypercholesterolemia in this case is high rate of shifting circadian rhythm of CYP7A1 gene expression in bile acid synthesis. Therefore, coordinated metabolism of cholesterol did not take place causing a reduced level of fecal bile acids. Additionally, the progressive rhythmicity of the clock quality DBP within the hepatic cells can be considered as another key factor for development of hypercholesterolemia. These results demonstrate that well-organized eating habits can normalize the hepatic clock gene and the rhythm of CYP7A1, and consequently, normalization of blood cholesterol levels. Moreover, Apolipoprotein A-I (Apo A1), the principal protein component of high-density lipoprotein (HDL), is also controlled by the D site binding protein (DBP) also. This indicates that irregular eating patterns may decrease HDL levels. In other words, regular eating patterns will lead to a decreased level of "bad" cholesterol and increased level of "good" cholesterol [87]. Everyday meals provide distinctive stimuli for timing events that occur regularly. For example, Glucose is the most important source for adjustment of circadian rhythms timing. Glucose also adjusts the rhythm of cultured cells directly. According to recent reports, carbohydrates and proteins are strong timing adjustment factors for the hepatic clock rhythmicity. In a study on rats it is demonstrated that the hepatic and suprachiasmatic nuclei (SCN) clock rhythmicity are adjusted after glucose and amino acid administration [88]. Some vitamins and salts also adjust the clocks [87]. Resveratrol supplement, as a non-nutrient source, also impacts the clocks [89]. The chrononutrition principals also relates to improving mood disorders and largely deals with meals and the serotonin levels. The serotonergic system is one of the neurotransmitter pathways associated with mood disorders. It may involve depression, anxiety, obsessive–compulsive and bipolar disorders among other psycholo-pathological behaviors [90]. Studies on non-alcoholic beverages have reported beneficial effects on anxiety and depression in stressful populations at a moderate overnight intake [91, 92]. Finally, the future of chrononrrition is in line with the future of nutrition in terms of therapeutic tools for indigenous pathologies in our societies. These indigenous pathologies include metabolic syndrome, obesity and neurological disorders in which diet management and design are related to the circadian patterns of consuming certain health-promoting nutrients.

Signals and Sensors in Health and Disease

Traditionally, nutrition science have prioritized what humans eat and the term "you are what you eat" has been used to explain the relationship between health and diets with low nutritional value.

The Mediterranean, Western and plant-based diets, are the main patterns of diets around the world. These diets are unique in terms of the composition of foods and nutrients. In fact, Western diets consist of large amounts of processed foods full of sugars, refined fats, animal proteins, and salts. However, the Mediterranean diet consists of vegetables, fruits, legumes, nuts and olive oil, fish and dairy products, which are consumed in moderation. Animal products such as poultry, meat and seafoods are not used in plant-based diets [93]. These diets primarily include foods rich in fiber and plant proteins as well as healthy fats. The cell's ability to detect and respond to fuel substrates like glucose is called nutrient sensing [94]. There is a need for an alternating functional pathway and accessory molecules for every fuel substrate consumed. A cell produces only molecules it needs at that given time to save resources. The type of enzymes needed to express the genome for utilization is determined by the level and type of fuel in the cell. Cell surface receptors can be activated when specific essential molecules bind to the cell nucleus in a cascading interactions. In this way, the cell can become aware of the nutrients available and produce only unique molecules for that type of nutrients. Transcription factors are one of the leading agents through which nutrients affect gene expression. Nutrients and their metabolites are bound together. For example, essential fatty acids, sometimes called, "vitamin F", are a group of fatty acids that are necessary for the health of human and other animals. This is because humans and most animals cannot produce essential fatty acids from other foods [95–97]. The term essential fatty acid refers only to the fatty acids needed for the body's biological processes. This term does not include fats that are used only as fuel in the human body. Today, omega-3 fatty acids and omega-6 fatty acids are the only two known essential fatty acids in the human body [2].

Signaling of Fatty Acids

Long-chain fatty acids can be detected by G-protein coupled receptors family, a well-characterized stimulant of GPR40 and GPR120. Free Fatty Acid (FA) stimulation of GPR40 increases the release of insulin at the plasma membrane of pancreatic beta cells [98]. Additionally, GPR120 promotes insulinotropic activity indirectly through GLP1 production. GLP1 is a component of the gastrointestinal hormones group called incretins. It protects the pancreatic beta cells from degeneration, stimulate their regeneration and increase insulin secretion of the beta cells. The above example indicates that increasing a specific nutrient (FA) predicts the response to

a probable increase in other nutrients (glucose). This is because food consumption rarely provides only one type of nutrient. Moreover, GPR120 activation at white adipocytes' plasma membrane causes signal-transduction cascades that stimulate the activation of PI3K/AKT and consequently, the cell-autonomous induction of glucose uptake [98]. Genetic mutations impair the function of GPR120 in obese individuals while ablation of GPR40 induced abnormalities in glucose homeostasis in mice [98]. It reflects the crucial role of this signal transduction pathway in the systemic control of nutrient homeostasis [98]. These findings have driven the interests of scientists in providing GPR120 agonists thereby preventing obesity [98]. FAT/CD36 receptor, in addition to GPR120, has been involved in biding and uptake of intestinal luminal FAs directly [99]. It is noticed that CD36, GPR120, and GPR40 have fatty acid-sensing properties in oral epithelial cells which are involved in gustatory perception [98].

Cholesterol-Signaling

Cholesterol is essential for all human and animal life. The primary regulation mechanism of cholesterol is performed by sterol regulatory element-binding proteins (SREBPs). SREBP cleavage-activating protein (SCAP) interacts with cholesterol directly which is dispersed over five transmembrane sterol sensing domains (SSD) [98]. SCAP is SREBP membrane-bound that transactivates the genes essential for the synthesis of cholesterol [100]. Binding of high levels of cholesterol to SCAP causes deformation and thereby affinity for the insulin induced gene (INSIG) protein increases the anchor of SCAP and SREBP in ER membranes [98, 101]. On the contrary, SCAP/SREBP tandem separates from INSIG and is transported to the Golgi apparatus [98]. SCAP are not attached to cholesterol when levels of cholesterol are low. This step is crucial because the problematic presence of SCAP/SREBP in Golgi leads to SREBP N-terminal cytoplasm cleavage and release by resident Golgi enzymes [102, 103]. Cytoplasmic cleavage of SREBP fragment is transported to the nucleus allowing its translocation into nucleus genes involving lipid anabolism. Next, the repletion of cholesterol levels starts the negative feedback via SCAP interaction and inhibition of further SREBP cleavage [104]. Hyperlipidemia and metabolic disorders such as type 2 diabetes and atherosclerosis (AS) are closely related. SREBPs are the main transcription factors in vivo studies regulating cholesterol, triglyceride (TG) and fatty acids (FAs) biosynthesis. As a result SREBP inhibition can be a promising treatment method for metabolic disorders. Another mechanism is a complex 37-step process that begins with HMG-COA reductase. Research evidence confirms an additional sterol-sensing event in the ER which consists of HMG-CoA Reductase enzyme. The rate-limiting step in the De Novo cholesterol is catalyzed by HMG-CoA reductase and it is considered to be a transcriptional target of SREBP in response to low levels of cholesterol. The C- terminal domain of HMG-CoA reductase is inserted into the cytoplasm. On the other hand, several domains of transmembrane including domain of sterol-sensing comparable with that of SCAP, are inserted into the ER membrane [105]. High levels of the intermediate lipid species in the synthesis of

cholesterol like lanosterol start the interaction between HMG-CoA reductase and INSIG, constitutively limited to an ubiquitination complex made by VCP, GP78 and UBC7. HMG-CoA reductase ubiquitin-mediated degradation improves by this interaction [106]. The early and rate limiting step in the synthesis of cholesterol is catalyzed by HMG-CoA reductase. However, HMG-CoA reductase levels are regulated by a slow, transcriptional mechanism which seizes to function after cholesterol levels are recovered. Therefore, HMG-CoA reductase interaction with Insigne which causes proteasome turnover, presents a more rapid regulatory loop. This aims at pausing the cholesterol synthesis while presence of precursor molecules guarantee. the likelihood of increased cholesterol synthesis [98].

Sensors of Adipokines

Adipokines or adipocytokines are a group of cytokines produced and secreted by adipose tissues. Upstream fat sensors, adipokines and secretion of hormones by adipocytes produce systemic effects including appetite regulation, energy expenditure and other processes which help homeostasis of nutrients. These levels do not necessarily indicate the levels of circulating lipids. However, organismal lipid storage reports and some adipokines like LEPTIN can be considered as lipid storage abundance. Interestingly, the nature of the sensor relating to high levels of stored lipids with LEPTIN development remains unknown, even regulatory elements in the PTIN gene promoter region to be known [107]. In both the central nervous system and peripheral tissues, the LEPTIN receptor is expressed. The amount of food consumed and the metabolism of the organism are coordinated with its activation. LEPTIN activity stimulates the action of neuropeptides and neurotransmitters in hypothalamic neurons that suppress appetite (anorexigenic) [108]. LEPTIN function alienates the influence of appetite-stimulating neuropeptides and neurotransmitters. Decreased LEPTIN production is the result of lipid mobilization by adipocytes just like in fasting conditions. This also leads to appetite stimulation and improved behavior of nutrient acquisition. Leptin receptor gene mutations are observed in obese patients [109]. Furthermore, in mice studies with inactivating mutations in the Leptin or its receptor genes causes hyper-fagic state to double the average mice's body mass. Adipocytes (also called ADIPOQ) also synthesize the hormone adiponectin (also called ADIPOQ) in addition to LEPTIN but its production regulation is even less known [98]. Circulating ADIPOQ levels, unlike LEPTIN, are inversely related to lipid storage. This adipokine has many systemic effects including insulin sensitivity, increased energy expenditure and appetite loss [110–112]. There is a significant vital relationship between mutations and polymorphisms in the ADIPOQ gene in humans and obesity and type 2 diabetes [98].

Nuclear Receptors

Nuclear receptors are a group of ligand-dependent nuclear receptors with various biological and physiological effects, such as glucose and lipid homeostasis, inflammation, and wound healing. For instance, in a large number of promoter gene regions, there is a binding between peroxisome proliferator activator receptors-(PPAR) (fatty acids binding) or receptor of liver X (cholesterol metabolites binding), or heterodimers and retinoid X receptor with specific sequences of nucleotide (response elements) [113]. In the process of ligand binding, nuclear receptors experience a conformational change [113]. This conformational change results in the separation of the compressor nuclei and employs coactivator proteins to activate transcription. In the gastric tract, liver and adipose tissue, which are metabolically active organs, factors of transcription act as nutrient sensors. They function by altering the level of DNA transcription from specific genes in nutrient changes responses. A key role of nuclear receptors is to regulate processes such as embryonic growth, nutrient metabolism, cell differentiation and cell proliferation. It would not be surprising if nutrients can be useful to a number of cellular functions by activating receptors. For example, the PPAR nuclear receptor group is a nutrient sensor for fatty acids which affect the expression of specific genes. In fasting, hepatic PPAR, one of the three isoforms PPAR (PPARα, PPARβ/δ, and PPARγ) in the liver, is important during the release of free fatty acids from adipose tissue which are eventually transported to the liver [114]. In the liver, partial or complete oxidation occurs and these fatty acids bind PPAR. As a result, in the increase of the expression in a set of genes. This increase occurs due to the binding of specific sequences in their regions of the promoters. Recently, direct regulation of gene expression involved in hepatic gluconeogenesis and glycerol metabolism via PPAR has been shown [113]. The second mechanism may explain the stimulatory effect of high plasma-free fatty acids on glucose output and hepatic gluconeogenesis. As a result, fatty acids are considered as ligands of PPAR. The role of PPAR and its influence on obesity as well as our physiological responses to food deprivation is not well understood [115, 116]. Elevated levels of free fatty acids are closely related to visceral obesity. In hepatic pathways these molecules may be regarded as signals of "hunger" or "need for glucose" [117]. Increased gluconeogenesis, in PPAR-dependent approach, is due to hepatic insulin resistance states. The importance of nucleus and transmutation proteins, in addition to a group of sensing transcription factors that are directly related to binding of specific response elements to DNA, are essential components of gene control for coactivators' expression. Co-activators are present in the form of multiprotein complexes. They bind to transcription factors and provide conditions for transcription by modifying chromatin configuration. Recent studies on two coactivators of PPARγ also known as peroxisome proliferator-activated receptor-gamma coactivator-1 (PGC-1α and PGC-1γ) is remarkable. There is a direct relationship between PGC-1 and homeostasis of energy, diabetes and regulation of lifespan [113] signifying an association between polymorphisms in the genes encoding PGC-1α, PGC-1γ and type 2 diabetes [113].

Glucose Sensing

One of the most crucial cellular mechanisms is glucose sensing. Deregulation of mechanisms of glucose metabolism including glucose sensing, import, storage and mobilization of glucose leads to the pathogenesis of type 2 diabetes and other diseases in humans [98]. Metabolic nutrient sensors like AMP-activated protein kinase (AMPK) are one of the most critical ways for glucose sensing [118]. When the intracellular level of ATP decreases, AMPK is activated, resulting in the breakdown of glucose and inhibition of carbohydrate and fat anabolism [119]. The central organ for glucose sensing in mammals is the pancreas which regulates blood glucose levels. Glucose reaches beta cells of the pancreas through the transporter GLUT2 [120]. Nutrient sensing is strongly influenced by a series of biochemical processes which involve the production of glucose- 6 phosphate and ATP and eventually results in increased intracellular Ca^{2+} [121]. Ca2-based exocytosis of insulin-loaded vesicles is the final result of this cascade [122]. As a result, there is a linear relationship between insulin release from these cells and intracellular glucose levels [123]. Systemically, the secreted insulin acts on multiple target tissues, most notably the liver, adipose, and muscle tissues, contributing to increased glucose absorption by a second glucose transporter, GLUT4, and ultimately to lower blood glucose levels. Insulin release ensures blood glucose levels remain within normal range [124]. Glucagon hormone is released from alpha-cells of pancreas, the second type of cell in the pancreas, in response to hypoglycemic states. Under the influence of glucagon action the liver breaks down the stored glycogen and releases glucose into the bloodstream. This hormonal pathway of counter-regulating glucose levels in alpha and beta-cells is not well studied. The central nervous system neuronal pathways are located predominantly in the hypothalamus and brainstem which respond to blood glucose levels, presumably control the actions of appetite and eating habits [125]. For instance, type 2 diabetes due to genetic dysfunction of the pro-opiomelanocortin (POMC) neurons are activated by glucose levels [126, 127]. In these cells, glucose sensing is likely to involve intracellular metabolic sensors that also act on pancreatic beta-cells. Primarily, GLUT2 mediated glucose transport increases intracellular ATP which leads to neural signaling through K+ channels dependent on ATP [128]. Utilizing intracellular metabolic nutrient sensors in hypothalamic neurons, much like melanin-concentrating hormone (MCH) response to glucose levels. Additionally, many hypothalamic neuron activity is suppressed with glucose levels while the mechanism and their significance is not well understood. These neurons express orexin and might depend on eternal sensing mechanisms like sodium-glucose co-transporters or TRP pathways in addition to intracellular metabolic processes [124].

Amino Acids Sensing

Other essential sensors include amino acid sensing. Amino acids are also precursors to many essential neurotransmitters such as serotonin, dopamine, etc. Excess amino acids are frequently stored or transformed to energy proteins (like hexamerins in insects). Mice seem to sense dietary amino acids inside the brain. Mice fed with amino acid–deficient diets reduced amino acid levels within 20 minutes. Scientists considered that such a quick response prevented the degradation of proteins. It is a regulated process that produces missing amino acids from stored proteins. Interestingly, animals with a diet deficient in a certain essential amino acid show more taste for this specific amino acid. Researchers have proposed that there must be at least one amino acid sensing in the anterior piriform cortex [129]. It involves translational control mediated by the translation initiation factor eukaryotic initiation factor 2 (eIF2) alpha in a way that one uncharged tRNA (one consequence in animal's amino acid deficiency) results in phosphorylation of this protein and a reduction of global translation [130, 131]. The regulation of blood amino acid levels occurs through neuronal activity in the hypothalamus in response to the flux of amino acids through metabolic intracellular nutrient sensors like mTOR. Essential amino acids such as Lucien activate mTOR, but its activation is also dependent on the levels of ATP inside the cell. Thus, mTOR is a sensor for both carbohydrates and amino acids. It is assumed that the lateral hypothalamus is a subset of neurons projecting most mammalian brains by orexin/hypocretin peptides signaling. In addition to being involved in sensing glucose, these cells also respond to dietary amino acids [132]. These neurons, in contrast to mTOR-mediated amino acid sensing, are activated selectively through non-essential amino acids. They use a mechanism involving the simultaneous stimulation of transporters of amino acid and ATP-sensitive potassium channel (KATP) channels inhibition [124]. Diets such as the Mediterranean diet, which are high in unsaturated fats, provide more natural ligands than the typical Western diet, which is high in saturated fats. Therefore, advising a person who favors increasing the number of natural ligands in their diet can result in prolonged and more sustained PPARγ activation. This in turn counteracts the influence of genetic variants, SNPs, that lower its DNA binding affinity [4]. A valuable candidate gene for insulin resistance is PPAR-γ which controls the weight of the body, adipocyte differentiation and glucose homeostasis [133]. Results showed approximately a 25% decrease in PPAR-γ mRNA expression following a 10% decrease in body weight [134]. These findings suggest necessary to maintenance of normal insulin sensitivity in mice and puts forth the intriguing idea that it may be required for the adverse effects of a high-fat diet on the metabolism of carbohydrates [133].

Gene-Disease Associations

Genetic performance has progressed rapidly in the quest for a better quality of life and disease prevention. This is not only due to the development of diagnostic tools that stimulate genomic personalization, but also because of the possibility of understanding each person as a unique being. To obtain a personalized diet, it is necessary to understand the genetic factors which regulate the different metabolic pathways through different nutritional elements. A personalized diet can be prepared by identifying these needs, enabling the supply of required nutrients, thereby supporting the outcome of an optimal condition in conjunction with their genetics. Risk factors are most often reported throughout childhood for several of the main chronic illnesses, including cardiovascular disease, hypertension, diabetes, obesity and cancer [135]. Preventive measures are enacted early in life which can help in lowering the incidence of these diseases during adulthood. Therefore, the type of diet is crucial in response to nutrient-gene interactions. For example, one of the most common Non-communicable diseases (NCDs) of metabolic syndrome includes obesity, increased blood triglycerides, glucose intolerance, hypertension and insulin resistance. Consequently, the diagnosis of metabolic syndrome in an individual can be a sign of the accumulation of risk factors for cardiovascular disease and diabetes, resulting in an increased mortality in human societies [136]. Obesity is a multifactorial medical condition stemming from an energy intake (EI) and total energy expenditure (TEE) imbalance accompanied by changes in various metabolic pathways [137]. This imbalance becomes evident through accumulation of excess body fat and appears as a weight control system dysfunction. It is considered the principal risk factor for type-2 diabetes development because 61% of people with obesity are estimated to develop type 2 diabetes in their lifetime [138]. Obesity also represents the world's main risk factor attributed to cardiovascular mortality [138]. Although obesity is associated with an energy imbalance, multiple metabolic and endocrine disorders can also be attributed to obesity. After all, although genetic factors may predispose a person for obesity, diet, exercise and lifestyle increase the probability of risk factors for diabetes [139, 140]. Nutrition Science has thus developed the concept of 'gene-nutrient interaction,' in which the gene expression is a key factor in influencing the risk and development of obesity [140]. Many other genes and SNPs have been closely linked to animal and human studies with obesity phenotypes, in which some have been discovered using GWAS technology [140]. Genes have an extensive role to play, and, apart from their influence on preferences in eating, their mutations may be among the factors causing the following diseases: Obesity (FABP2, ADRB2, PPARG, LEPR, ADRB3, MC4R and FTO); Type 2 diabetes (TCF7L2,ADRB2, FABP2, CETP, PPARG, GLUT2 and CD36); Cardiovascular diseases (ApoA5, ApoE, CETP, ADD1, CYP11B2 and MnSOD); Cancer (GSTP1, MnSOD, CYP1A2, CHRNA3 and CHRNA5); Metabolic syndrome (ADRB2, CD36 and TAS2R38) [141].

GWAS's have become state-of-the-art since 2007 to encourage people to understand more about complex disease genetics. GWAS explores the relation between millions of SNPs and disease by the comparison of subjects with and without the

disease. In GWAS, common allele variants of PNS occurring in at least 1–5% of the population are studied to identify their contribution to the disease. As of today, in incredibly more significant populations, multiple GWAS's have been conducted on CAD. Several SNPs have been recognized for being closely linked to CAD by both candidate gene and GWAS methods Including APOB, PCSK9 and LPA. This then led to the emergence of drugs designed for these genes including PCSK9, APOB and LPA [142]. MetS heritability has been reported to range from 20 to 60%, implying that genetics is an important part of the pathogenesis of this condition [4]. In family studies, twin studies, candidate gene association studies, and genome wide association studies (GWAS), the genetic basis of MetS has been explored [4]. To this date, around 60 genetic variants related to obesity, 90 related to hypertension, 160 related to dyslipidemia, 90 related to glucose homeostasis and 30 related to MetS have been identified by GWAS. These genetic investigations have established a catalog of candidate genes to be considered in MetS-related gene-lifestyle studies, and their impact on the response of a person to diet and/or exercise interventions [4]. For example, biological research is based on access to molecular and demographic information. Hence, the study of polymorphisms in the genome can be considered as an appropriate starting point for research at the molecular level based on the structure of complex biological systems. The study of their relationship with each other can then be used to estimate the level of community health. Researchers have proposed that nucleotide polymorphisms (SNPs, defined by unique rs numbers) impact lifestyle response interventions targeting various elements of Metabolic Syndrome. However, most gene-diet interaction studies in humans have been conducted using lipid and lipoprotein phenotypes. The end product of these experiments include the family nature of Metabolic Syndrome (MetS), the apparent discrepancy in the incidence of MetS in different racial groups 3 and the different prevalence rates of MetS in monozygotic twins [143]. Genetic variation throughout many genes of apolipoprotein (APO A-I, APO A-IV, APO B, APO C-III, and APO E), genes of LDL receptor, and LDL subclass phenotypes (pattern A versus pattern B) are engaged in the modulation of dietary response [135].

APOA1/APOE3

In a case–control nested study the interaction between food group intakes and APOA1/APOC3 genetic variants (rs670, rs5069, rs5128) in relation to the MetS risk was investigated [143]. Sugar intake was correlated with lower MetS risk among A allele carrier of rs670, T allele carriers of rs5069, the APOA1 coupled GA+AA/CT+TT/CC genotypes. SSB and fish groups' intakes were correlated with higher MetS risk among persons with combined genotypes of GA+AA/CT+TT/CC. The results demonstrate the relationship of dietary food groups (fish, sugar and sweet drinks) in reducing APOA1/APOC3 SNPs related to MetS [143].

High-Density Lipoprotein Cholesterol (HDL-C)

Two major risk factors for MetS are elevated triglyceride and reduced high-density lipoprotein cholesterol (HDL-C) levels. According to twin studies, triglyceride and HDL-C heritability range from 60 to 80% [4]. In extensive genomic screening of more than 100,000 people of European descent, 95 genetic loci were identified to account for 25 to 30% of the change in blood lipids [4]. Nevertheless, some of these SNPs were examined for lifestyle interventions. Identifying the impact of SNPs on the variable lipid response levels found between individuals during lifestyle interventions can help develop more effective measures for improving lipid profiles. Some SNPs also have been discovered to influence the response of interventions of diet modifications [144].

Fat Mass and Obesity-Associated Gene (FTO)

FTO Gene encodes a DNA/RNA methylase dependent on FE (II) and 2-Oxoglutarate. Further elaboration is needed for the exact molecular connection between FTO methylase activity and body weight [4]. At rs9939609 (T/A) SNP, individuals homozygous for the A risk allele weigh 3 kg more and had a 1.7-times higher obesity risk than those with the AT or TT genotypes [145]. Most human genetic studies in this area indicate an association between this gene and the incidence of diseases such as type 2 diabetes mellitus and obesity.

The Cholesterol Ester Transfers Protein (CETP)

This gene of cholesterol ester transfer protein is located on chromosome 16, which is widely expressed in peripheral tissues and the liver [146]. One of the most important functions of this gene is the transfer of cholesterol esters, which reduces the amount of HDL-C cholesterol in the blood plasma, showing the relationship of this gene with metabolic syndrome. On the other hand, the results of various research have indicated the wide correlation of the genome on the importance of this gene in regards to metabolic processes, in which genetic changes in CETP have shown direct effects on the development of metabolic syndrome. Among the many studies on gene changes, the most common are polymorphisms called rs708272, commonly referred to as (TaqIB G/A) [147, 148]. Other well-known polymorphisms have been introduced for this gene including rs173539, rs3764261 and rs9939224 associated with components of the metabolic syndrome [149]. This increases HDL-C levels and decreases triglycerides. Also, rs247617 polymorphism is strongly associated with HDL as one of the most potent metabolic syndrome [150].

Melanocortin-4 Receptor

In the hypothalamus, the gene Melanocortin-4 receptor (MC4R) is involved in appetite and satiety regulation. Compared to TT homozygotes, the rs17782313 (T/C) SNP area, C-allele had higher BMI, body weight, total fats and non-visceral fat mass. Conversely, during the intervention, there was no effect on alterations in weight loss or fat deposition. The rs1943218 (T/C) SNP area has been shown to consistently influence the changes in weight. In particular, TT homozygotes for rs1943218 displayed a higher level of short- and long-term weight loss relative to people with CC and CT genotypes. Nonetheless, such correlations were statistically insignificant. In another lifestyle intervention study, SNP areas for MC4R were also found to be associated with weight loss maintenance [4].

Peroxisome Proliferator-Activated Receptor Gamma 2

The PPARγ2 gene is an important receptor of nuclear hormones expressed primarily in adipose tissue and play a major role in adipogenesis and fat metabolism regulation [151]. There is substantial evidence to suggest that essential polyunsaturated fatty acids as well as their derivatives are natural PPARγ2 ligands and a possible link between the quality of dietary fat and transcriptional activity. The rs1801282 (C/G) SNP area in PPARγ2-also called Pro12Ala- was correlated to differences in weight loss in response to lifestyle interventions [152]. Notably, the PPARγ2 Ala allele was related to a general decrease in PPARγ transcriptional activity due to a lower DNA binding affinity than the Pro allele [153].

Adrenoceptor Beta 3 (ADRB3)

Adrenoceptor beta 3 (ADRB3) gene is a part of the family of adrenergic receptors that play arole in regulating energy homeostasis and thermogenesis in adipose tissue [154]. Multiple gene population analysis have introduced that carrying the C-allele (i.e. CC + CT) is related to decreased weight loss following a life style intervention in comparison with TT-genotype individuals [4]. Similarly, Sakane et al. reported a relationship between rs4994 and weight loss in Japanese diabetes prevention programs in adults [155]. In particular, individuals undergoing the lifestyle intervention with the CC or CT genotype lost less significant weight than those with TT-genotype. Despite the demonstrated relationship between rs4994 and weight loss, the role of this SNP area is still questionable [4].

ABCA1 Gene

Since low HDL-C plasma concentration is one of the most common blood lipid disorders in the Iranian population, some studies have isolated the ABCA1 gene to find genetic changes influencing this disease. The ABCA1 gene is considered as one of the factors that reduces plasma HDL levels. In a study in Tehran, the relationship between blood lipid levels and rs2230806 gene was investigated. The investigation found that this polymorphism is associated with a nucleotide change at position 1051 on chromosome 9 [156]. Except for the concentration of APO A1, it did not show any significant relationship with the blood lipids level. According to the researchers, this polymorphism is considered as a suitable indicator for investigation of HDL-C in Iranian society [156].

Glucokinase (Hexokinase 4) Regulator

These genes are primarily expressed in hepatocytes and pancreatic beta cells. Their product of this gene is the glucokinase regulator, which is responsible for regulating glycolysis [157]. Extensive investigations on this gene indicate its direct association with metabolic syndrome and its risk factors such as insulin levels, fasting blood sugar and insulin resistance. The association between one of the well-known polymorphisms of this rs780094 gene and metabolic syndrome with TG/HDL/WC and TG was identified as a positive relationship even though this polymorphism is negatively associated with blood sugar. The rs780093 polymorphism is also associated with high blood pressure, triglycerides and waist circumference. GCKR is also associated with serum triglycerides and 2-h post-prandial blood sugar levels (OGTT) as well [157]. Numerous studies have identified an association between genetics and predisposition to obesity and related co-morbidities.

The following Table describes the role of genes in energy balance (Table 3.2).

Identification of genes responsible for metabolic syndrome as a multi-gene disease can help improve prevention and treatment of metabolic syndrome. In general, population genetics requires collaboration in genetic studies among different populations to investigate metabolic syndrome. Identification and prioritization of genetic studies is a step forward in examining the various aspects of lifestyle genomics.

Table 3.2 The population genetics of genes responsible for carbohydrate and fat absorption

Gene	Gene name	Role of gene in energy balance
ADRB2	β2-adrenergic receptor	The role of the gene product in energy balance involves pulmonary, cardiac, vascular, endocrine, and central nervous systems regulation [158]

(continued)

Table 3.2 (continued)

Gene	Gene name	Role of gene in energy balance
ADRB3	Adrenoceptor beta 3	Regulation of Lipolysis and Thermogenesis [159]
ApoA5	Apolipoprotein A5	It plays a vital role in regulating the level of blood plasma triglycerides and HDL [160]
ApoE	Apolipoprotein E	This gene is a protein involved in the metabolism of fats. It is implicated in Alzheimer's and cardiovascular illness [161]
ADIPOQ	Adipocyte-, C1q-, and collagen domain-containing	Adiponectin is produced by fat cells and promotes energy consumption [162]
CETP	The carrier protein of cholesterol ester	This gene transforms HDL cholesterol "good" into LDL "bad" (low densitylipoprotein) [163, 164]
FTO	Fat mass- and obesity-associated gene	Improves food intake. The adiposity risk alleles of this gene predispose diabetes mellitus, hypertension and cardiovascular events in populations at high risk. It has been suggested that several SNPs in the *FTO* gene associate with increased body mass index (BMI), hip circumference, and weight [140]
FABP2	Fatty acid-binding protein 2	Genetic polymorphisms at codon 54 recognized an alanine-encoding allele and a threonine-encoding allele. Thr-54 protein is related to expanded fat oxidation and insulin resistance [140, 165]
LIPC	Hepatic lipase	An important determinant of HDL plasma concentration and distribution of subclass LDLs. LIPC polymorphism in a deleterious serum lipid profile and several cardiovascular risk factors, including obesity, type 2 diabetes mellitus, atherosclerosis, and calcification of coronary arteries [164]
LEP	Leptin	Generated by fat cells. Fat accumulates in cells, more leptin is produced [166]
LEPR	Leptin receptor	Inhibits appetite when bound by leptin [167]
INSIG2	Insulin-induced gene 2	Cholesterol regulation and the synthesis of fatty acids [168]

(continued)

Table 3.2 (continued)

Gene	Gene name	Role of gene in energy balance
MC4R	Melanocortin 4 receptor	Stimulates appetite when bound with alpha-melanocyte stimulating hormone [169]
PCSK1	Proprotein convertase subtilisin/kexin type 1	Regulates biosynthesis of insulin [170]
PPARγ	Peroxisome proliferator-activated receptor gamma	Stimulates the absorption of fatty tissue and its development [171]
TCF7L2	Transcription factor and participates in the formation of pancreatic β-cells producing insulin	Decreases blood sugar [172]

CREBRF *Gene Variants*

CREBRF (CREB3 Regulatory Factor) had recently been identified as obesity gene in a genome wide association study (GWAS) in Somoans, a Polynesian population [173]. In another recent study, family investigation of nephropathy and diabetes (FIND), the association of CREBRF variants with Obesity and diabetes were investigated by a genome wide association study (GWAS) in Pacific Island populations in Micronesia and Marianas [174]. The FIND study demonstrated that the G allele at rs12513649 in different Marianas and Micronesian populations was associated with higher BMI as was the A allele at rs373863828. The global population frequency was 0.004% in the Exome Aggregation Project: https://www.ncbi.nlm.nih.gov/snp/, compared to 1.1% to 5.4% in Marianas and Micronesian populations. Furthermore, the same alleles were associated with lower risk of diabetes. This study confirms the association of CREBRF variants with higher body mass index (BMI) and lower risk of diabetes which suggests that these variants are important determinants of disease and contribute to the risk of obesity and diabetes in Marianas and Micronesian populations [174].

Additionally, the A allele at rs373863828 was associated with taller individuals suggesting that factors involved in bone formation, mineralization and remodeling by osteoblastic activity may confer protection from developing metabolic syndrome and diabetes. The above findings have achieved genome wide statistical significance [174].

Understanding the mechanisms by which different genes or gene variants confer risk for metabolic syndrome, obesity or diabetes may lead to new therapies for these conditions.

Exercise Genomics

Exercise has long proved to bring about many health benefits. One's genes can affect how he/she responds to exercise, weight loss chances, improvement of cholesterol levels among other health benefits. Previous efforts to illustrate interactions of gene and diet have for the most part centered on composition. Nonetheless food structure impacts the speed at which dietary composition substrates and intermediates of metabolic pathways flow into circulation and affect metabolic pathway regulating hormones and enzymes. For example, low- vs. a high- glycemic index dietary challenge given after a period of exercise inflated the organic phenomenon and supermolecule levels of the carboxylic acid transporter (FAT/CD36) of muscle tissue. This partly explains how low- glycemic meals increase oxidation of fatty acids. Carbohydrate structure changes the serum metabolic profile using an integrated 'omics approach, involving lysophosphatidylcholine species and mRNA expression of genes related to stress reactions and adipose cell differentiation in adipose tissue [175]. This illustrates that high-glycemic carbohydrates cause proinflammatory reactions involving adverse alterations in insulin and glucose metabolisms. Producing foods that may target related metabolic pathways needs a better understanding of the interactions between composition and structure of foods and the dynamic complexity of metabolic processes [175].

Lifestyle Interventions and the Gut Microbiome

Several factors, such as genetic, epigenetic, and environmental factors, such as diet, can influence microbiota [176]. Diet has been proposed as one of the major contributing factors in differences between the gut microbiota in different geographical areas of the world. Notably, long-term dietary habits, including specific nutrient composition in addition to mealtimes and food behaviors, account for more profound and chronic alterations in the gut microbiota compared to short dietary interventions [93].

In this day and age, people are increasingly trying to personalize their lifestyle choices to improve healthy eating habits so they can prevent chronic diseases such as hypertension, diabetes and obesity. Feeding is also among the many factors that can influence this process. Our choices of foods are reflected in our organism's molecular and physiological mechanisms. What is suitable for one's diet may not be right for another. People may benefit more or less from specific vitamins or minerals, such as folic acid, iron and vitamin D, based on the genetic composition that is essential elements of the metabolic pathways to physiological homeostasis.

The largest repository of human microbiota can be considered as intestinal microbiota. They consist of types of microorganisms coexisting with the host in the gastrointestinal tract, approaching tens of 10^{14} [177]. They consist of at least 1,000 identified bacterial species involving more than 3 million genes (150 times more

than genes in human) [177, 178]. While the human gut contains more than a thousand different species of bacteria, only 150 to 170 of them are common in different individuals [178].

The digestive system of humans contains a vast and varied population of microorganisms that function with the host in a symbiotic way, contributing to metabolism, immune response and intestinal architecture. Regardless, it has been shown that disturbance of a healthy and diverse community called "dysbiosis" has a significant influence on health and disease [179].

Glucose uptake and flow to the liver are regulated by intestinal microbes. As a result, intestinal microbes play an important role in regulating insulin availability. Intestinal dysbiosis is a common feature of type 2 diabetes and obesity. Sucrose is a disaccharide consisting of fructose and glucose, or ordinary sugar. For the most part, sugars are absorbed in the small intestine while some gut microbial species can also metabolize the sugars. There is little evidence in human studies examining the effects of sucrose or fructose, which are primarily the result of studies with Western diets indicating that there is a relationship between lower bacteria diversity and refined-sugar-enriched diets [93]. One of the main components of personal nutrition can be considered the modulation of intestinal microbes. It has been shown that gut microbiota and its by-products change the genome, metabolome, proteome, transcriptome and health status of the host. Individual gut microbiome leads to alteration in systemic energy balance [180]. Urinary metabolites (metabolomics) are signatures of human adiposity indicating the metabolism of the human intestine and the phenotype of obesity [181].

The metabolism of intestinal microbiota indigestible carbohydrates can alter the host's energy extraction from the diet. Short-chain microflora-produced fatty acids reflect 7% of the gluconeogenesis substrates and 5%-15% of the overall human energy needs [182, 183].

Diet can change the host- microbial composition according to the number of carbohydrates and fiber, the number of vegetables and fats consumed, or direct inoculation of fermented or processed foods [184]. It has been shown that prebiotics alters the host microbiota. Infants excluding other bacteria and prebiotic Panose, a new prebiotic candidate, reveal in vitro stimulation of growth of *Bifidobacterium* and growth decline of *Bacteroids* and *Clostridium*. Prebiotic modulation of gut bacteria has been indicated to reduce intestinal barrier dysfunction, endotoxemia and liver inflammation caused by a high-fat diets and improvement of cholesterol homeostasis [175].

In diabetic patients, obesity and insulin resistance increases risks of high blood pressure (BP). Studies have shown the effects of Lactobacillus species on reduced BP in patients with hypertension. According t published studies, high BP can be controlled with probiotics by reducing inflammatory cytokines and intestinal permeability through splanchnic vasodilation resulting in decreased BP [140].

In a study where probiotic soy milk fortified with *Lactobacillus planetarium A7* was used for patients with type 2 diabetes mellitus (T2DM) and Hypertension both systolic and diastolic BPs were decreased significantly compared to the control group [133]. Another study showed that 200 ml of soy milk containing *Lactobacillus*

plantarum A7 has antioxidant properties and can reduce the risk of mismatch base pair due to DNA damage in T2DM patients [185].

Diets can influence the viability and functionality of the microbiome [186]. In a comparison of women on semi western diets with those rich in fish and vegetables, the former reported a higher cervical intrauterine neoplasia (CIN). Additionally, the sex-hormone-microbiome-immune system can impact the vulnerability of women to HIV-1. Severe hormonal shifts can alter the proportion of anaerobic bacteria to those affected by lactobacilli. Studies have demonstrated that when the estrogen levels significantly decrease in menopausal women, lactobacilli will less likely be the dominant vaginal microbiome [176].

According to Krautkramer et al., gut microbes and related metabolites impacts the state of host chromatin which in turn results in elevated histone polystyrene and the production of short-chain fatty acids (SCFAs) [187]. A "Western-type" diet that is high in processed foods and high sugar beverages was reported to constrain the production of microbial SCFAs; to prevent numerous microbiota-dependent incidents and eventually to lead to changes in the expression of hepatic genes. Another example of this case is related to the effects of ketogenic diets on Alzheimer's disease (AD). It has been observed that this diet rescues hippocampal memory deficiency in a model of Kabuki syndrome of rats which is characterized by a loss of site-specific histone methylation and chromatin release deficiency of accessible regions (opening). This diet promotes the HDAC inhibitor, β-hydroxybutyrate formation. In mice models, this diet causes changes in H3ac and H3K4me3 which cause changes in the hippocampal neurogenesis and memory phenotypes rescue [188].

Neurological disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), Migraine and Multiple Sclerosis (MS) are common and highly prevalent disorders worldwide [189] which are significant causes of morbidity and mortality. Critical elements of the pathophysiology of neurological disorders are enhanced inflammatory markers and oxidative stress, dyslipidemia and impaired glucose metabolism. Recent estimates suggest that in 2030, neurological disorders will contribute to 12% of the percent of worldwide disability- adjusted life year [190].

Many preclinical and clinical studies have shown a strong impact of probiotic supplementation on inflammatory biomarkers, oxidative stress, serum lipoproteins and glycemic regulation in patients with certain neurological disorders. Lavasani et al., demonstrated that probiotic administration had positive effects on animal model of MS regulated by an interleukin-10 (IL-10)-dependent mechanism generating regulatory T cells [191]. Probiotic supplementation in a randomized clinical trial (RCT) for 12 weeks in patients with PD decreased C-reactive proteins (CRP), malondialdehyde (MDA), insulin levels and insulin resistance, while it increased insulin and glutathione sensitivity (GSH).t However, it did not impact the total level of antioxidant capacity (TAC), nitric oxide (NO) or fasting plasma glucose (FPG) [192]. Martami et al. observed that the use of probiotic supplementation for ten weeks in patients with chronic or episodic Migraines improved their headaches, but it did not improve the inflammatory markers [193].

Many cancers in general and in particular risk of colon cancer development is associated with environmental and epigenetic factors. Understanding the environmental

factors that influence the risk of developing colon cancer and how they influence the pathogenesis of this malignancy is of high importance.. Among the environmental factors, microbiota has important role throgh structural elements, enzymes, metabolites and oxygen-free radical production may facilitate the development of this cancer.. Changes in gut microbiota in patients with colorectal cancer have been reported in many studies. Recently, the abundance of *Fusobacterium nucleotum* in human tumors has been proven by RNA-seq method. *Fusobacterium nucleotum* has been noted for its high levels of virulence factors such as *FadA, Fap2* and *MORN2* proteins. *Fusobacter nucleotum* is not a common bacterium of the normal colon flora but it is linked to development of colon cancer cells. Many Studies have shown that the colon cancers tissues contain significantly high numbers of—*Fusobacterium.* Additionally, other studies have associated the bowl Fusobacterium colonization and infection with development of Ulcerative Colitis which in turn increases the risk of colon cancer development.

The risk of ovarian cancer is determined by diet [194], inflammation, family history, age and reproductive factors. An imbalance in cervical microbiome has been recognized in women with ovarian cancer [195]. Microbiome dysbiosis is found to be correlated with pathological issues including cancers [176]. For example, dietary fiber is useful in the formation of gut bacteria and a decrease in the β-glucuronidase activity in the intestines. As a result, estrogen reabsorption and subsequent deconjugation process may be decreased [176].

Some studies have shown that dietary regulation of intestinal bacteria has a positive effect on symptoms of anxiety, apprehension and fears [196, 197]. The number and type of bacteria in the gut changes with our diets, thereby, a good diet can result in a peaceful mind. The most inexpensive and simple way of having excellent and diverse bacteria in the gut is the consumption of variety of foods [198]. If at a minimum five vegetables in different colors are consumed on daily bases, will result in production of high fiber elements which in turn ferments the gut and helps with bacterial overgrowth [199]. As part of the fermentation process, bacteria release essential chemicals and acids that interact with the rest of the body's cells which promotes health of immune system. The Mediterranean diet contains large amounts of fibers, which by fermentation improves people's immune systems and healthier body and minds [200]. Foods such as kombucha, kefir, yogurt, butter, milk and whey, primarily utilized in Eastern cultures, help the formation of probiotics in the intestine. By consuming prebiotics, the lifespan of intestinal bacteria increases. In a meta-analysis by Tamtaji demonstrated that probiotic supplements in patients with neurological disorders had positive effects on CRP, MDA, insulin, HOMA-IR, triglycerides, VLDL-cholesterol and HDL-cholesterol levels [192].

Human gut microbiota has a great impact on human metabolism, expression of gene and health [186]. For example, *Fusobacterium nucleatum* is considered as a risk factor for colorectal cancer. Immune modulation is considered to be the most important mechanism of *Fusobacterium* playing a pivotal role in development of colorectal cancer [186]. The identification of these microbial-food interactions has biological potential and promises innovative development of new metabolically targeted foods that can result in better health, metabolism and protection [175].

Genetics and Nutrition

One of the lifestyle genomic objectives is to provide personalized diets that are quite promising in preventing disease processes. However, personalized nutrition relies not only on a person's genetic make up,, but also on his or her psychoemotional needs [200]. Nutrition can influence health outcomes through directly affecting gene expression in critical metabolic pathways and/or indirectly affecting genetic mutation incidence at chromosomal levels or the base sequence that in turn leads to gene dosage and gene expression alterations [2]. Nutrioms and nutrient health effects (combinations of nutrients) rely on the inherited genetic variants that change the absorption and metabolism of nutrients and/or the molecular interaction between enzymes and their nutrient cofactors followed by biochemical reaction activity [2]. Nutritional Genomics suggests that various genetic polymorphisms may impact function of protein structure [201]. Thus, genetic differences may lead to differences in food choices. Therefore a food that tastes sweet to an individual may seem normal or even unpleasant to another. Taste receptor 2 member 38 (TAS2R38) gene in humans plays a role in sensing the taste of some foods, genetic differences in the expression of this gene in different people can affect the type and amount of nutrition one consumes [202]. Genetic differences also lead to different responses in the nervous system of individuals in perceiving the degree of satiety, sensing the taste and most importantly the absorption of vitamins and elements. According to results of a number of studies, the ability to absorb vitamin D, and other fat-soluble vitamins, such as vitamins A and E, maybe up to 34 times different for two different people. Race and ethnicity are other causes of genetic differences between individuals. Given that the degree of genetic similarity between members of a family varies according to the degree of their relationship with each other, groups of a particular race or ethnicity can also be compared to large families with significant genetic and nutritional relationships between members [203].

These common genetic and nutritional traits are often passed down through the inheritance of specific common ancestral genes. Identification of specific gene markers to explain the presence of specific traits or diseases in ethnic and racial groups may help identifying environmental factors that cause variations in incidence of specific disease among different populations or ethnic backgrounds. The results of several studies on identical and dizygotic twins indicates that genetic factors play a role in the occurrence of obesity among members of each family. Differences in the level of enzyme activity leads to heterogeneity in dietary requirements. Popular dietary guidelines such as the Recommended Dietary Allowances (RDA) or the recommended intake of a dietary substance are based on the metabolic consequences of consuming or not consuming specific foods. Although these diets provide a standard for determining the adequacy of specific foods; they are not tailored to the nutritional needs of different groups of people. Thus, regardless of dietary modifications according to better known nutritional differences between different cultures and communities, they may still pose a threat to the health of many smaller subgroups. Differences between racial and ethnic groups are undeniably paramount in

the formulation of nutritional guidelines. Moreover, diets are adjusted according to the characteristics of a particular racial group, other groups will not be able to follow them. Improved health outcomes can be obtained through personalizing the nutritional requirements for each person by taking its inherited and acquired genetic characteristics into account based on the stage of life, dietary preferences and state of health [2].

Given that the development of personalized diet plans will accelerate health promotion and disease prevention strategies for individuals, we are faced with three key factors of ethnic diversity, food supply, and malnutrition. Different groups of people follow a specific diet according to cultural, environmental and economic differences, which is formed based on factors such as food supply, cost, quality of taste perception and food habits. Chronic malnutrition can affect genome stability and gene expression while genome instability also leads to mutations in gene sequences. Despite the evidence confirming the effect of genetics on nutrition, up to date no fully valid and credible study has been performed on the effects of genetic factors on nutrition. Although the science of nutrigenetics and nutrigenomics have cultivated a high level of understanding on nutrition at the genetic level, absence of scientific studies with power, credibility, and reproducibility renders difficult task to formulate recipes based on genetic tests.

The Importance of Knowing About the Genetic Nature of Lifestyle

The importance of knowing this concept is that with the increasing advancement of genetics, development of stem cell-based therapies, genomic editing techniques, and the enormous potential for rendering the desired changes to any individual is conceivable by considering their genetic nature. Furthermore, it is possible to achieve the best results in order to obtain ideal fitness, desired exercise, and an appropriate ideal lifestyle by managing nutrition and lifestyle.

Overview of Nutrigenetics and Nutrigenomics

The unique composition of genes illustrates the nutritional needs of an individual. Therefore, adjusting the diet based on a genetic profile is an important contributing factor in maintaining a healthy state while it may prevent disease occurrence and development. The science of the effect of genetic variation on dietary response and the role of nutrients and bioactive food compounds in gene expression is described as nutrigenetics and nutrigenomics [113]. Nutrigenetics focuses primarily on evaluating genetic and epigenetic changes in response to a specific dietary component, resulting in a change in the disease status [4]. A personalized diet will be developed in the future

based on a specific dietary counseling SNP-based test. This important development can be achieved based on information collected from new high-throughout 'omics' technologies. Combing these data supports the development of so-called "personalized nutrition" in a way that it maintains a healthy body thereby preventing a diseases state or help with treatment strategies [204]. An example of personalized nutrition is the bioactive components of olive oil (oleic acid, biophenols and vitamin E) capable of modulating patterns of gene expression with proven effectiveness in chemoprevention [205]. There are two parts of Nutritional Genomic Area: Nutrigenetics essentially describes the modulating effects of inheritance (or mutations acquired in the case of cancer) in nutrition-related genes on the absorption and metabolism of micronutrients and dietary impacts on the health of individuals [2]. In response to dietary nutrients, nutrigenomics is applied to evaluate an altered genomic profile and to develop new strategies that can be utilized in personalized nutrition and medicine. In 2001, Pelegrin was the first to recognize and define Nutrigenomics [206], while Van Ommen and Stierum continued of the investigation and application of nutrigenomics [207]. Evaluation of the biological action of a natural compound in multiple metabolic pathways has become possible by system biology tools which include interrelationships with other nutrients linked to genotype, all of which intended to achieve benefits for human health. Dietary released agents have multifaceted functions and are associated with genomic alterations with environmental factors. Nutrigenomics provides significant added value for the prevention of cancer and other chronic diseases.

There are three major factors that incorporate nutrigenetics and nutrigenomics as an important science. First, there is a large variation in the inherited genome among ethnic groups or populations that influence bioavailability and metabolism of nutrients. Second, individuals vary significantly in their accessibility to food/perception of cultures, economics, geographies and tastes. Third, malnutrition (deprivation or excess) may by itself impact the expression of target genes and the stability of the genome; the second one leads to gene sequence or chromosome mutations that may produce an abnormal dosage of genes and gene expression resulting in adverse phenotypes throughout the different stages of life [2]. In preclinical and clinical studies, several phytochemicals are approved to have an anti-carcinogenic impact. Flavonoids are candidates in signaling pathways as genomic modulators for invasive n and metastatic cancer cell inhibition in colon, breast, prostate, liver, ovarian and lung cancers [208]. A phytoalexin called resveratrol (trans-3, 4′, 5-tri-hydroxystilbene) is found in peanut skins, berries, grapes, and some other fruits. It is thought to cause promising therapeutic antioxidant and anti-inflammatory impact on cancer cells by preventing its proliferation. Resveratrol's antiproliferative effect is mediated by inhibiting multiple transcription factors, up-regulation of p53, caspases and Bax, and down-regulation of survivin, cyclines, and Bcl-2. Increased Bax/ Bcl-2 ratio and increased caspase regulation results in cellular apoptosis [209]. Rhus verniciflua (Toxicodendron vernicifluum) is also called the "lacquer tree". It has been used in traditional Korean medicine for many years due to its antioxidant, antimicrobial, anti-inflammatory and anti-cancer properties [209]. According to experimental studies, *Rhus verniciflua* flavonoids have an antiproliferative and anti-apoptotic roles in several tumor cell lines such as human lymphoma, osteosarcoma, breast cancer and

hepatocyte alterations [209]. *Allium sativum*, green tea, *Panax ginseng*, camptothecin, curcumin, resveratrol, *Rhus verniciflua* and *Viscum album* have shown adequate clinical evidence to support their effects on cancer cells. Hence it appears that they can be utilized in combination with existing chemotherapy medications against various types of cancers as adjuvant therapies [209]. The process of discovering new drugs or designing medications from natural ingredients is based on a combination of nutrigenetics and nutrigenomic data. Due to the heterogeneity of the different molecular structures recovered from natural sources, the natural compounds have multifaceted properties. Despite all these obstacles, it is essential to define personalized diets in daily practice that supports chemotherapy [208].

Epigenetics

Unique components in foods can stimulate or inhibit a gene or gene promoter. Familiar foods with these properties include whey, turmeric, and isothiocyanates in cruciferous family plants and genistein in soy foods. Whey, for example, shuts down genes involved in inflammation while isothiocyanates activates genes that help with active detoxification in liver inferring that what one consumes can affect the gene expression in epigenetic modulation [210].

The theory behind cellular proliferation of abnormal cells or tumors is that a mutation occurs in a gene that affects DNA, causing a cell to grow out of control invading normal tissues. These mutations are characterized by actual changes in the program or map that drives a cell. Epigenetics also plays a role in tumor growth. Epigenetic changes can occur and turn off or activate genes within a cell [211]. Studies of medieval medicine, history of medicine and relevant sections of the Canon of Medicine, the first text book of medicine by Avicenna have indicated that he was the first physician to debate on factors of lifestyle. He had precise knowledge of the factors in lifestyle and how they influenced human health. He claims that lifestyle alterations should be considered the key part of preventing or reducing development of a wide range of diseases, and as a consequence a healthy and balanced life. Thus, he has attempted to describe and categorize these factors based on their importance and effectiveness in ensuring optimal health and disease elimination. He conceptualized that many diseases are related to errors in the six factors that are essential for promoting health and preventing disease. These six essential factors were described by Avicenna as air, body movements, sleep and wakefulness, psychic movements and rest, foods and drinks, evacuation and retention [212]. In today's standards of practical medicine, the six factors mentioned by Avicenna are defined as epigenetics. Embryologist and geneticist C.H. Waddington first suggested the term Epigenetic (EG). In 1942 Waddington explained the development of multicellular organisms and their cell differentiation. The term "epigenetics" is a combination of epigenesis and genetics. It is a biological branch that studies the cause, effects, and interactions between genes and genetic products (environment) that induce phenotypes (2). Epigenetic changes are described as the hereditary alterations in gene expression occurring in the DNA

sequence with no changes. EG plays a vital role in normal development through transcriptional regulation of the different genes. The main epigenetic mechanisms in mammals are DNA methylation and histone alterations, both linked to the configuration of chromatin [213]. Diet by itself or by interaction with several other environmental factors might induce epigenetic changes which can turn on or off certain genes. As a result, epigenetic silencing of genes that might usually defend against a disease can make people more likely to develop a certain disease in the future. The heritable and dietary modifiable epigenome is the global epigenetic pattern established by the methylation of global and gene-specific DNA, histone modifications and the proteins associated with chromatin that controls the expression of household genes and impedes parasitic DNA expression, including transposons [2]. Wang et al. introduced two phytochemicals— dihydrocaffeic acid (DHCA) and malvidin-3′-O-glucoside (Malgluc), grape seed extract, metabolic intermediates derived from grape juice of Concord and transresveratrol that decrease depression-like behaviors in mice. Wang et al. used a mouse model to show treating mice with DHCA and Mal-guc added to drinking water that increased stress persistence and reduced depression-like behavior patterns [214]. The authors especially noticed that DHCA decreased the expression of "methyl-DNA writer," the methyltransferase 1 DNA (DNMT1). DNMT1 methylates interleukin 6 (IL-6) intronic sequences, reducing the level of this pro-inflammatory cytokine previously involved in the development of depressive disorders. On the other hand, mal-gluc decreased the expression of an "acetyllysine eraser" histone deacetylase 2 (HDAC2), that resulted in a significant rise in histone H3 acetylation of the RAS-related botulinum toxin substrate 1 (Rac1) gene, the expression of which was found to be down-regulated under acute stress. A combination of the treatment of DHCA and Mal-gluc reduced IL-6 level to baseline and simultaneously increased Rac1 expression leads to endurance against the growth of depression-like phenotypes in rats. Generally, Wang et al.'s report provides remarkable evidence about how grape-derived phytochemicals may also impact inflammation and brain synaptic plasticity, thereby promoting stress resilience in rats. This increases the possibility that such compounds might be combined with previously existing antidepressants that may be of interest as therapeutic measures for treating of patients with depression and anxiety [213]. DNA methylation occurs primarily on CpG islands and in repetitive genomic sequence (e.g. sequences LINE-1). It directly represses transcription by hindering the binding of particular transcription factors and indirectly through recruiting binding methyl-CpG proteins remodeling chromatin to an inactive state [2]. Post-translation alterations occur to histones that change their interaction with nuclear proteins and DNA. The tails of histones H3 and H4 in particular could be covalently altered by methylation, acetylation, and phosphorylation at several residues. These alterations have an impact on gene expression, DNA repair and condensation of chromosomes [2]. Lack of methylation due to deficiency of methyl donors (e.g. folate, vitamin B 12, choline and methionine) or lifetime inhibition of DNA methyltransferases leads to activation of the transposon and silencing of promoters as the activated transposons are inserted adjoining to a household gene promoter [211, 215, 216]. As a result of these stochastic mishaps, there is a relentless shift towards global hypomethylation of DNA and age-silencing of tumor suppressor

genes leading to changes in genotype (due to chromosome missegregation), gene expression profile, cellular phenotype and increased cancer risk.

Early-life malnutrition has been directly and indirectly related to several adult disorders, eventually leading to an epigenetic memory hypothesis. Lactation in mice induces epigenetic changes which later in life influence the likelihood of obesity development [217]. It is known that milk lipids can activate PPARα, the nuclear receptor, an important transcriptional hepatic liver metabolism regulator. Yuan et al. determined several target genes for PPARα by genome-wide analysis of DNA methylation. It included the fibroblast growth factor-21 (Fgf21), which develops demethylation of PPARα-dependent DNA after pharmacological activation of PPARα in mice [217].

Fgf21 is an essential liver hormone with many metabolic functions, which includes maintenance of body weight and the regulation of energy homeostasis. Yuan et al. found that Fgf21's DNA (de)methylation status, when founded in early life, remains intact in adulthood. Moreover, they found that reduced Fgf21 DNA methylation is correlated with decreased diet-induced obesity in older animals. The researchers also illustrated that demethylation of Fgf21 is triggered throughout lactation period of newborn rats. This study's results are astonishing and may have a significant impact on our insight into the mechanisms by which promotes obesity. These data suggests an association between breastfeeding and weight loss, and also eloquently reveals how specific early life built epigenetic modifications generate a long-lasting effect [213]. Biomarkers of DNA damage are currently at various validation levels based on evidence of association with nutrition (cross-sectional epidemiology and intervention findings) and disease (cross-sectional epidemiology and prospective cohort findings) [218]. The cytokine blocked lymphocytes micronucleus assay is currently the best-validated biomarker for DNA damage nutritional genomic studies. Given the advances in diagnostic technologies assessing DNA damage, it has now become possible (a) to determine dietary reference values for DNA damage prevention and implement the concept of DNA damage prevention in the Genome Health Clinic [2, 216, 218]. A study conducted by Mitra Hariri et al. found the impacts of probiotic soy milk and soy milk on MLH1 and MSH2 promoted methylation and oxidative stress among patients with T2DM.. Probiotic soy milk reduced promotor methylation significantly in the proximal and distal MLH1 promoter region compared to baseline values while the plasma concentration of 8-hydroxy-20-deoxyguanosine (8-OHdG) reduced significantly in comparison with soy milk. Additionally, there was a significant increase in the activity of superoxide dismutase (SOD) in the probiotic soy milk group in comparison with the baseline values. No substantial changes were observed in the promoter methylation of MSH2 within either group from baseline. The use of probiotic soy milk improved antioxidant status in T2DM patients and may reduce promoter methylation within these patients. This indicates that probiotic soy milk is a promising agent for the management of diabetes [185]. Perturbations in one-carbon metabolism can significantly improve carcinogenesis by triggering the methylation and synthesis of aberrant DNA. Choline and its betaine metabolite are essential methyl nutrients that affected the one-carbon metabolism. A low choline

and betaine status may interrupt the methyl pool and may be attributed to carcinogenesis. In genes that encode choline-related one-carbon metabolism enzymes, including phosphatidylethanolamine N-methyltransferase (PEMT), choline dehydrogenase (CHDH), and betaine-homocysteine methyltransferase (BHMT), functional polymorphisms have vital roles in choline metabolism. Thus it may interact with dietary intake of choline and betaine to alter the risk of breast cancer [219]. The risk of breast cancer was substantially increased for women with low choline intake and wild genotype of PEMT rs7946 or BHMT rs3733890. The field of nutrigenomics exploits numerous disciplines and involves dietary impacts on genome stability (DNA damage at molecular and chromosome level), epigenome modifications (DNA methylation), expression of RNA and micro-RNA (transcriptomics), expression of the protein (proteomics) and metabolite alterations (metabolomics) that can all be explored individually or in an integrated way to identify the health status and/or the trajectory of the disease. Of these biomarkers, however, only DNA damage is an obvious biomarker of fundamental pathology that may be alleviated by promoting genetically aberrant cell apoptosis or lowering the rate of accumulation of DNA damage. Changes in the levels of the epigenome, transcriptome, proteome and metabolome may reflect changeable homeostatic responses to changed nutritional exposure. It may not be sufficient alone to demonstrate specific irreversible pathology at the genome [2]. Several chemicals have been reported to induce transgenerational phenotypic effects in animal studies which include cyclophosphamide, alloxan and vinclozolin. For these effects, transgenerational transmission of chemically generated epigenetic alterations has been proposed as potential mechanism. Anyway. Demonstrated that, at the time of gonadal sex determination, gestational exposure of female rats to endocrine disruptor vinclozolin triggered a wide range of abnormalities in offspring then transmitted down the male line for at least 3 generations. The high rate of the defects (about 90% of all males in all generations) and eliminating abnormalities proposed gametic epigenetic inheritance once passed down the female line. In the present study, changed methylation of DNA was shown in two candidate genes in sperm from males exposed to vinclozolin, and these abnormal patterns of methylation were inherited. These findings suggest that exposure of germ cells is essential to generate heritable epigenetic alterations, probably at a particular developmental stage [220]. The sensing and signaling of nutrients is the main regulator of epigenetic cancer machinery. CARM1 arginine methyltransferase is activated during glucose deficiency by the AMPK energy sensor and mediates histone H3 hypermethylation (H3R17me2) leading to increased autophagy. O-GlcNAc transferase (OGT) also signals the availability of glucose to TET3 and hinders TET3 either by decreasing its dioxygenase activity or by enhancing its nuclear export. OGT is also viewed to modify the O-GlcNAc histones directly. These findings firmly indicate that nutrient signaling targets epigenetic enzymes directly to control epigenetic changes [221]. The second one is highlighted that genome damage maybe the principal cause of degenerative and developmental diseases. It can be diagnosed accurately and avoided by adequate dietary and lifestyle intervention at a genetic subgroup and personalized level.

MicroRNAs and Diet

MicroRNAs are a group of small non- coding RNAs (18 to 25 nucleotides) that play important roles in many physiological processes and gene expression regulation [222, 223]. These molecules can control the expression of more than 60% of human genes [224]. MicroRNAs execute their gene-regulating activities at intracellular and extracellular levels. The miRNAs enclosed in apoptotic bodies, microvesicles, and exosomes can be absorbed by other organisms, which influences gene expression in recipient cells [225, 226].

There are two different views on the relationship between dietary compounds and miRNAs: 1) dietary compounds can target mammalian endogenous microRNAs and regulate their expression, and 2) food-derived miRNAs (or xenomiRs) as bioactive molecules can pass through the gastrointestinal tract and regulate the expression of target genes in other organisms, a phenomenon is known as "cross-kingdom" regulation [227, 228] (Fig. 3.1).

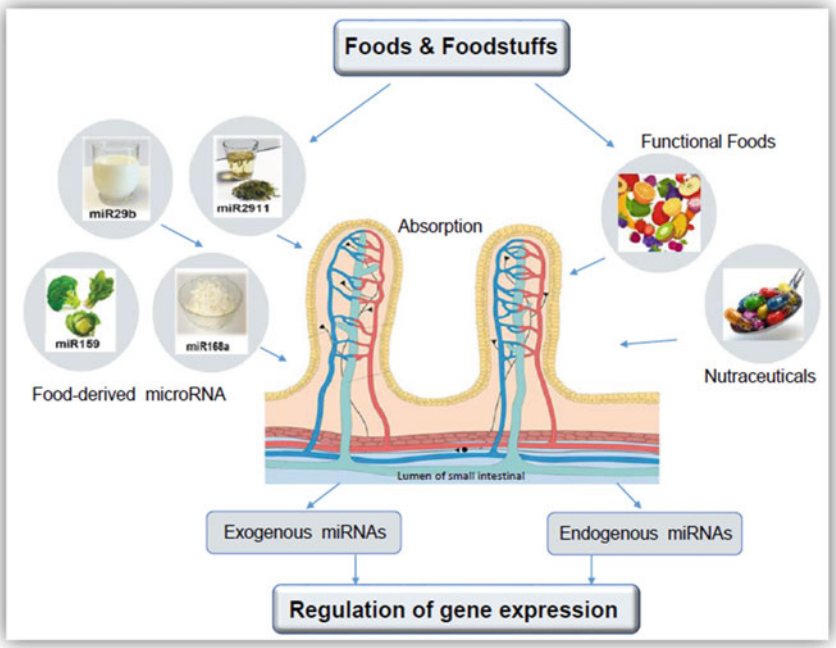


Fig. 3.1 Regulation of gene expression by dietary factors

The Impacts of Dietary Compounds on MicroRNAs

Bioactive dietary compounds may influence endogenous miRNAs production in humans and animals [227, 229]. Several studies have reported that bioactive dietary components in foods (like vitamins, selenium, polyunsaturated FAs, and dietary fibers) can alter the expression of many cardiovascular-related miRNAs such as miRNA-199, miRNA-155, miRNA-21, miRNA-34, and miRNA 30 family [230]. Dietary polyphenols present in fruits, wine, tea, and coffee can modulate the expression of miRNAs in chronic diseases. Although their functional mechanisms are not exact, miRNAs are involved in different biological processes such as cell migration, apoptosis, inflammation, etc. [231]. Davidson et al. stated that fish oil (containing n–3 FAs) had chemoprotective effects in the colon of the rat exposed to a carcinogen. Dietary n-3 polyunsaturated FAs can protect the colon against the development of malignant tumors through modulating miRNAs dysregulation [232]. Furthermore, a diet rich in polyunsaturated FAs reduced miR-21 level and inhibited the expression of pro-inflammatory medsiators and cytokines in chronic diseases [233]. Overall, nutrients contain several bioactive components that have the ability to regulate miRNA expression in cancer cells. The microarray analysis of miRNAs revealed that polyphenols such as EGCG present in green tea could change the expression profile of specific microRNAs in human hepatocellular carcinoma HepG2 cells. Human miR-16, which was up-regulated after EGCG treatment, was shown to target Bcl-2 and induce apoptosis in cancer cells [234]. In a study, Garzon et al. demonstrated that miR-181b was downregulated whereas some miRNAs involved in hematopoietic differentiation and apoptosis (let-7c, let-7d, miR-15a, miR-15b, miR-16-1, let-7a-3, miR-223, miR-342, and miR-107) were up-regulated in acute promyelocytic leukemia (APL) patients after all-trans-retinoic acid (ATRA) treatment [235]. In vivo and in vitro experiments on human lymphoblastoid cells under various treatments showed that reduced dietary folate could increase the level of hsa-miR-222 in human peripheral blood and a lymphoblastic cell line. Then the level of hsa-miR-222 returned to normal when folate was added to the culture medium of the cell line again [236]. Another clinical trial identified that the consumption of a diet rich in lean red meat (HRM) altered the expression of oncogenic microRNAs in rectal mucosal tissues. In the recent study, two different diets (the HRM containing 300 glean red meat per day and the HRM plus 40 g butyrylated resistant starch) were tested on 23 healthy volunteers for 4 weeks. While the recent HRM diet induced the expression of miR-21 and miR17–92 cluster miRNAs in the rectal mucosa, which are upregulated in colorectal cancer, the latter HRM diet (i.e., plus butylated resistant starch) restored the expression of miR17–92 to the baseline. These results suggested that consuming resistant starch and the HRM diet could reduce colorectal cancer risk [237]. Although the list of dietary components that can change miRNAs expression is lengthy, molecular mechanisms linking miRNAs and these components are not well understood. Thus, many more in-depth investigational and longitudinal studies are needed to better understand the underlying mechanisms.

Dietary MicroRNAs

Evidence suggests that various miRNAs present in foods can modulate the expression of target genes in humans and other animals. In 2012, Zhang et al. reported that miR-168a present in rice could target mammalian low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) mRNA and increase LDL plasma level [238]. These researchers provided the first evidence for the effects of food-derived miRNAs on gene expression regulation in mammals. Despite the controversial nature of this report, food-derived miRNAs have attracted a lot of attention among scientists working in this field. Subsequently, many studies have tried to find dietary miRNAs in other dietary resources including animals and plants.

Wang et al. stated that the oral consumption of miR-451 increased blood miR-451 levels and protected erythroid cells from oxidative stress in miR-144/451 null mice [239]. In 2013, Dickinson et al. tried to replicate Zhang et al.'s experiment, but they failed to demonstrate the effects of rice miR168a on LDLRAP1 expression in mice liver and plasma [240]. Then Witwer et al. after the reanalysis of the available data claimed that human sequences had been misidentified as plant miRNAs. Therefore, it was stated that the detection of some plant miRNAs (MIR2911, MIR2910) in sequencing resulted from contamination with human sequences [241]. Furthermore, Mico et al. failed to detect plant miRNAs in human plasma after virgin olive oil consumption [242]. Recent study has demonstrated that after oral consumption of corn, a significant number of corn-derived miRNAs were destroyed in the gastrointestinal tract of C57BL/6 mice, and no differences were observed between the miRNA profile of corn and that of the animals' blood and tissues [243].

In the study of Xiao et al., plant miRNAs from broccoletti sprouts were analyzed by deep sequencing and bioinformatic approach. Although they found 747 miRNAs in the broccoli, their results could not support cross-kingdom regulation by the dietary miRNAs in pancreatic cancer. Also, broccoletti-derived miRNAs did not affect the viability and proliferation of pancreatic ductal adenocarcinoma (PDA) cells [244].

Several studies have detected various dietary miRNAs. In 2014, Lukasik et al. by high-throughput sequencing analysis identified plant miRNAs in human and porcine breast milk exosomes. The identifying plant miRNAs such as ath-miR166a, pab-miR951, ptc-miR472a, and bdi-miR168 in human breast milk samples indicates that these molecules may have the potential to regulate human target genes [245]. Baier et al. demonstrated that a remarkable number of cow's milk miRNAs could be internalized by and then modify gene expression in human white blood cells, as well as mouse liver and HEK-293 cells [246]. Furthermore, computational analyses on microRNA-sequencing data after eating milk validated that nine cow's milk miRNAs were present in human plasma. This result approved that exogenous miRNAs can be transferred by consuming milk [247]. Also, both food-derived exogenous miR-166a and miR-159 were found in the sera of the mice fed with rapeseed bee pollen [248].

Recently, several studies reported that dietary miRNAs might have therapeutic effects on human diseases such as viral infections and cancers. For example, honeysuckle-derived miR2911 could target influenza type A viruses and inhibit viral

replication in mice [249]. Similarly, plant-derived miR159 can be absorbed in human serum through dietary intake and also inhibit cell proliferation in non-GI cancers (e.g., BC) by targeting transcription factors in the Wnt signaling pathway [250]. Furthermore, the oral consumption of a cocktail of miRNAs (miR34a, miR143, and miR145), as a new chemo preventive strategy, inhibited tumorigenesis in the ApcMin/+ mouse model of colon cancer [251].

Dietary miRNAs' Stability

Interestingly, plant-derived miRNAs seem to be highly stable during food processing and cooking [222]. O-methylation loci at the 3′ ends and a high GC content in their structure enhance the stability of plant miRNAs [249, 252]. Dietary miRNAs can bind to other molecules in the food matrix and protect themselves from degradation [253, 254]. One study reported that maize-derived miRNAs were resistant to harsh cooking conditions. Only a minimal number of miRNAs were degraded after puffing treatment, and these cooked maize miRNAs then could cross the GI tract and enter porcine bloodstream [255]. Philip et al. revealed that miRNAs from soybean and rice had good stability (for more than 1 h) in the digestive system without any considerable decline in their concentration. Under a similar conditions however, synthetic cel-lin-4 miRNA did not show the same stability during simulated digestion and cooking [256].

Milk-derived miRNAs, which are permeable to intestinal barriers, are encapsulated in exosomes and can mainly survive within the human digestive system [257]. Zhao et al. also showed that extracellular vesicles could protect milk-derived miRNAs from microwave heating [258]. These results suggested that factors such as the intrinsic structure of miRNAs, their ability to form complexes with other molecules and extracellular vesicles (micro vesicles, exosomes, apoptotic bodies, etc.) determine miRNAs stability during food processing and against digestive enzymes.

Although the above-mentioned observations suggest both advantages and disadvantages for dietary miRNAs, we cannot ignore their existence and roles in gene expression regulation. There is currently inadequate evidence about the mechanisms of dietary miRNAs' actions and further studies are needed to clarify these concepts.

Concluding Remark

In this chapter a comprehensive overview of genomics-lifestyle-diet interactions was presented. However due the wide range of the topics and space limitation a more detailed account of the topics is left for future manuscripts. Nutrigenetics, nutrigenomics and diet-environment related epigenetic alterations are currently under extensive studies. Employment of the research outcome in this field would be an effective

and innovative modality for the human health protection, and disease prevention for generations to come. It is our hope that this chapter has provided meaningful insights into healthy populations and wellbeing of future generations through better understanding of interactions between nutrients, life style, epigenetics and genomic variants.

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Chapter 4
Impact of Behavioral Adversities During Life on Individual's Long-Term Health Status—A Three-Year Follow-up of 403 Middle-Aged PEP—Participants

Gerda-Maria Haas and Peter Schwandt

Abstract Numerous observational studies over the past 80 years have explored the association of lifestyle risk factors, individually and, more recently, collectively, with the risk of mortality and chronic diseases. Findings suggest that being physically active, being of normal weight, avoiding smoking, and consuming a moderate amount of alcohol confer the lowest risk of total mortality and chronic, noncommunicable disease, particularly cardiovascular disease. *Subjects and Methods*: 403 healthy adults (aged 19 to 73 years) without known Cardiovascular Disease (CVD) who participated for the first time in the PEP Family Heart Study Nuremberg were examined and measured for anthropometric and laboratory CVD risk factors, lifestyle in year 1, and 2 years later after they had yearly health and nutrition passports and advice. *Results*: Middle-aged women had less CVD RF than men, but the effects of adverse behavior were stronger in women than in men. Highest negative influence on laboratory measurements were observed for elevated Triglycerides and NonHDL-Cholesterol by less physical activity, for low HDL-C by cigarette smoking, and for obesity by the consumption of fat more than 30% of the daily energy. *Conclusion*: Consequent following lifestyle recommendations should start as soon as possible, because age is an independent factor which strengthens all other adversities.

Keywords CVD risk factors · Physical activities · Dietary habits · Sitting times · Life-style consulting

Introduction

Numerous observational studies over the past 80 years have explored the association of lifestyle risk factors, individually and, more recently, collectively, with the risk of mortality and chronic diseases [1, 2]. Findings suggest that being physically active, being of normal weight, avoiding smoking, and consuming a moderate amount of alcohol confer the lowest risk of total mortality and chronic, noncommunicable

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disease, particularly cardiovascular disease. Recently Hamer et al. [3] reported the positive effect of healthy lifestyle even in hospitalized COVID-19 patients. Because prevention by lifestyle should begin with the childhood, we started the PEP Family Heart Study [4–7] with first graders, their parents and siblings. Here we report about the parents and their lifestyle components when at the begin.

Subjects

In 403 healthy adults (aged 19 to 73 years) without known Cardiovascular Disease (CVD) who participated for the first time in the PEP Family Heart Study Nuremberg we measured anthropometric and laboratory CVD risk factors (RF) according to the recommendations of the European Society of Cardiology (ESC) [8] as well as of the National Cholesterol Program (NCEP) [9] and the International Diabetes Federation (IDF) [10].

Weighed nutritional intake was assessed by dietary protocols over 7 consecutive days before fasting blood sampling (including the weekend) using the computer program PRODI version 4.5 [7], the American Standard Code ASCI, SPSS 21 and the recommendations of D-A-C-H 2019 [11].

Methods

Measurements

At each survey, we measured at home weight and height to the nearest 0.1 cm and 0.1 kg using a calibrated electronic scale SECA (Vogel & Halske, Hamburg, Germany). We calculated body mass index BMI (kg/m^2), measured waist circumference (WC), hip circumference (WHR), waist-to-height ratio (WHtR). All calculations are performed with IBM SPSS Version 21. For all regression models and bivariate correlations, p-values were calculated for 0.01. For regression models, we used univariate regression models for estimating the differences between the single fat patterns and multivariate models for calculating the age-, sex- and bias- adjusted associations between fat patterns and further cardio-vascular risk factors.

Categorization of adverse variables.

As adverse factors for life long health were defined.

Smoking

Smoking was divided in:

1. Non-smoker
2. Ex smoker
3. Active smoker
4. Occupational smoker
5. Passive smoker
6. Ex-passive smoker.

For univariate as well as for multivariate logistic regression models categories 1,2,5, and 6 were summed up as non-smokers, 3 and 4 as smokers.

Unhealthy **nutrition** was defined by German (D)—Austria—Switzerland (CH). (D-A-C-H) recommendations 2018 [12], defined as recommended and more than recommended.

Unhealthy alcohol consumption was defined as 40 mg/d for men and 20 mg/d in women. [12], adverse was defined as high alcohol consumption.

Less Leisuretime Physical Activity (LTPA):

LTPA was calculated in terms of Metabolic Equivalents (METs) from structured interviews using the compendium 2007 of Ainsworth BE [13].

Adverse behavior: less Metabolic Equivalents than 2,040 min per week.

Sitting Time:

Time watching TV or screens (STV)**.** STV high was defined >2 h /d (office resp. household).

Weight:

Overweight/general obesity BMI $\geq$25 kg/m^2 $-$ < 30 kg/m^2/BMI $\geq$30 kg/m^2 [8].

Abdominal Obesity*:* WC > 104 cm for men, > 88 cm for women [10].

Hypertension: ESC Guidelines 2018 [8].

Dyslipidemia: NCEP [9].

Increased Low Density Cholesterol (LDL-C) > 160 mg/dL.

Increased Total Cholesterol (TC) > 200 mg/dL.

Decreased High Density Cholesterol (HDL-C) < 40 mgdL for men, > 50 mg/dL for women.

Increased Non High Density Cholesterol (NonHDL-C) < 130 mg/dL [11].

Hypertriglyceridemia: Triglycerides (TG) > 145 mg/dL [10].

Increased Fasting Plasma Glucose (FPG) > 100 mg/dL [10].

Statistical Analysis

All statistical analyses were performed using actual SPSS (Chicago, IL, USA). Bivariate and multivariate analysis were conducted, and multivariate regression analysis was used for age and gender adjustments. Generalized estimating equations 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. All variables were tested for normal distribution. Statistical tests were two-sided, and $P < 0.05$ was considered statistically significant, for correlations with $P < 0.01$ and significances for paired differences and regression coefficients, respectively, odds ratios (ORs), with $P < 0.001$. Self-reported physical activities were calculated with a given manual in metabolic equivalents (METs).

Results

Basic Results

Only 76 women and 27 men had no risk factor at all.

Because of the diversity of the theme here we report only some selective results.

47% of men were non overweight (♀ 67.1%), 44% were overweight (♀ 24.9%) and 9% of men vs. 8% of women were (general) obese; whereas 88% of men and 84.8% of women had non increased WC, that means only 12% of the men and 15.2% of the women were abdominal obese (Table 4.1).

Except of thickness of triceps skinfold all measured and laboratory results were higher in men than in women (Table 4.2).

Except of age all tested mean values differed significant in both genders. The second difference was observed for age: Women without any RF were significant younger than women with RF. The means of riskful adults were significant higher than the means of the adults without any CVD RF (Table 4.3).

Compared with men's proportion free of risk was doubled for women (38.1% versus 19.4%).

Prevalences of Rfs are given for anthropometric and laboratory RFs as well as for behavior risk factors in the following tables and figures. More than 1 CVD Risk Factor was observed in the other 166 "healthy" men and 147 "healthy" women as shown in 42.9% of the man had 1 to 3 RF compared 43.4% women. 6.4% of the man and 2.1% of the women even had 7 or more CVD RF (Figs. 4.1 and 4.2).

The most frequent adverse factor in men was BMI $\geq$25 kg/m^2 the most frequent in women was found for consuming more fat than recommended.

Fathers were at higher risk than mothers.

CVD risk factors in men and women are demonstrated (below) (Fig. 4.3).

The prevalence of hypertriglyceridemia is about threefold higher in men than in women.

Compared with men the mothers improved their risk significantly more.

Table 4.1 Characteristics year 1

	Men	Women
	Year 1	Year 1
n	166	237
Mean age (years)	41.1 (7.7)*	38.8 (7.3)
Median age (years)	40.0	38.0
Age range	18.0–73.0	25.0–70.0
Weight (kg)	82.7 (11.8)*	66.1 (10.8)
Height, (cm)	179.7 (7.2)*	165.9 (5.9)
BMI (kg/m^2)	25.6 (3.2)*	24.0 (3.8)
WC (cm)	91.9 (9.6)*	78.6 (9.7)
WHtR	0.51 (0.1)*	0.47 (0.1)
HC (cm)	102.4 (6.6)*	99.9 (7.9)
WHR	0.90 (0.1)*	0.79 (0.1)
SFT triceps (mm)	11.6 (4.5)	17.9 (5.7)*
SFT subscap (mm)	15.8 (5.9)	15.1 (6.9)
SBP (mm Hg)	131.3 (14.4)*	118.6 (13.5)
DBP (mm Hg)	84.6 (10.0)*	77.0 (9.5)
TC (mg/dL)	194.6 (36.1)	193.0 (36.3)
TG (mg/dL)	106.8 (52.7)*	78.7 (39.6)
HDL-C (mg/dL)	47.8 (11.8)	62.3 (15.3)*
LDL-C (mg/dL)	125.5 (30.9)*	114.9 (31.3)
Non HDL-C (mg/dL)	146.8 (35.2)*	130.7 (35.0)
LDL-C/HDL-C	2.77 (0.9)	1.98 (0.8)*
FPG, mg/dL	103.7 (14.9)*	99.2 (12.4)

*$P < 0.05$

Behavioral Adversities

Alcohol Consumption

1.7% of fathers and 14.7% of mothers consumed more alcohol than recommended.

Smoking

Although of warning posters from governments all over the world we find smokers in parents too (Table 4.4 and Fig. 4.4).

In between smokers were 13.1% persons with hypertriglyceridemia versus 9.4% in nonsmokers and 34.4% with decreased HDL-C compared to 20.5% in nonsmokers.

Only 15% of (+3% occupational ones) of the parents were active smokers.

Table 4.2 Comparison of means between parents without any RF and those with CVD RF

	Men		SD	Women		SD
Age	Without RF	41	1.2	Without RF	37	0.5
Age	With RF	41	0.7	With RF	40*	0.7
SBP	Without RF	123	2.5	Without RF	115	1.0
SBP	With RF	133*	1.2	With RF	120*	1.2
BMI	Without RF	24	0.5	Without RF	23	0.3
BMI	With RF	26*	0.3	With RF	24*	0.3
TC	Without RF	163	4.0	Without RF	170	2.4
TC	With RF	201*	3.0	With RF	204*	2.9
TG	Without RF	76	4.9	Without RF	68	2.9
TG	With RF	113*	4.6	With RF	84*	3.5
HDL-C	Without RF	52*	1.8	Without RF	65*	1.2
HDL-C	With RF	47	1.0	With RF	61	1.3
LDL-C	Without RF	97	3.6	Without RF	92	2.3
LDL-C	With RF	131*	2.5	With RF	126*	2.3
NonHDL-C	Without RF	112	4.1	Without RF	105	2.4
NonHDL-C	With RF	154*	2.8	With RF	143*	2.7
FPG	Without RF	91	2.3	Without RF	91	0.8
FPG	With RF	105*	1.4	With RF	103*	1.2

*$P < 0.05$

Calculating with **Pearson correlations** strong relation was observed between age and year of age increases 1 unit of the CVD RF above. E.g., 1 year of life increases TG with 0.212 mg/dL more (Table 4.5).

A strong correlation between age as a CVD RF was found for smoking behavior correlated with hypertension (Fig. 4.5).

For smoking women older than 35 years the prevalence of hypertension is more than fivefold higher than in women younger 35 years (Fig. 4.6).

In men highest prevalence besides smoking was found for prehypertension followed by increased Non-HDL-C. In women overweight/obesity was higher than in men. Hypertension as well as laboratory values (increased and decreased. also) were higher in men than in women (Table 4.6).

Few LTPA had a higher negative effect in men whereas the negative effects of fat rich meals where different for BMI, WC, compared with WHtR and WHR between the sexes (Fig. 4.7).

Significant Linear Relationship Was Observed E.g.

1 kcal energy consumption corresponded with 0.006 mmHg DBP or 0.01 mg/dL NonHDL-C. 1 g fat with 0.10 cm WC. 0.08 mmHg SBP. 0.02 mg/dL TC or 0.13 mg/dL NonHDL-C.

Table 4.3 Prevalence of CVD RF and adverse behavior in year 1. Same observation was made for unhealthy anthropometric as well as for laboratory risk values respectively behavior

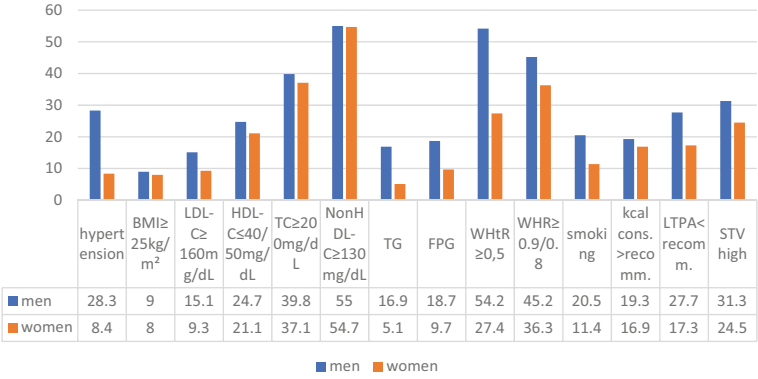
	Men	Women
	Year 1	Year 1
n	166	237
IncreasedWC, ♂ > = 102 cm, ♀ > = 88 cm	13.9%	17.8%
IncreasedWHtR, > 0.5	54.2%	27.5%
Increased BMI, > = 30 kg/m^2	9.1%	8.0%
SBP > = 140 mmHgI DBP 90 mmHg (prehypertension)	88.6%	50.2%
SBP > = 130 mmHgI DBP85 mmHg (hypertension)	28.3%	8.4%
Increased TC, > = 200 mg/dL	39.8%	37.1%
Increased TG, > = 145 mg/dL	16.9%	5.1%
Increased LDL, > = 160 mg/dL	42.8%	27.0%
Increased NonHDL-C, > = 130 mg/dL	67.5%	47.3%
Decreased HDL, ♂ < 40 mg/dL, ♀ < 50 mg/dL	24.7%	21.1%
Increased LDL_HDL, > 3	33.7%	10.5%
Increased FPG, > = 100 mg/dL	26.3%	14.9%
Smoking	20.5%	11.4%
Less LTPA	27.7%	17.3%
kcal > recommended	19.3%	16.9%
Fat > recommended	59.6%	41.4%
Alcohol > recommended	1.7%	14%

57.5% of these adults had no CVD RF at all

Fig. 4.1 Prevalence of number for anthropometric and blood CVD RF observed in year 1

1 unit METs per week corresponded with −0.001 cm HC. 0.002 mg/dL HDL-C or −0.006 mg/dL TG.

Each gram fat corresponded with 0.06 mg/dL TG. each g saturated fat (SAFA) with 0.06 mg/dL LDL-C. or each g carbohydrates corresponded with 0.02 kg weight in parents.



	hypertension	BMI≥ 25kg/m²	LDL-C≥ 160mg/dL	HDL-C≤40/50mg/dL	TC≥200mg/dL	NonHDL-C≥130mg/dL	TG	FPG	WHtR ≥0,5	WHR≥ 0.9/0.8	smoking	kcal cons. >recomm.	LTPA< recomm.	STV high
men	28.3	9	15.1	24.7	39.8	55	16.9	18.7	54.2	45.2	20.5	19.3	27.7	31.3
women	8.4	8	9.3	21.1	37.1	54.7	5.1	9.7	27.4	36.3	11.4	16.9	17.3	24.5

Fig. 4.2 Prevalence of adverse factors

Relationship Between Nutrition and CVD RF

Both raw mass of energy and fats too and percentage of saturated as well as mono-unsaturated or polyunsaturated in fat consumption were higher in men than in women (Table 4.7).

An example for the relationship of macronutrients is given below answering the question, whether there are any effects between macronutrients and blood pressure (Table 4.8).

We observed higher energy consumption for hypertensive adults than in normotensives. Their energy consumption contained more fat less carbohydrate more protein and alcohol percentages than the energy consumption of the normotensive ones. Same result was observed for prehypertension.

All dyslipidemic RF were related with higher energy consumption.

Significant higher alcohol consumption percentage was observed for increased Non-HDL-C.

For hypertriglyceridemia we observed significant higher energy consumption too for hyperglycemia significant higher protein consumption (Table 4.9).

For both gender fat consumption for adults with low LTPA was significantly higher than in adults with high LTPA in men with low LTPA only SAFA and MUFA were higher too. In women consumption of carbohydrates was significant higher with low LTPA as well as the consumption of polysaccharides.

Univariate Relationship Between Adverse Behavior and CVD Risk Factors

Adverse behavior resulted in different Odds for the risk of hypertriglyceridemia between men and women (Fig. 4.8).

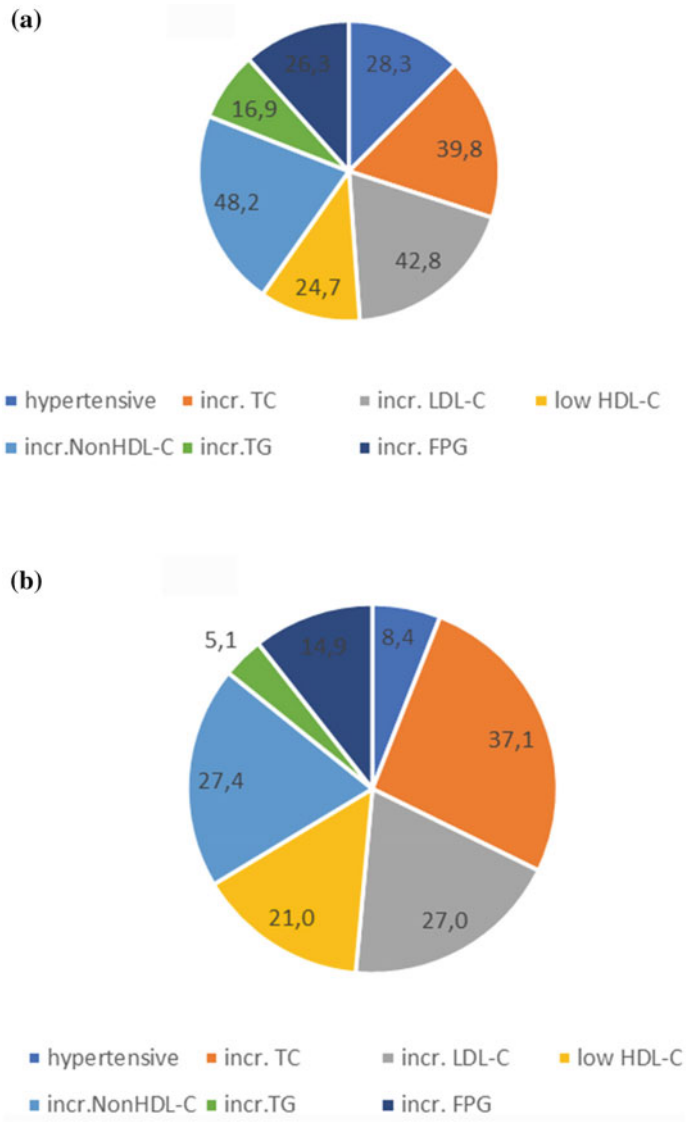


Fig. 4.3 **a** CVD risk factors (year 1) in men. **b** CVD risk factors (year 1) in women

For hypertension associations were found for obesity—hypertension with OR 9.2 (3.1–27) in women and 2.2 (1.3–3.7) and in men 1.2 (1.0–1.8).

For abdominal adiposity were found significant effects of fat consumption, too, in women and men (3.7; 2.3).

Table 4.4 Smoking in Germany

Age	Men (%)	Women (%)
18–20 y	26.1	18.7
21–24 y	36.2	23.4
25–29 y	31.9	34.1
20–39 y	35.0	27.4
40–49 y	32.1	28.2
50–59 y	30.0	24.8
50–64 y	22.0	19.4

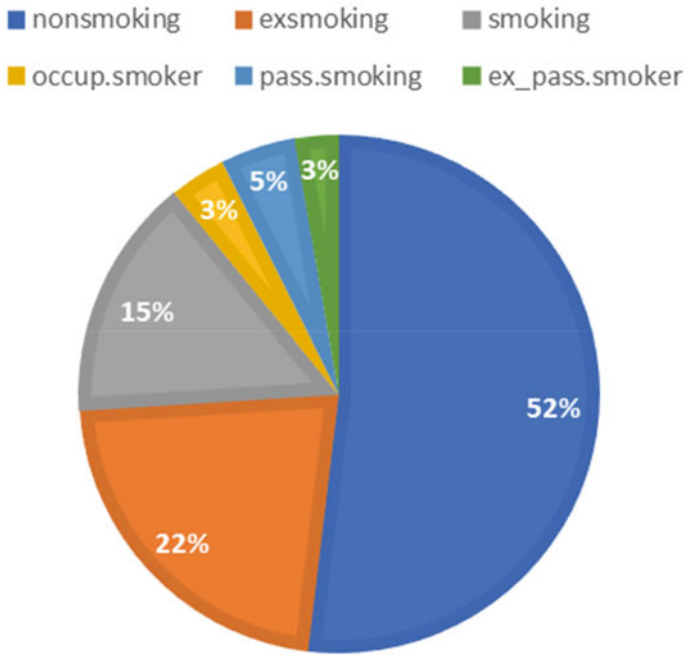


Fig. 4.4 Distribution of the exactly defined smoking behavior

Table 4.5 Significant correlations were observed for age and CVD RF

	WC	SBP	BMI	TC	TG	LDL-C	NonHDL-C	FPG
Age	0.224**	0.357**	0.182**	0.170**	0.212**	0.179**	0.213**	0.293**

**$P < 0.001$

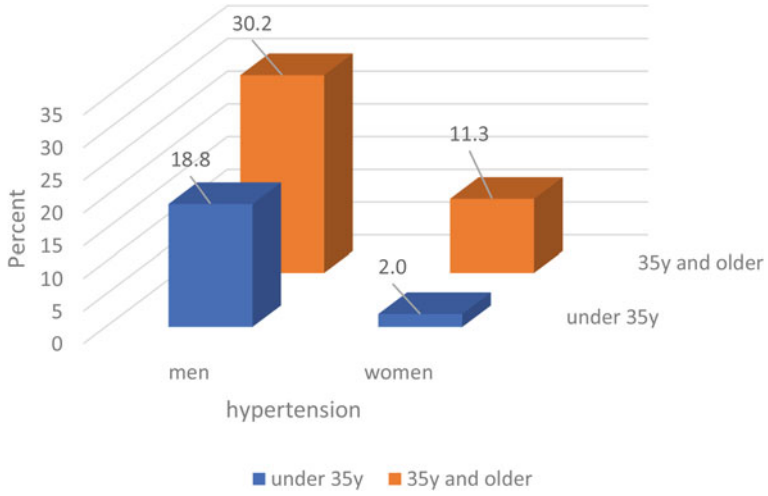


Fig. 4.5 Distribution of hypertension in smokers depending on age

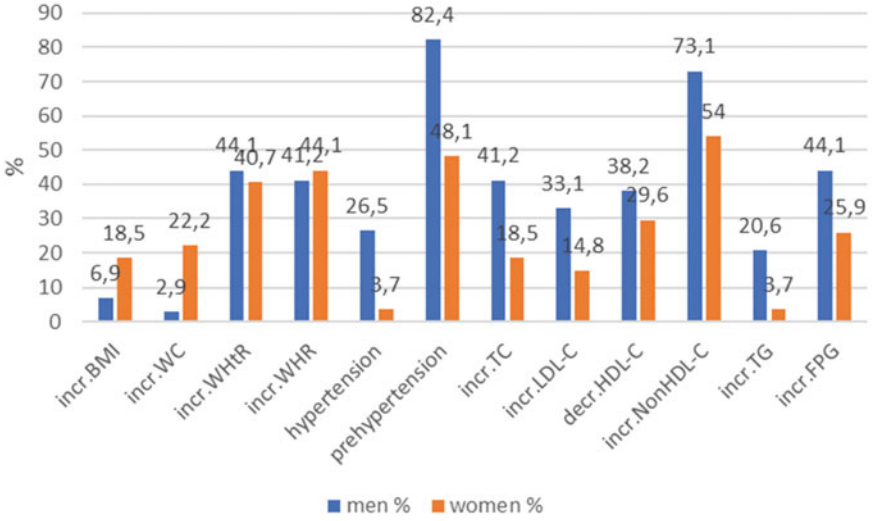


Fig. 4.6 Prevalence of further CVD RF in smokers

More than recommended consumption of fat (30% was recommended) was the most adverse factor of macronutrients. E.g. for hyperlipidemia except of LDL.C and hypertriglyceridemia in men and women too.

For increased LDL-C was found a significant effect of saturated fats consumption (♂ OR 3.2. CI 95% 2.0–5.6. ♀ OR 4.4 (CI 95% 2.5–7.7).

Table 4.6 Prevalences of further CVD RF in adults with less LTPA and more energy consumption than recommended

Riskfactor	Less LTPA		More fat than recommended	
	Men	Women	Men	Women
	%	%	%	%
Incr.BMI	17.8*	9.8	7.8	11.7*
Incr.WC	21.7	24.4	9.4	19.5*
Incr.WHtR	67.4*	41.5	54.7*	32.5
Incr.WHR	54.3*	46.3	43.8*	3.7
Hypertension	37.0*	4.9	25.0*	11.7
Prehypertension	87.0*	58.5	92.9*	54.5
Incr.TC	47.8*	29.3	61.0	60.9
Incr.LDL-C	43.5*	24.4	71.9*	58.4
Decr.HDL-C	39.1*	22.0	21.9	39.0*
Incr.NonHDL-C	85.9*	75.3	71.0*	52.4
Incr.TG	37.0*	7.3	6.3*	2.6
Incr.FPG	9.0	48.3*	42.2*	26.0

*$P < 0.05$

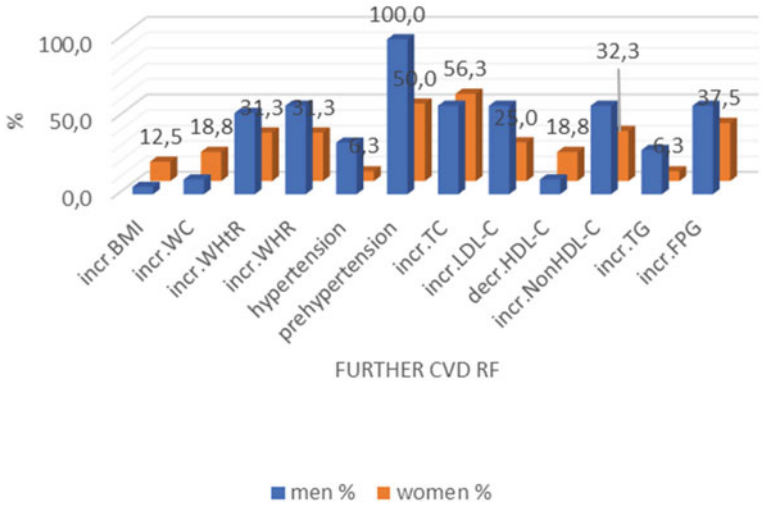


Fig. 4.7 Prevalence of further CVD RF besides more energy consumption than is recommended by D-A-C-H

Table 4.7 Results of the weighed 7-days dietary protocols. The PEP-mothers consumed significant less energy and fat than men. but the percentage of polyunsaturated fat in their nutrition behavior was not better than in fathers

		Kcal/d	Fat (g)/d	SAFA(g)/d	MUFA(g)/d	PUFA(g)/d
Men	Mean	2423*	98*	41*	35*	15*
	N	166	166	166	166	166
	SD	513	26	12	10	5
	Minimum	1093	26	9	9	4
	Median	2370	95	39	34	14
	Maximum	3694	172	80	62	34
Women	Mean	1915	79	35	28	12
	N	237	237	237	237	237
	SD	384	21	10	8	4
	Minimum	717	29	11	10	3
	Maximum	3371	154	73	49	30
	Median	1878	77	33	27	11

*$P < 0.05$

Table 4.8 Macronutrients in normotensive and hypertensive adults

		N	Mean	SD
Kcal	Normotension	336	2105	499
Kcal	Hypertension	67	2219*	538
Fat. %	Normotension	336	35	6
Fat. %	Hypertension	67	37*	5
Carbohydrates (%)	Normotension	336	47*	6
Carbohydrates (%)	Hypertension	67	44	7
Protein. %	Normotension	336	14	2
Protein. %	Hypertension	67	15*	2
Alcohol. %	Normotension	336	3*	4
Alcohol. %	Hypertension	67	4	4

*$P < 0.05$

Only for men the effect from higher alcohol consumption to LDL-C was tested with an OR of 4.6 (95% CI 1.7–12.8).

Table 4.9 Comparison between high LTPA and low LTPA for energy in kcal and fats and carbohydrates in gram/day in year 1 of participation

LTPA	Men		Women	
	>2040 METs	≤2040 METs	>2040 METs	≤2040 METs
Kcal	2418	2424	1867	1970*
Fat	92	99*	78	81*
SAFA	38	42*	34	35
MUFA	33	36*	27	28
PUFA	15	15	12	12
Carboh	267	258	210	224*
Monosacch	42*	36	34	38*
Disacc	72	71	65	65
SACCH	59	58	53	55
POLYsacch	141	140	108	116*
FIBER	20	21	18	19
PROT	87	88	65	68*
Plant.PROT	33	33	26	27

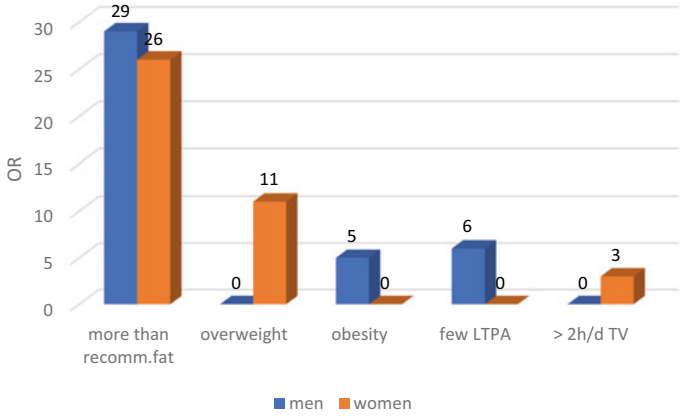


Fig. 4.8 Probability of hypertriglyceridemia tested by univariate logistic regression model

Multivariate Relationship Between Adverse Behavior and CVD Risk Factors

Not only one adverse lifestyle factor does improve or worsen the CVD risk.

Below are demonstrated some examples:

What about elevated TC and the influences of more than 1 adverse behavior fact? (Table 4.10).

Table 4.10 Multivariate relationship between adverse behavior and CVD risk factors

	Sig	OR	95% CI)	
			Lower level	Upper level
A				
TC ≥ 200 mg/dL				
High alcohol consumption	**0.021**	**2.624**	**1.16**	**5.935**
Sex°	0.206	1.386	0.836	2.298
Age	0.919	1.002	0.97	1.035
Less LTPA	0.255	0.700	0.379	1.293
More kcal consumption	0.932	1.028	0.55	1.919
Sitting time TV > 2 h/d	0.095	0.622	0.356	1.086
Smoking	0.076	0.532	0.265	1.068
More than recommended fat consumption	**0.000**	**5.021**	**3.456**	**7.295**
Constant	0.019	0.19		
B Alcohol and fat as influencers				
BMI ≥ 25 kg/m^2				
High alcohol consumption	0.928	0.941	0.251	3.53
Sex*	0.431	1.376	0.622	3.043
Age	0.985	1	0.955	1.046
Less LTPA	0.300	1.549	0.677	3.546
More kcal consumption	0.986	1.008	0.389	2.611
Sitting time TV > 2 h/d	0.056	2.102	0.982	4.502
Smoking	0.655	1.246	0.475	3.264
More than recommended fat consumption	**0.000**	**2.392**	**1.575**	**3.634**
Constant	0.000	0.023		
C				
Low HDL-C				
High alcohol consumption	0.010	0.131	0.028	0.616
Sex°	**0.007**	**3.02**	**1.35**	**6.755**
Age	0.032	0.943	0.893	0.995
Less LTPA	0.895	1.062	0.437	2.581
More kcal consumption	0.857	0.918	0.361	2.333
Sitting time TV > 2 h/d	0.168	1.786	0.782	4.08
Smoking	**0.026**	**2.798**	**1.129**	**6.932**
More than recommended fat consumption	**0.000**	**43.05**	**17.798**	**104.127**
Constant	0.004	0.036		

Legend: sex° reference value is male
P < 0.001

The most important lifestyle factor for hypercholesterolemia seems to be the consumption of more than recommended fat per day. This risk could be fivefold higher than for the adults who do not eat more than recommended by D-A-CH.

Overweight was found 2.4—fold higher for adults with fat rich nutrition compared with adults who consumed as much fat as recommended.

Decreased HDL-C was threefold higher observed in women compared to men and threefold higher too for smokers compared to nonsmokers.

The most adverse factor was given for hypertension from elevated WC with the probability of 4.6 (CI95% 2.3–9.2) followed by elevated WHtR with 3.8 (CI05% 2.1–6.9). WHR with 2.3 (CI 95% 1.3–4.0) and 1.7 (CI 95% 1.0–3.0) for consuming more fat than recommended by D-A-C-H.

Last not least: Middle-aged women had less CVD RF than men but the effects of adverse behavior were stronger in women than in men.

Results Over 3 Years

Compared with men the mothers improved their risk significantly more (Table 4.11 and Figs. 4.9, 4.10).

Alcohol Consumption

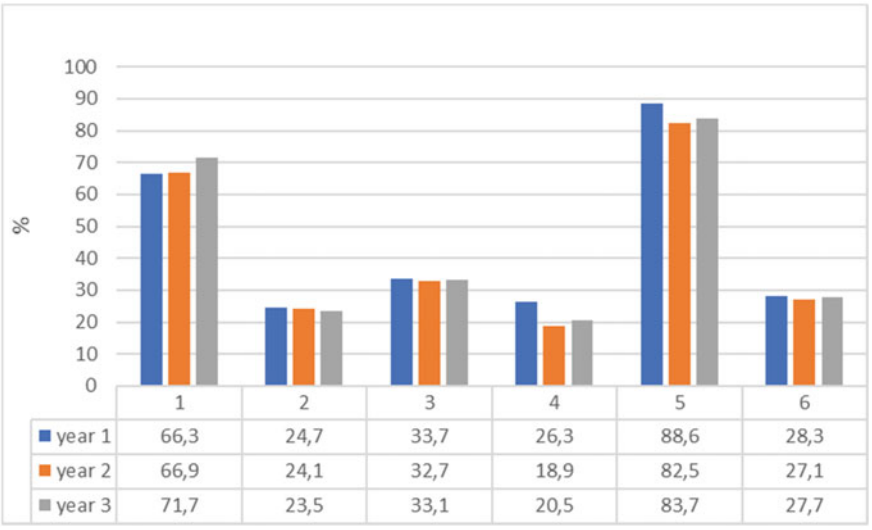
41% of fathers and 43.9% of mothers did not reduce their alcohol consumption. Alcohol intake >40/20 g per day in year 3 was only 3% in women and 11.7% in men. No remarkable relation was observed with other CVD RF (Table 4.12).

Compared to average of smokers in Germany we found in the PEP cohort (median age 41 y/38 y) less smokers, namely fathers with 20.5% (mothers 11.4%) (Fig. 4.11).

Two years after the start with PEP 3% of the former smoking fathers became nonsmokers; in between the smoking mothers.

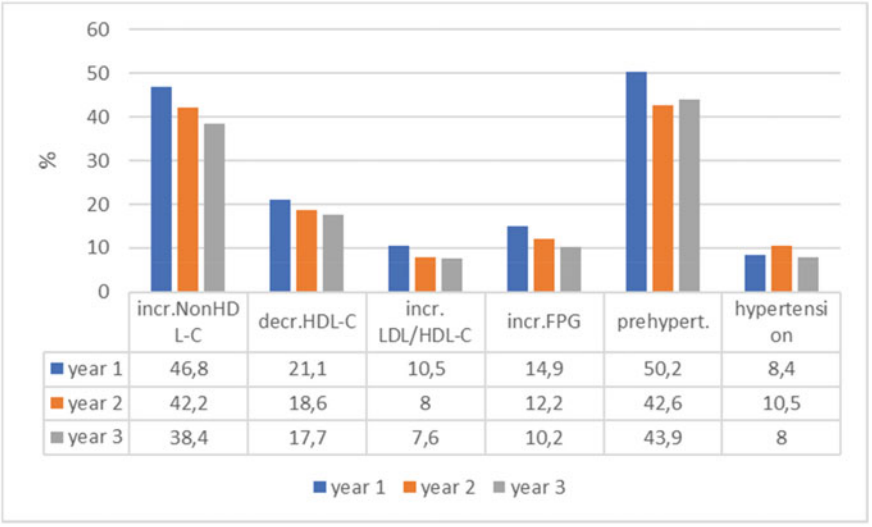
Table 4.11 Bad behavior

	Men	Women
	%	%
Smoking	20.5	11.4
Less LTPA	27.7	17.3
Kcal > recommended	19.3	16.9
Fat > recommended	59.6	41.4



	1	2	3	4	5	6
year 1	66,3	24,7	33,7	26,3	88,6	28,3
year 2	66,9	24,1	32,7	18,9	82,5	27,1
year 3	71,7	23,5	33,1	20,5	83,7	27,7

Fig. 4.9 Prevalence of CVD RF of 166 men 3 years follow up



	incr.NonHDL-C	decr.HDL-C	incr. LDL/HDL-C	incr.FPG	prehypert.	hypertension
year 1	46,8	21,1	10,5	14,9	50,2	8,4
year 2	42,2	18,6	8	12,2	42,6	10,5
year 3	38,4	17,7	7,6	10,2	43,9	8

Fig. 4.10 Prevalence of CVD RF of 237 women 3 years follow up

Diet

After 2 years with multiple counselling offers the results seem to be sufficient for the average of the participants as shown in the next 4 figures (Fig. 4.12).

These results demonstrate how successful Lifestyle changing can be.

Table 4.12 Smoking in Germany [11]

Smoking in Germany		
Age	Men (%)	Women (%)
18–20 y	26.1	18.7
21–24 y	36.2	23.4
25–29 y	31.9	34.1
20–39 y	35.0	27.4
40–49 y	32.1	28.2
50–59 y	30.0	24.8
50–64 y	22.0	19.4

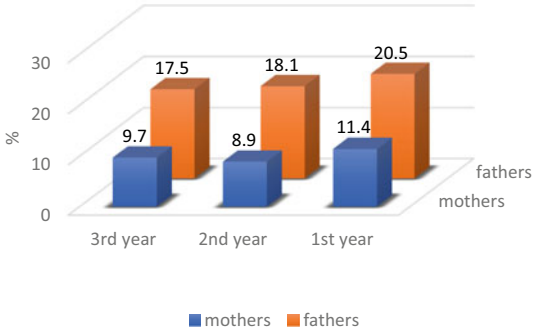


Fig. 4.11 Development of smoking over 3 years

But 56.0% of the men and 54.4% of the women could not minimize their number of CVD RF.

For example did the CVD RF depending on the number of their Metabolic Equivalents differed from year to year. We show the distribution of CVD RF correlated with recommended and not recommended LTPA below (Table 4.13).

The proportion of mothers with sufficient METs or more could enlarge per 6.5% whereas the proportion of men with sufficient LTPA decreased per 0.4% (Fig. 4.13).

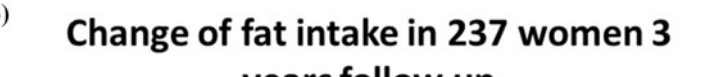
The development of CVD RF for men and women strongly differed between adverse LTPA behavior and recommended behavior. E.g. the proportion of men with hypertension and recommended LTPA decreased from 28.8% to 26.0% whereas the proportion of men with low LTPA increased from 27.4 to 36.5%. For women these effects were not similar.

Best influences of Physical Activity were observed for all anthropometric factors.

(a)

	Fat g/d	SAFA g/d	MUFA g/d	PUFA g/d	% fat (kcal)
year 1	97,5	40,8	35,2	14,9	36,4
year 2	91,2	37,7	32,9	14,2	35,5
year 3	91,8	37,6	33,3	14,6	35,4

(b)



	Fat g/d	SAFA g/d	MUFA g/d	PUFA g/d	% fat (kcal)
year 1	79,3	34,6	27,5	11,7	37,2
year 2	73,1	30,8	25,6	11,8	35,8
year 3	72,0	29,8	25,0	12,1	35,8

Fig. 4.12 **a–b** Changing dietary habits

Comparison of the Dietary Development Over 3 Years in 403 Parents

6% of the fathers and 7.2% of the mothers did not follow the recommendations of D-A-C-H (regarding kcal corresponding weight (BMI) and age) 0.48.8% of fathers and 42.6% of mothers could not follow the recommendations for fat consumption. 44 (30.8) % for Saturated Fatty Acids (SAFA) 0.53.6 (50.6) for Monounsaturated Fatty Acids (MUFA) and 51.5 (46%) for Polyunsaturated Fatty Acids (PUFA). Our purpose

Table 4.13 Recommended LTPA versus less LTPA than recommended

	Men			Women		
	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 1 (%)	Year 2 (%)	Year 3 (%)
LTPA recommended						
Increased WC ♂ ≥102 cm. ♀ ≥88 cm	12.9	11.0	15.5	7.7	5.8	8.7
Increased WHtR >0.5	46.2	46.2	42.3	23.2	16.8	25.2
Obesity ≥30 kg/m^2	5.8	8.7	5.8	6.5	7.1	8.4
Overweight ≥25–<30 kg/m2	39.4	33.7	35.6	21.9	24.5	21.3
Prehypert SBP ≥140 mmHg IDBP ≥90 mmHg	89.4	80.8	82.7	52.3	41.9	43.9
Hypert.: SBP ≥130mmHg IDBP ≥85 mmHg	28.8	26.0	26.0	8.4	10.3	8.4
Increased TC ≥200 mg/dL	38.5	48.1	41.3	36.1	34.8	27.1
Increased TG ≥150 mg/dL	14.4	16.3	18.3	4.5	5.8	4.5
Increased LDL-C ≥160 mg/dL	43.3	48.0	10.6	23.9	34.0	5.8
Increased NonHDL-C ≥156 mg/dL	47.1	51.0	47.1	25.2	26.5	19.4
Decreased HDL-C ♂ <40 mg/dL. ♀ <50 mg/dL	15.4	16.3	18.3	17.4	14.8	14.8
Increased LDL-C/HDL-C >3	28.8	26.0	27.9	7.7	5.8	5.8
Increased FPG ≥100 mg/dL	36.5	41.9	43.3	28.4	33.5	31.6
LTPA less than recommended						
Increased WC♂ ≥102 cm. ♀ ≥88 cm	19.5	21.0	19.4	19.4	20.7	28.0
Increased WHtR >0.5	47.7	66.1	67.7	37.8	30.5	36.6
Obesity ≥30 kg/m^2	14.5	12.9	11.3	11.0	8.5	9.8
Overweight ≥25–<30 kg/m2	51.6	53.4	50.0	30.5	35.4	25.6
Prehypert SBP ≥140 mmHg IDBP ≥90 mmHg	87.1	85.5	85.5	46.3	43.9	43.9
Hypert.: SBP ≥130mmHgIDBP ≥85 mmHg	27.4	29.0	30.6	8.5	11.0	7.3
Increased TC ≥200 mg/dL	41.9	50.0	48.4	30.0	35.4	31.7
Increased TG ≥150 mg/dL	21.0	25.8	22.6	6.1	6.1	3.7
Increased LDL-C ≥160 mg/dL	14.5	12.9	11.9	11.0	11.0	4.9
Increased NonHDL-C ≥156 mg/dL	56.0	53.2	61.3	31.7	20.7	24.4
Decreased HDL-C ♂ <40 mg/dL. ♀ <50 mg/dL	40.3	37.1	323	28.0	25.6	23.2
Increased LDL-C/HDL-C >3	41.9	43.5	41.9	15.9	12.2	11.0

(continued)

Table 4.13 (continued)

	Men			Women		
	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 1 (%)	Year 2 (%)	Year 3 (%)
LTPA recommended						
Increased FPG ≥100 mg/dL	27.4	19.4	14.5	7.3	6.1	2.4

$p > 0.05$ same year

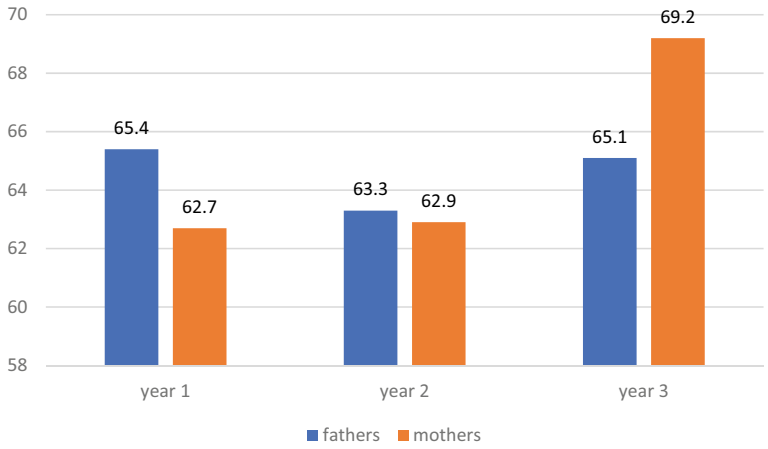


Fig. 4.13 Proportion of parents with sufficient LTPA over the years

was to compare the different means for CVD RF of participants with improved behavior in year 3 compared to year versus worsened behavior (Table 4.14).

The relationship with good and worse behavior influenced the prevalence of selected anthropometric and blood CVD RF (Table 4.15).

As observed before the prevalence of hypertension in men was higher when LTPA in year 3 was less than in year 1 and higher when PUFA percentage was less than in year 1 too. In women except smoking (explained in the results of year 1) all effects of bad behavior seem stronger for hypertension than in men.

With univariate logistic regression models for all behavior risk factors associations were calculated between these factors and the anthropometric and blood CVD RF based on better respectively worse behavior in year 3 compared to year 1 (Table 4.16).

Table 4.14 **a–c** Development of CVD RF (means) between worsened and improved diet

	Men			Women		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
A Development of CVD RF (means) between worsened and improved energy intake						
n	166	166	166	237	237	237
Mean age, years	41.1 (7.7)	42.0 (7.6)*	43.0 (7.6)	38.8 (7.3)	39.8 (7.3)*	40.8 (7.3)
Median age, years	40.0	41.0	42.0	38.0	39.0	40.0
Age range	18.0–73.0	19.0–74.0	20.0 – 75.0	25.0 – 70.0	26.0 – 71.0	27.0 – 72.0
Energy kcal/d	2422.8 (512.8)*	2306.8 (478.1)	2322.6 (501.4)	1915.1 (383.6)*	1829.5 (411.9)	1805.2 (371.8)
Fat g/d	97.5 (25.5)*	91.2 (25.1)	91.8 (26.0)	79.3 (20.9)*	73.1 (22.0)	72.0 (20.8)
Saturated Fat g/d	40.8 (12.1)*	37.7 (11.3)	37.6 (11.8)	34.6 (10.4)*	30.8 (10.9)	29.8 (9.9)
Monounsaturated Fat g/d	35.2 (9.8)*	32.9 (10.4)	33.3 (10.6)	27.5 (7.5)*	25.6 (8.2)	25.0 (7.7)
Polyunsaturated Fat g/d	14.9 (5.4)	14.2 (4.8)	14.6 (4.8)	11.7 (3.7)	11.8 (4.1)	12.1 (4.2)
Cholesterol (mg/day)	362.3 (114.6)*	339.0 (109.4)	338.6 (106.7)	299.0 (87.1)*	255.2 (87.4)	255.1 (88.3)
PFA_SFA	0.38 (0.2)	0.40 (0.1)	0.41 (0.1)	0.35 (0.1)	0.41 (0.2)*	0.44 (0.2)[2]
Fat % kcal	36.4 (6.0)*	35.5 (5.3)	35.4 (5.2)	37.2 (5.3)*	35.8 (5.6)	35.8 (5.8)
Carbohydrates g/d	260.0 (66.8)*	251.9 (60.3)	255.6 (61.9)	216.7 (52.5)	211.8 (52.2)	210.0 (49.9)
Monosaccharide g/d	37.2 (24.5)	36.3 (22.2)	39.1 (23.9)[2]	35.7 (19.7)	34.9 (17.0)	34.0 (17.1)
Disaccharides g/d	71.6 (34.7)*	66.0 (28.9)	67.2 (29.5)	65.8 (27.4)*	60.4 (26.0)	59.6 (24.4)
Saccharose g/d	58.5 (32.2)*	53.1 (26.0)	54.7 (26.5)	54.0 (24.6)*	48.8 (22.3)	48.1 (20.8)
Polysaccharides g/d	140.1 (36.2)	139.3 (37.2)	139.2 (33.5)	111.6 (30.9)	112.9 (29.5)	113.0 (26.1)
Fiber g/d	20.8 (6.5)	21.5 (7.4)	21.7 (6.6)	18.8 (5.5)	19.4 (5.7)*	19.6 (5.9)
Carbohydrates % kcal	43.6 (5.6)	44.6 (5.9)*	45.0 (5.7)	46.1 (5.6)	47.3 (6.0)*	47.5 (6.4)
Protein g/d	87.7 (19.4)*	84.2 (18.7)	84.0 (19.0)	66.2 (13.2)*	64.3 (14.1)	63.3 (12.4)

(continued)

Table 4.14 (continued)

	Men			Women		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Veget. Protein g/d	33.0 (8.7)	32.2 (8.1)	32.3 (7.9)	26.1 (6.1)	26.3 (6.4)	26.4 (5.9)
Protein % kcal	14.9 (2.3)	15.0 (2.3)	14.8 (2.3)	14.3 (2.2)	14.5 (2.2)	14.5 (2.3)
Alcohol g/d	19.0 (17.3)	17.3 (16.8)	16.6 (15.0)	7.1 (8.1)	6.8 (7.7)	6.3 (7.5)
Alcohol % kcal	5.2 (4.7)	4.9 (4.7)	4.8 (4.3)	2.6 (2.9)	2.4 (2.7)	2.3 (2.8)

	Less fat over 3y			More fat over 3y		
	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 1 (%)	Year 2 (%)	Year 3 (%)
B Development of CVD RF (means) between worsened and improved fat consumption						
Elevated WC♂ ≥ 102 cm, ♀ ≥ 88 cm	15.9	13.2	15.2	16.6	16.4	23.7
Elevted WHtR >0.5	33.9	28.4	32.0	46.4	44.7	49.3
Obesity ≥ 30 kg/m^2	8.0	8.4	8.5	9.2	9.2	8.6
Overweight ≥ 25 − < 30 kg/m^2						
Prehypertension: SBP ≥ 140mmHgIDBP 90 mmHg	65.3	60.2	57.8	67.1	57.2	64.5
Hypertension: SBP ≥ 130mmHgI DBP ≥ 85 mmHg	15.1	15.1	14.7	19.1	21.1	18.4
Elevated TC ≥ 200 mg/dL	37.5	39.8	31.9	39.5	42.1	40.1
Elevated TG ≥ 150 mg/dL	10.4	11.2	10.8	9.2	12.5	10.5
Elevated LDL-C ≥ 130 mg/dL	33.1	34.0	29.1	34.2	34.9	33.6
Elevated NonHDL-C ≥ 156 mg/dL	24.3	23.5	21.9	26.3	27.6	19.1
Low HDL-C ♂ < 40 mg/dL, ♀ < 50 mg/dL	22.3	21.9	22.3	23.0	19.1	16.4
Elevated LDL-C/HDL-C > 3	19.5	18.0	18.7	21.1	18.4	17.1

(continued)

Table 4.14 (continued)

	Less fat over 3y			More fat over 3y		
	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 1 (%)	Year 2 (%)	Year 3 (%)
Elevated FPG ≥ 110 mg/dL	20.9	15.6	14.2	18.4	14.2	15.4

	Less P/S-ratio over 3y			Increased P/S-ratio over 3y		
	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 1 (%)	Year 2 (%)	Year 3 (%)
C Comparison of means for Improved versus worse P/S-ratio						
Elevated WC ♂ ≥ 102 cm, ♀ ≥ 88 cm	17.1	15.8	19.4	15.6	13.7	17.9
Elevted WHtR > 0.5	41.4	38.8	41.7	37.0	32.3	36.9
Obesity ≥ 30 kg/m^2	11.4	12.2	11.6	6.9	6.8	6.9
Overweight ≥ 25 − < 30 kg/m^2						
Prehypertension: SBP ≥ 140mmHgIDBP 90 mmHg	70.7	68.6	65.0	63.5	54.0	57.8
Hypertension: SBP ≥ 130mmHgI DBP ≥ 85 mmHg	19.3	19.3	20.7	15.2	16.3	13.7
Elevated TC ≥ 200 mg/dL	35.0	42.9	32.1	39.9	39.5	36.5
Elevated TG ≥ 150 mg/dL	10.0	13.6	9.3	9.9	10.6	11.4
Elevated LDL-C ≥ 130 mg/dL	33.6	36.7	30.7	33.5	33.1	30.8
Elevated NonHDL-C ≥ 156 mg/dL	25.0	24.3	19.3	25.1	25.5	21.7
Low HDL-C ♂ < 40 mg/dL, ♀ < 50 mg/dL	22.1	20.0	19.3	22.8	21.3	20.5
Elevated LDL-C/HDL-C > 3	22.1	16.5	16.4	19.0	19.0	19.0
Elevated FPG ≥ 110 mg/dL	20.4	13.8	16.0	19.6	15.7	13.9

*$P < 0.05$ between two groups same year

Table 4.15 Different prevalence of hypertension depending on different factors of lifestyle behavior

Men	Men	Women	Women
%	%	%	%
Smoking	Non smoking	Smoking	Non smoking
26.7	27.9	9.5	7.9
LTPA improved	LTPA worsened	LTPA improved	LTPA worsened
26.9	29.3	6.1	12.3
FAT improved	FAT worsened	FAT improved	FAT worsened
55.0	58.0	16.9	22.8
SAFA improved	SAFA worsened	SAFA improved	SAFA worsened
58.0	54.1	18.1	21.9
MUFA improved	MUFA worsened	MUFA improved	MUFA worsened
51.1	9.6	19.2	3.3
PUFA improved	PUFA worsened	PUFA improved	PUFA worsened
54.4	60.3	16.4	25.6
p/s improved	p/s worsened	p/s improved	p/s worsened
56.5	56.7	17.5	23.0
Sacch. improved	Sacch. Worsened	Sacch. improved	Sacch. Worsened
57.9	54.9	16.4	23.7
Kcal improved	Kcal worsened	Kcal improved	Kcal worsened
56.4	56.9	17.4	22.7

Other Remarks:

60.8% of the adults. Who consumed more kcal in year 3 than in year 1, had 0–3 CVD RF.
65.6% of the adults. Whose energy expenditure was less in year 3 than in year 1, had 0 to 3 CVD RF.
59.3% of the adults. Who consumed more fat than in year 1, had 0 to 3 CVD RF.
64.5% of the adults. Who consumed less PUFA than in year 1, had 0 to 3 CVD RF.
About 60% of the participants did not improve their adverse behavior, smokers were 4% less than in year 1.
About 20% of all with adverse behavior in year 3—nutrition as well as activity—had no CVD RF at all.
Out of 34 adults belonging to all negative balances only 2 were without any CVD RF.

Table 4.16 Associations between behavior factors worse compared to year 1 and anthropometric and laboratory measured CVD RF

	OR	Lower level	Higher level
Less LTPA			
TG ≥ 150 mg/dL	2.0	1.0	3.7
HDL-C ≤ 40/50 mg/dL	1.7	1.0	2.8
TC ≥ 200 mg/dL	1.7	1.1	2.7
NonHDL-C ≥ 156 mg/dL	2.0	1.3	3.1
Overweight	1.8	1.2	2.8
WHtR ≥ 0.5	1.8	1.2	2.8
More fat than recommended			
Obesity	2.2	1.3	3.7
Overweight	1.8	1.2	2.8
Prehypertension	1.6	1.1	2.4
Smoking year 3			
TG ≥ 150 mg/dL	2.4	1.2	5.0
HDL-C ≤ 40/50 mg/dL	2.9	1.6	5.2
LDL/HDL-C < 3	2.8	1.6	5.2

As reported in part 1 middle-aged women had less CVD RF than men. But the effects of adverse behavior were stronger in women than in men.

Discussion

The observation of this cohort of middle-aged persons demonstrated that there is not only one lifestyle factor which has an effect for the development of CVD RF beside the individual genes [6, 15]. Our findings are an impressive documentation for that and demonstrate that it is recommended to start with lifestyle change in young years. because all these participants seemed to be healthy at all. As demonstrated in 2019 by Lelong et al. [16] the combination of drug treatment with healthy lifestyle was very successful, too, when they found the importance of promoting healthy lifestyle habits at midlife in order to age in good health. “Even following only a selection of various healthy behaviors can have important public health impacts, and larger benefits can be expected” what Dungling et al. found in their systematic review. Their results stand for associations between hypertension in young adults with long term cardiovascular events [17]. The HUNT Study from Norway did associate physical activity with reduced CVD risk [18]. “Those who maintained their physical activity from adolescence to young adulthood demonstrated a significantly lower CVD risk and better mental health, compared to inactive maintainers”.

Conclusions

Men's risk prevalence measured by all participants was threefold higher for being hypertensive or hypertriglyceridemic. Twofold higher for hyperglycedemia as well as for elevated WHtR as for active smoking than in women who were about two years younger. Men's prevalence for increased LDL-C or Non-HDL-C was 1.5-fold higher. Active smoking behavior was doubled comparing men with women. Mens' physical activities were 1/3 higher and their time watching TV was 1/3 less than in women.

Energy consumption as well as fat consumption was higher in adults with less LTPA compared to adults with recommended or more METs/ week.

Hypertension and smoking were highly associated in persons elder than 35y. Overweight was observed more than twofold higher with fat rich nutrition.

Overweight as own risk factor was associated with Non-HDL-C (OR 1.7; CI95% 1.1–2.7). Hypertriglyceridemia (OR 2.3; CI 95% 1.1–4.5). Low HDL-C (OR 1.8; CI 95% 1.1–3.0) or hypertension (OR 1.7; CI 95% 1.1–3.0).

Highest risk for hypertension was found for all anthropometric measures as elevated BMI, WC, WHtR or WHR. As consequence the consumption rich fat meals should be avoided.

Whereas the prevalence of hypertriglyceridemia was threefold higher for adults with less physical activity than in adults with recommended LTPA. Higher for elevated LDL-C. Non-HDL-C and decreased HDL-C. Higher for elevated LDL-C and TG for those with more kcal consumption than recommended and LDL-C $\geq$160 mg/dL with 23.6%. TG $\geq$145 mg/dL with 20.3% and HDL-C $\leq$40/50 mg/dL were found in adults who consumed more fat than recommended. No worse values for LDL-C. TG and HDL-C were found for persons who consumed no more fat per day than recommended by D-A-C-H.

Age is an independent factor which strengthens all other adversities. Consequent following lifestyle recommendations should start as soon as possible. Because our findings in the PEP Family Heart Study demonstrated that the lifestyle behavior of the parents is like a mirror for the behavior of children [4, 5].

Strength and Limitations

Certainly, this cohort brought with them a very motivation how to learn about preventive lifestyle behavior to avoid strong illnesses in their later life. They came as voluntaries with the only purpose to participate until to 13 following years with medical examinations, blood giving, writing 7-days nutrition protocols to receive their yearly health passport, and their yearly nutrition passport, the offers of cooking courses, courses for LTPA, or to get dietary recommendations directly in their own households correcting the negative results which were found in their health and nutrition passports.

Compliance with Ethical Standards

Funding The PEP Study was funded by a grant of the Arteriosklerose-Praeventions-Foundation (Bürgerliche Stiftung Öffentlichen Rechts).

Disclosure of Interests All authors declare they have no conflicts of interest.

Ethical Approval All procedures performed involving human participants were in accordance with the ethical standards of the national research committee, and with the 1964 Helsinki declaration and its later amendments. Approval was granted by Ethical Committee of the Medical Faculty of the Ludwig-Maximilians-University, Munich.

Informed Consent Informed Consent for participation and publication was obtained from all individual participants included in the study.

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Chapter 5
The Role of Dietary Habits on Development and Progress of Risk Factors of Chronic Non-communicable Diseases

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Let food be thy medicine and medicine be thy food.
—Hippocrates

Abstract According to the World Health Organization "Noncommunicable diseases (NCDs) tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioral factors". Diet is related to the modifiable behavioral risk factors and metabolic risk factors in different ways, as a protection or a risk factor. The role of dietary habits is a key point in the prevention and treatment of NCD during all life. In childhood, the most important action is the prevention of obesity as a driver for other NCDs. In adolescence, the importance of dietary habits is boosted with behaviors that are established in this life stage (use of alcohol, tobacco, sedentary lifestyle, and an unhealthy diet). Unhealthy diets are characterized by low consumption of fruits, vegetables, whole grains, cereals, meat, legumes, dairy, among other "basic food", and the high consumption of ultra-processed food, fast food, and sugar-sweetened beverages. Adulthood is a life stage strongly marked by the appearance of NCDs (although it's already observed in adolescents, especially the ones with obesity) and the insertion on the work market. The life changes during adulthood are strongly related to the NCDs and the diet is one of the most important. The evidence points that energy balance or restriction, sodium intake until 2 g/day, Mediterranean diet, replacement of saturated for unsaturated fatty acids (poly or mono), fruits and vegetables, higher dietary fiber, whole grains, omega-3 and omega-6 fatty acids, low glycemic index/load food, DASH diet, Nuts, Plant-based diet/vegetarian diet, dairy products (especially low fat and fermented products), fish and, coffee have protective action against NCD. Meanwhile, there is a group of food that represents more risk

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to develop NCDs: high intake of the salt and preserved salt food, high intake of the red meat and processed meat, high alcohol consumption, high saturated fatty acids intake, high intake of the sugar/sweetened beverages, trans-fatty acids, diet higher in glycemic index and load, Western diet pattern (large portion size, high intake of the energy-dense food, fast food, red meat, and processed meat), very hot drinks and foods, dietary cholesterol, diet with high inflammatory index. Elderly is marked by the presence of multiple NCDs. In this life stage diet quality has a huge effect on physical condition, cognitive condition, bone health, eye health, vascular function, and the immune system. Therefore, actions for the prevention and control of NCDs should be recognized as a health priority and should adopt a life-course approach.

Keywords Chronic disease · Food Consumption · Nutrient Intake · Children · Adulthood · Elderly

Introduction

According to the World Health Organization (WHO) "Noncommunicable diseases (NCDs) tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioral factors". The more recurrent NCDs are cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes. The risk factors to the development of NCD could be classified into different groups: modifiable behavioral risk factors (tobacco, excess sodium intake, alcohol use, and insufficient physical activity) or metabolic risk factors (raised blood pressure, overweight/obesity, hyperglycemia—high blood glucose levels, and hyperlipidemia—high levels of fat in the blood) [1]. Diet is related to the modifiable behavioral risk factors and metabolic risk factors in different ways, as a protection or a risk factor. The role of dietary habits is a key point in the prevention and treatment of NCD during all life.

The study of the relation between diet and NCD could be examined at different levels comprising intake of nutrients, foods, food groups, and/or dietary patterns. It should highlight the increasing importance of food processing in global food supplies and dietary patterns. In this context, NOVA is a classification system based on the nature, extent, and purpose of industrial food processing [2]. The NOVA is organized in four groups: unprocessed or minimally processed foods; processed culinary ingredients; processed foods; and ultra-processed foods as described in Table 5.1.

A systematic analysis for the Global Burden of Disease Study 2017 assessed the effect of foods and nutrients consumption across 195 countries worldwide on NCDs mortality and morbidity among adults. The authors found that suboptimal diets were responsible for 22% adult deaths globally. Approximately 11 million deaths and 255 million disability-adjusted life-years (DALYs) were attributable to dietary risk factors. A diet rich on sodium was responsible by 3 million deaths and 70 million DALYs globally and in many countries. On the other side, a low intake of whole

Table 5.1 Description of NOVA groups

Food group	Description
Unprocessed or minimally processed foods	Unprocessed (or natural) foods are edible parts of plants or animals (fruits, vegetables, eggs, milk, meat, etc.) which are fresh or processed in ways that do not add substances such as salt, sugar, oils, or fats, and infrequently contain additives
Processed culinary ingredients	Substances extracted from unprocessed foods or from nature by processes such as pressing, refining, grinding, milling, and spray drying (salt, oil, sugar, etc.)
Processed foods	Simple products manufactured by adding processed culinary ingredients to unprocessed foods (i.e., canned fruit or vegetables, salted nuts, cured and smoked meats, cheese, etc.)
Ultra-processed foods	Industrial formulations of food-derived substances (oils, fats, sugars, starch, protein isolates) that contain little or no whole food and often include flavorings, colorings, emulsifiers, and other cosmetic additives (e.g., carbonated drinks; sweet and savory packaged snacks; ice-cream, chocolate; mass-produced packaged bread and buns; margarines and spreads; cookies, pastries, cakes, and cake mixes; breakfast "cereals,"; "energy drinks"; milk drinks, and "fruit" yogurts; meat and chicken extracts and "instant" sauces; infant formulas, follow-on milks; "health" and "slimming" products; many ready-to-heat products; poultry and fish "nuggets" and "sticks," sausages, burgers, hot dogs, and other reconstituted meat products; and powdered and packaged "instant" soups, noodles, deserts and many more)

Adapted from Monteriro et al. [2]

grains account 3 million deaths and 82 million DALYs, and a low intake of fruits answered 2 million deaths and 65 million DALYs [3].

The association between dietary habits and NCDs has been extensively explored. In this chapter we discuss the role of diet on NCDs, considering a life course perspective since the risk factor exposure can begin in early life and persist until aging.

Childhood

Childhood (or the beginning of human life) is considered an important benchmark to prevent NCDs. Is the period that represents the first 10 years of life and can be

divided into early childhood (preschool age) and middle childhood (school age). It is characterized as a period of intense growth and it is marked by the difference between the age stages. The diet quality could interfere with the development of tissues, organs, and systems being a risk factor to develop the NCDs in adolescence and adulthood. Early childhood is the first stage and includes breastfeeding and complementary feeding—when the food is introduced on the diet. Food habits during childhood could affect food habits and health during life [4].

Obesity

Obesity is the most important risk factor associated with NDCs among children and it is the major risk factor to the precocious development of NCDs still in childhood. According to the WHO, overweight in children under the age of five is an important question to deal with worldwide, the Global prevalence in 2020 was around 5% [5]. An important aspect related to the diet in the first years of life is weight gain, especially the excessive weight gain that can be a risk of obesity and diabetes in adulthood. Breastfeeding has an essential role in the prevention of NCDs. During the first two years, the type (exclusive until six months and continued until at least two years or mixed with infant formulas or other milk) and duration of breastfeeding influences allied to the complementary feeding: the timely introduction of and their characteristics and composition. The introduction of foods before four months is associated with obesity in older ages [6]. A study conducted in 22 European countries corroborates with the findings that breastfeeding protects from obesity. The never breastfed or breastfed for a shorter period has a likelihood of 1.22 to became obese when compared with breastfed children for at least 6 months [7]. The food consumption and high-dense calories diets (based in ultra-processed foods) are also related to rising obesity during childhood [8].

Diabetes Type 1

As in other NDCs, breastfeeding has a protective role on the development of diabetes type 1 while infant formula represents an increased risk of developing type 1 diabetes. The early food introduction also represents risk for diabetes type 1. In older ages the high consumption of cow milk and sweeteners could be a factor for the development of this disease [9].

Asthma

Asthma is one of the leading respiratory NCDs, commonly occurs in children and the pathogenesis and progression could be affected by dietary habits. The relation between food habits and the disease is observed in all life stages. In childhood, the consumption of fast food, ultra-processed food, and processed meat is associated

with asthma development. The food groups related to protection against asthma are vitamins A, D, and E, Zinc, fruits, vegetables, and the Mediterranean diet [10]. Breastfeeding is an important protective factor to asthma development in children beyond the first 2 years of life [11].

Evidence affirms that NCDs are preventable and its prevention is an essential issue during infancy, childhood, and adolescence [12]. The promotion of healthy and adequate diets, based on unprocessed and minimally processed foods has the potential to prevent NCDs throughout life [13].

Adolescence

Adolescents are young people between 10 and 19 years of age. This period is characterized by a rapid growth velocity and changes in the body and social relationships [14]. In adolescence, choices are made, including food and nutrition practices, and these will affect their future, including health status. NCDs are associated with behaviors that are established in adolescence, including the use of alcohol, tobacco, a sedentary lifestyle, and an unhealthy diet [15].

For reversing the NCDs epidemic, preventive interventions are needed as early as possible, like in childhood and adolescence to minimize risks at all stages of life. In this way, it is necessary to consider the modifying factors that are associated with NCDs, especially physical activity and diet [16]. According to the WHO, 81% of adolescents do not get enough physical activity and 11.7% of adolescents partake in heavy episodic drinking [17].

A study with 101,607 adolescents from the Brazilian National Survey of School Health (PeNSE) 2015 observed irregular consumption of fruits and vegetables in 80.7% and regular consumption of ultra-processed foods in 60.6% of the students analyzed. Besides that, the authors observed a high prevalence of insufficient physical activity (65.6%), and alcohol consumption (23.8%) [18].

Poor eating habits characterized by the low consumption of fruits and vegetables, the high consumption of fast food and sugar-sweetened beverages are responsible for increasing the total energy intake, which is consequently associated with overweight and obesity in this age [19]. Overweight and obese children are likely to continue obese into adulthood and more likely to develop noncommunicable diseases like diabetes and cardiovascular diseases at a younger age [20].

Data from the WHO (2016) estimated that the global number of obese children and adolescents (5–19 years) rose from 11 million in 1975 to 124 million in 2016 and 216 million children were overweight [8]. In the USA, the latest data from the National Health and Nutrition Examination Survey shows that the prevalence of obesity among adolescents from 12 to 19 years was 20.6% [21]. In Brazil, a systematic review with 65 studies pointed to a prevalence of 17% of overweight and 11.6% of obesity in Brazilian children and adolescents [22]. Data from 73,399 students with a mean age of 14.7 years, participants in the Brazilian Study of Cardiovascular Risks in Adolescents (ERICA), showed a prevalence of obesity of 8.4% [23]. Overweight

and obesity are strongly associated with high blood pressure and those are potential risk factors to increase cardiovascular disease [23].

Cardiovascular Disease Risk Factors in Adolescents

The efforts to prevent cardiovascular disease in adulthood implies to control the risk factors, especially dyslipidemia, hypertension, and type 2 diabetes mellitus, and should be initiated earlier in life (childhood and adolescence). Some evidence indicates that atherosclerosis began at fetal age [24].

The prevalence of dyslipidemia in adolescence has been increasing in the last years. Data from the Study of Cardiovascular Risks in Adolescents (ERICA) showed that 21% of adolescents between 12 and 17 years old had high total cholesterol, especially adolescents' girls (24.9%) compared to boys (15.3%) [25]. Hypertension, another risk factor to CVD, has been tough to define in children and adolescents once changes in blood pressure usually occur with increasing age and body size. Therefore, higher blood pressure in adolescence could be usual when compared to children but lower compared to adults [26]. However, in a systematic review and meta-analysis with 47 articles of the global prevalence of hypertension in children, the pooled prevalence of hypertension was 4% and prehypertension was 9.67% in children and adolescents [26]. Type I Diabetes Mellitus is the most common of diabetes in children and adolescents [27], nonetheless, some studies have begun to present an increased incidence of type 2 diabetes mellitus worldwide in these stages of life [28], especially in the USA.

Understanding the risk factors of CDV and NCD is fundamental is the sense to analyze and intervene in the modifiable risk factors for NCD in adolescence. An Integrative Review of the literature showed as the main risk behaviors in adolescence: alcohol consumption, tobacco use, overweight and obesity, physical inactivity, and diet patterns with low consumption of fruits and vegetables and high consumption of fat and sugar [16].

Type 2 Diabetes Mellitus

The prevalence of type 2 diabetes in adolescents increased in the last decades. In the United States (US), there was an increase of 31% in type 2 diabetes among adolescents aged 10–19 years between 2001 and 2009 [29]. A review suggests that 8–45% of cases of diabetes in children and adolescents are of type 2 in the US [30]. The increase of type 2 diabetes occurs in parallel with an increase in body mass index of the global population. Moreover, there is evidence that DM2 could be a consequence of overweight and obesity [31].

Some risk factors are associated with type 2 diabetes development in adults and young people: family history of DM2, obesity, physical inactivity, arterial hypertension, and dietary patterns [32]. The diet is one of the main modifiable risk factors to prevent the DM2 [33].

A study realized with 37,038 high school participants from the Nurses' Health Study II cohort demonstrated that western pattern diet, characterized by food with high glycemic load (sugar sweetened beverages, desserts, processed meats and refined grains) was associated with 29% greater risk of T2DM development in the middle-aged women [34].

To prevent diabetes in adolescence, one must invest in weight reduction and changes in eating patterns. In this sense, nutritional intervention should stimulate physical activity, increase of consumption of healthy foods (unprocessed and minimally processed foods), including fruits, vegetables, full-grain, eggs, milk, and others, and reduce ultra-processed food consumption, characterized by high calories and sugar and fat content (Table 5.1).

Habits acquired at this stage of life are generally maintained in adult life and are associated with development of NCDs in the adult and elderly age.

Adulthood

People with age between 19 to 59 years are considered an adult. This life stage, as the others, is heterogeneous as well as the health status. Young adults (people in their twenties years) have a lower prevalence and incidence of diseases than middle-aged and older adults (30–59 years). Opposite, injuries due to road traffic accidents are more common in young than middle-aged and older adults. The adult phase is marked by psychological, social, economic, and functional modifications associated with the environment, resulting in changes in the dietary pattern. The exposure to early-life risk factors can set patterns that have a cumulative effect on health into adulthood, resulting in non-communicable diseases [35].

Table 5.2 shows dietary patterns and nutrients recommended in different guidelines (published worldwide) or evidence from systematic reviews and/or meta-analysis, associated with the risk of the NCDs in adulthood. This summary is not provided by an extensive review, and some evidence/recommendation can also be applied to the elderly population. The level of evidence varies from weak (heterogeneous observational studies) to strong (well-conducted randomized clinical trials), and the effect sizes ranged from marginally significant to a large effect size. For more information as identification of the specific disease related to the dietary variable, the level of evidence, and the effect sizes please see the references.

The evidence, described in Table 5.2, indicates that dietary patterns based on fresh fruits and vegetables, fish, vegetable oils, and whole grains can protect against obesity, type 2 diabetes, cancer, CVD, and mental diseases. However, the high consumption of red meat and processed meats, ultra-processed foods, free sugar, or sugar-sweetened beverages, and trans-fatty acids is related to the increased risk of NCDs.

The paradoxes involving the effects of dietary fatty acid consumption on CVD is surrounded by controversies. (1) Dietary cholesterol does not appear to increase the blood cholesterol and therefore, does not promote CVD: most foods that contain cholesterol are also high in saturated fatty acids (SFA). Consequently, the increasing

Table 5.2 Summary of evidence and recommendations to the dietary patterns related to increase or decrease risk of NCDs in adulthood

Dietary patterns/variable	Non-communicable disease					Reference(s)
	Obesity	Type 2 diabetes	Cardiovascular disease[e]	Cancer[f]	Mental disease[g]	
Energy balance or restriction	↘	↘	↘	↘	↘	[36, 37]
Sodium intake until 2 g/day			↘			[38]
High intake of salt and preserved salt food			↗	↗		[38–40]
High intake of red meat and processed meat			↗	↗		[39, 41, 42]
High alcohol consumption	↗	↗	↗	↗		[37, 39, 40, 43, 44]
Mediterranean Diet	↘	↘	↘	↘	↘	[42, 45–51]
High intake of saturated fatty acids		↗[a]	↗[a]			[37, 52]
Replacement of saturated by unsaturated fatty acids (poly or mono)			↘			[53]
High intake of the sugary/sweetened beverages	↗	↗	↗	↗	↗	[37, 43, 54–58]
Fruits and vegetables	↘	↘	↘	↘	↘	[37, 39–41, 57, 59, 60]
Trans fatty acids		↗	↗	↗		[37, 40, 52, 61]
High dietary fiber	↘	↘	↘	↘		[37, 40, 43, 62, 63]
Whole grains	↘	↘	↘	↘		[37, 40, 41, 57, 59, 64]
Omega-3 fatty acids		↘	↘[a]		↘	[37, 40, 52]

(continued)

Table 5.2 (continued)

Dietary patterns/variable	Non-communicable disease					Reference(s)
	Obesity	Type 2 diabetes	Cardiovascular disease[e]	Cancer[f]	Mental disease[g]	
Omega-6 fatty acids			↘	↘		[65]
Low glycemic index/load food	↘	↘				[43, 52]
Diet High in glycemic index and load		↗	↗	↗	↗	[47, 66–68]
Western diet pattern (large portion size, high intake of energy dense food, fast food, red meat and processed meat)	↗	↗	↗	↗	↗	[42, 43, 51, 69]
Very hot drinks and foods				↗		[39]
Dietary cholesterol			↗[a]	↗		[40, 70, 71]
DASH diet	↘	↘	↘	↘	↘	[48, 51, 72–74]
Nuts	↘	↘	↘	↘		[37, 41, 57, 59, 75]
Plant based diet/vegetarian diet[b]		↘	↘	↘		[48, 76–79]
Diet with high inflammatory index[c]	↗	↗	↗	↗	↗	[80–82]
Ultra-processed foods	↗	↗	↗	↗	↗	[83–87]

(continued)

Table 5.2 (continued)

Dietary patterns/variable	Non-communicable disease					Reference(s)
	Obesity	Type 2 diabetes	Cardiovascular disease[e]	Cancer[f]	Mental disease[g]	
Dairy products (especially low fat and fermented products)		↘	↘	↘	↘	[58, 88–90]
Fish	↘		↘	↘	↘	[57, 91–95]
Coffee	↘	↘	↘	↘	↘	[96–101]
Tomatoes/lycopene			↘	↘	↘	[102–105]

↗—increase the risk; ↘—reduce the risk

[a]See the text for other considerations

[b]Diets including higher amounts of less healthy plant foods, such as refined grains, potatoes/fries, and foods and beverages high in added sugar are linked to increase the risk of non-communicable diseases [106]

[c]Diet inflammatory index (original and derivative) assessed by a tool developed by Shivappa and cols [107]

[d]Coffee intake reduces the risk of oral, pharynx, liver, colon, prostate, endometrial cancer and melanoma and increases the risk of lung cancer [101]

[e]Include Hypertension, Stroke, heart attack, coronary disease. Some dietary patterns are related to one or more of these events

[f]Include one or more types of cancer site-specific, or all causes of cancer

[g]Include neurodegenerative disease, depression, anxiety, mood, stress, and other

risk of CVD could be due to the content of SFA [108, 109]. (2) Omega-3 fatty acids may not reduce CVD: in an extensive literature review of 86 studies, the consumption of omega-3 fatty acids, from foods or supplements, does not significantly reduce the CVD risk [110]. However, a protective effect, especially for secondary prevention of CVD and for high doses of omega-3 fatty acids was also found [110–112]. (3) SFA may not increase the risk of CVD and type 2 diabetes: a meta-analysis of 14 studies showed a reduction in the risk of stroke in the high-intake strata of SFA [113]. Higher levels of very-long-chain saturated fatty acids in erythrocytes were positively associated with cardiovascular health, in another study [114]. A meta-analysis showed that only even chain SFA can be associated with type 2 diabetes, while odd chain STA reduced this risk [115]. Despite this controversy, the guidelines for the prevention of CVD still recommend the replacement of SFA by unsaturated fatty acids. Trans-fatty acids should be avoided.

The International Agency for Research on Cancer (IARC) lists a complementary role of dietary carcinogens, such as aflatoxins, food additives, heterocyclic amines, foods contaminated with heavy metal, and other substances that can be found in foods (to find out the list, visit: https://monographs.iarc.fr/agents-classified-by-the-iarc/). Additionally, once obesity is recognized as a risk factor for several cancer types, dietary approaches to prevent obesity can also be effective to protect against cancer [39, 116]. Furthermore, obesity prevention also reduces the risk of type 2 diabetes and CVD [40, 52].

Other dietary patterns and interventions, such as the Paleolithic diet [117] fasting and time-restricted feeding [118, 119], low-carb diets [120] and regular breakfast intake [121] can prevent the development of obesity and its metabolic complications (comorbidities). The benefits of fruit consumption in reducing the incidence of NCDs are only observed with the consumption of fresh fruits or pure juices not sugar-added. Whereas the consumption of processed fruits (dried fruits and sweetened fruit juices) can be associated with an increased risk of NCDs [122].

The last discoveries about the role of the intestinal microbiota and the health of the host have made it possible to recognize several relationships between intestinal dysbiosis and NCDs. The use of prebiotics or probiotics found in whole and fermented foods, respectively, can modulate this relationship. The intestinal microbiota can be a promising field in the prevention and treatment of metabolic and mental disorders related to NCDs [123–127]. Another emerging area of study involves the temporal regulation of an organism's internal metabolism (the circadian rhythm). Results from animal and human studies demonstrate that there is an appropriate timing to eat, to avoid disruptions of the temporal coordination of metabolism and physiology, and thus, prevents the development of obesity and metabolic diseases. Disturbances in the circadian rhythms can be related to the pathogenesis of these diseases [128, 129].

Worldwide and in all WHO regions, the prevalence of Heavy Episodic Drinking—HED (60 g or more of alcohol) is higher among young people of 20–24 years than in the total population. The prevalence of HED is particularly high among men. Excessive alcohol consumption is associated with several chronic diseases (see Table 5.2) and premature deaths and disability. In the age group of 20–39 years, approximately 13.5% of the total deaths are alcohol-attributable [44]. On the other hand, moderate

alcohol consumption (12–15 g/day for women and 24-30 g/day for men), mainly wine and beer, was related to the prevention of CVD and cancer due to the combination of alcohol and antioxidants contained in these beverages [37, 40, 130]. However, a meta-analysis indicated that whilst low levels of alcohol ($\leq$100 g/week) were associated with a lower risk of myocardial infarction, there were no clear thresholds below which lower alcohol consumption stopped being associated with lower disease risk for other cardiovascular outcomes such as hypertension, stroke, and heart failure [131]. Based on these findings, the 2019 European Society of Cardiology—ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases do not recommend moderate alcohol intake for protection against CVD [108].

Elderly

Aging is a natural and complex process that reflects physiological and psychological changes that occur throughout a person's life [132]. Individuals worldwide are living longer. According to the WHO, most people can expect to live into their sixties and beyond. By 2050, the world's population aged 60 years and older is expected to total 2 billion [133]. Health is a determining factor for this longevity and it is strongly influenced by genetics, the environment, and lifestyle. If these added years are dominated by decreases in physical or mental capacity, the repercussions for older people and for society are negative [134]. Among these implications, the progressive loss of ability to adapt to the environment can lead to greater vulnerability and the occurrence of diseases, such as NCDs. These diseases can diminish the quality of life, raise health-care costs, and increase pressure on family members who are responsible for their care.

Older people have unique nutritional needs since aging affects the absorption and excretion of nutrients. Moreover, illnesses, medications, as well as poor oral health could interfere with the diet. Under these conditions, some nutritious foods (e.g., whole grains, fresh fruits, and vegetables) could be avoided [135]. A nutrient-dense diet is critically important for older people. Diet quality has a huge effect on physical condition, cognitive condition, bone health, eye health, vascular function, and the immune system [136].

Contrary to what has been thought for decades about risk factors among older people, changes in habits are effective in preventing and treating NCDs. There are benefits for older individuals in changing risk factors and adopting health-promoting behaviors, such as healthy diets [37].

There is strong evidence of a dose–response relation between increased sodium intake and increased blood pressure [137]. Most SFAs increase low-density lipoprotein cholesterol (LDL-c) concentrations, a major risk factor for heart disease [138], moreover, high dietary saturated fat also may be a marker of poor food choices. The impact of sugar on health is controversial, however, the consumption of added sugars has been associated with increased risk of a variety of chronic diseases including

obesity, cardiovascular disease, diabetes, cognitive decline, and even some cancers [139].

On the other hand, fruit and vegetable consumption has consistently been associated with beneficial effects on health, including a reduced risk of cancer, stroke, diabetes, hypertension, and cardiovascular diseases [140–143].

Cardiovascular Disease (CVD)

Several studies found that dietary patterns characterized by high intake of vegetables, fruit, legumes, whole grains, fish and poultry decrease the risk of CVD [144, 145]. Additionally, DASH diet (dietary approaches to stop hypertension), originally designed to decrease hypertension—rich in fruits, vegetables, low-fat dairy products, grains, poultry, fish and nuts, and low in saturated fat, red meat, sweets, and sugar-containing beverages—is associated with decreased incidence of CVD. DASH diet also improves blood pressure with evidence of other cardiometabolic advantages in several studies among adults and older people [73]. Although claims about the potential benefits from the Mediterranean dietary pattern (characterized by the use of olive oil as the main cooking ingredient and/or consumption of other traditional foods high in monounsaturated fats such as tree nuts and high intake of plant-based foods, including fruits, vegetables, and legumes, moderately high intake of fish, moderate intake of dairy products mostly in the form of cheese or yogurt, low intake of meat and poultry, and regular but moderate intake of wine during meals) [146] especially on chronic disease outcomes, a systematic review showed that there is still uncertainty regarding the effects of a Mediterranean diet on CVD occurrence [147].

In contrast, dietary patterns characterized by a high intake of red meat, processed meat, refined grains, and sweets increase the risk of CVD [145, 148]. In a systematic review of 17 cohort studies, consumption of red and processed meat increased diabetes and coronary heart disease risk [149]. Red meat is traditionally suggested to increase CVD due to its saturated fat and cholesterol content [150]. However, common ingredients added to processed meat products (e.g. sodium or other preservatives) should be also considered as potential risk [149]. Additionally, heme iron has been associated with an increased risk of diabetes [151].

Cancer

In 2007, the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) formulated recommendations for cancer prevention. In general, the main recommendations include: eat mostly foods of plant origin; limit the consumption of energy-dense foods, red meat, salt, and alcoholic drinks; and avoid the consumption of sugary drinks, and processed meat [152]. A study evaluated whether these recommendations support the prevention of cancer in an exclusively elderly population. The results showed that eating according to the WCRF/AICR

dietary guidelines is associated with a lower risk of developing diet-related cancers in the elderly from Europe and the United States [153].

A review evaluated the Mediterranean diet in the context of cancer incidence. It was argued that the Mediterranean diet may contribute to the reduction of cancer since it is characterized by a series of foods that, due to their antioxidant and anti-inflammatory properties, are able to prevent and slow down the development of various forms of cancer [154]. Table 5.3 describes the association of the foods present in the Mediterranean Diet and the specific types of cancer.

Musculoskeletal Diseases

Osteoporosis, a gradual loss of bone mass, is a complex, chronic, multifactorial process, which is a normal part of aging. Both men and women are affected, but the main burden of disease is in post-menopausal women [155]. The deficiency of micronutrient and macronutrient appears to be strongly implicated in the pathogenesis and consequences of fractures in the elderly [156].

Regarding dietary patterns, a scoping review showed that adult and older people with patterns characterized by the consumption of processed food, red meat, candy, sweet baked products, and alcohol had a lower bone mineral density when compared with participants with patterns characterized by the consumption of low-fat milk, fruit, vegetables, and cereal [157].

A systematic review investigating the association between adherence to a Mediterranean diet and frailty in community-dwelling older people showed a suggestive effect protective but further longitudinal studies are needed to confirm this association [158].

Cognitive Disorders

Cognitive disorders are responsible for an important public health issue with the aging of the population. Dementia is an umbrella term for several diseases affecting memory, other cognitive abilities and behavior that interfere significantly with a person's ability to perform everyday activities. Alzheimer's disease (AD) is the most common form of dementia, and possibly contributes to 60–70% of cases [159].

Certain dietary patterns, especially the Mediterranean diet, are associated with a reduced risk of dementia. An updated systematic review of longitudinal studies provided significant evidence of an inverse association between the Mediterranean diet and the risk of developing cognitive disorders. However, they emphasized the need for further randomized controlled trials to confirm the observed association [160]. Similar results were also found in another review. Different types of studies (cross-sectional, case–control, cohort and intervention studies) were included and the results suggested that higher adherence to the Mediterranean or DASH diets was associated with less cognitive decline, and a lower risk of AD. They highlighted

Table 5.3 Association of the foods present in the Mediterranean Diet and the specific types of cancer

Foods	Type of Cancer
Fruits & Vegetables (Antioxidants and micronutrientes) Recommendation of Consumption: High	Less risk of: – Epithelial – Digestive tract – Breast – Female genital tract – Urinary tract
Olive oil (Oleic acid, poly unsaturated fatty acids (PUFA), low n-6 PUFA/n-3 PUFA ratio) Recommendation of Consumption: High	Less risk of: – Breast – Ovarian – Upper aero-digestive tract – Colorectal
Whole grains (Vitamin E, selenium, copper, zinc, lignans, phytoestrogens, and phenolic compounds, and dietary fiber) Recommendation of Consumption: High	Less risk of: – Colorectal – Upper aero-digestive tract – Stomach – Breast – Ovarian – Kidney
Fish (Long-chain omega-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid) Recommendation of Consumption: Moderately High	Less risk of: – Liver – Colorectal High risk of stomach (Heterocyclic amines and polycyclic aromatic hydrocarbons may be formed when fish is cooked on a grill or barbecue)
Dairy Products (Calcium, lactic acid-producing bacteria, vitamin D, linoleic acids, lactoferrin) Recommendation of Consumption: Moderate	Less risk of: – Breast – Colorectal Higher risk of prostate (dairy products with high level of calcium)
Meat (Heterocyclic amines, polycyclic aromatic hydrocarbons, and advanced glycation endproducts (AGEs) formed when meat is cooked at high temperatures) Recommendation of Consumption: Low	High risk of: – Colorectal cancer – Nasopharynx cancer – Pancreatic cancer – Bladder cancer – Esophagus cancer – Stomach cancer – Pancreatic cancer

Adapted from Mentella et al. [154]

the olive oil consumption as an important component underlying these associations [161].

Only a few studies have evaluated the impact of ultra-processed food on health in older people. In a cross-sectional study with the elderly population of the

"Seguimiento Universidad de Navarra (SUN) Project", it was observed that higher consumption of UPF (>3 servings/d) was associated with a higher risk of having shorter telomeres, a marker of biological age that may be affected by dietary factors through oxidation and inflammation mechanisms [162].

Conclusion

NCDs constitute a significant burden for the global economy, with substantial adverse impacts not only on human health and well-being but also on the health care system and economy. Although most NCD-related morbidity and mortality occurs in adulthood, many risk factors have their origins in early life. Unhealthy eating patterns, physical inactivity, tobacco, and harmful use of alcohol represent risk factors that can be modified. Increasing fruit and vegetable consumption and reducing salt, sugar, and saturated fat consumption could be achieved by the implementation of policies and regulations that affect the supply or prices of food products, regulatory controls on the marketing of ultra-processed foods, effective taxes on unhealthy food, and beverages, product reformulation (e.g. lower salt, sugar and/or fat) and, food labeling. Therefore, actions for the prevention and control of NCDs should be recognized as a health priority and should adopt a life-course approach.

Adequate and healthy eating should be practiced throughout the life course for prevention and care. It's never late to start.

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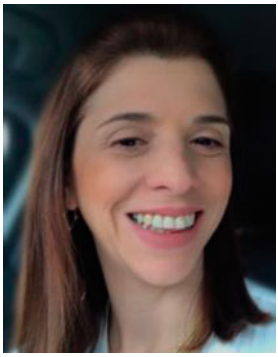

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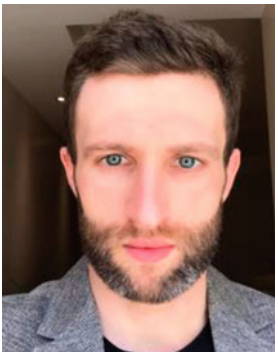

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Chapter 6
Physical Activity and Prevention of Chronic Non-communicable Diseases

Lidia Ostrowska-Nawarycz, Mariusz Nawarycz, and Tadeusz Nawarycz

Stillness is disease, movement is recovery.
— Gabriella Roth (1941–2012)

Abstract Movement is naturally related to human life. Especially the first years of life are characterized by high mobility of children and this activity should not be restricted. It has a great influence on many physiological and anthropometric parameters and on the organism's efficiency, both in developmental age and in adulthood. Physical activity (PA) is one of the recognized methods of non-pharmacological treatment of non-communicable diseases (NCD), including arterial hypertension, excess body weight and the increasingly common type II diabetes in developmental age. It is also an important element in cardiological rehabilitation of people in various ages. There are methods to assess both the efficiency of the body and physical activity. There are various tests used for this purpose and the Internet tools, including calculators, are also increasingly used. An important element of the prevention of chronic non-inflammatory diseases is encouraging appropriate PA among young people and presenting them with methods of activation. The paper presents the current state and the observed trends in the last decades of the PA and physical fitness (PF) for Polish children and youth. Selected own experiences related to the assessment of PF in developmental age are also presented.

Keywords Physical fitness · Prophylaxis · Body weight · Children and youth

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Abbreviations

BMI	Body mass index
H-RF	Health–related fitness
H-RF	Health related fitness
LTPA	Leisure–time physical activity
MVPA	Moderate-to-vigorous intensity PA
NCD	Non-communicable diseases
PA	Physical activity
PF	Physical fitness
VPA	Vigorous intensity PA
WC	Waist circumference

Introduction

Regular physical activity (PA) as well as its influence on health, shaping and keeping skills [1, 2]. A healthy lifestyle is also an important non- the human body in the best shape for many years are considered increasingly important. They are part of a healthy lifestyle that stimulates the proper development of a child and results from inborn needs and acquired pharmacological element in the prevention of many diseases.

WHO defines PA as any bodily movement produced by skeletal muscles that requires energy expenditure—including activities undertaken while working, playing, carrying out household chores, travelling, and engaging in recreational pursuits [3].

The terms PA and physical fitness (PF) should not be considered synonymous. PF is a conscious and planned type of activity, often repetitive, defined, intended to maintain or improve one or more elements of physical fitness.

Everyday PA is divided into: home, professional, sports and other activities. All these activities bring beneficial health effects. PA, both professional and non-professional, is related to such determinants of health as: gender, age, level of education, level of urbanization and others. It has been shown that non-professional activity undertaken consciously in leisure time has clearly beneficial health effects. It should be remembered that the influence and example of parents and teachers who shape the health behaviour of the young generation are important here. The view that the influence of parents (the awareness, knowledge and financial situation) on the PA of children and adolescents is significant [4–6]. It is especially important to practise various forms of exercise in the family. It was noticed that children of active parents are more often (than children of inactive parents) physically active. Regular, moderate-intensity PA has a beneficial effect on the body. It develops muscles, affects the proper growth and shape of bones, develops the circulatory and respiratory system and increases dexterity and physical efficiency [7, 8]. A beneficial hypotensive effect is observed not only in people with elevated blood pressure. Movement is also a factor

that hardens the body preventing many childhood diseases. An important function of PA is its influence on one's psychological health, well-being, and coping with stress, can also support treatment of depression [9, 10]. Moreover, it helps to improve some mental skills such as planning or speed of decision-making [11]. It facilitates both short-term and long-term memory, the ability to divide attention and to focus. It has also been observed that movement reduces anxiety and improves the quality of sleep. It influences the development of responsibility, self-confidence and self-esteem, stimulates empathy, creativity and social skills [12]. Therefore, children's physical activity is important for their psychomotor development.

As a result of reduced PA the developing organism does not fully develop: it has weaker muscles, smaller lung capacity and lower physical performance, slower reflexes and poorer coordination of movements. Limiting movement and spending a long time in front of a computer, mobile phone or TV results in: reduced learning ability, physical exhaustion, reluctance to learn and concentration problems, irritability, and even aggression [13, 14].

Reduced activity is indicated as one of the causes of overweight and obesity. It is estimated that in 2016, the global number of overweight children under the age of five was 41 million, and over 340 million children aged 5–19 were overweight or obese. According to the data of the World Health Organization (WHO), overweight and obesity are the biggest public health problems of the twenty-first century [15].

PA also has a prophylactic effect in many diseases, e.g., hypertension, type II diabetes, depression or colon cancer. It affects the process of the final bone mass building, which also contributes to the fractures, e.g., of the hip bone in menopause and post menopause. In addition, regular physical activity is conducive to maintaining a regular body weight, prevents overweight and obesity, and affects one's well-being. Improving the well-being or mood is associated with endorphins produced during exercise, which are called the happiness hormone [16, 17]. It has been observed that the athletes' levels of endorphins increase during competitions. Stopping exercising involves the risk of complications in adulthood, e.g., ischemic heart disease, hypertension, diabetes and tumors.

Moderate activities include cycling, dynamic walking, dancing and water aerobics, whereas activities such as fast walking, running, fast cycling and swimming fall into the category of intensive exercise.

WHO provides recommendations for PA for children and adolescents up to 17 years of age. They involve 60 min of moderate to vigorous activity per day consisting of endurance exercise, exercising flexibility, balance and muscle endurance (Exercise prescription for Health), strengthening muscles and bones at least 3 times a week [18].

The types of activities recommended for children are presented in the activity pyramid. Various forms of PA that affect health and good physical condition are shown there. The activities presented in the lower part of the pyramid should be performed daily, much more often than the activities presented in the upper part of the pyramid. These are activities that do not require physical activity restrictions. In order to encourage children and adolescents to become interested in physical activity, exercise should be enjoyable and varied and comprise physical education

Fig. 6.1 Physical activity pyramid for children according to WHO

lessons, additional school activities as well as out-of-school sports and recreational activities. Children's PA is influenced by the knowledge, motivation and activity of parents who, by setting an example, organizing family recreational sports activities, participating in such activities with children and encouraging children to take part in physical activities at home, school and with friends can shape pro-health behaviour and promote increased physical activity. It is parents who, to a large extent, shape pro-health attitudes and active relaxation habits of their children by setting an example (Fig. 6.1).

Increased physical activity has an impact not only on the body mass reduction and the change of its components, but it can be considered a routine non-pharmacological method of lowering blood pressure. The mechanisms responsible for the reduction of blood pressure accompanying regular physical exercise are multidirectional. They may be related to: reduction of catecholamines, normalization of the activity of the autonomic nervous system (increased activity of the sympathetic part and decreased activity of the parasympathetic part), decreased activity of the renin–angiotensin–aldosterone system or increased vasodilation capability of skeletal muscles. In the search for relationships between regular exercise and its cardioprotective effects, changes in the functions of the vascular endothelium are of great importance.

Reduced PA of children and adolescents, and the accompanying reduced physical fitness, are a growing problem of the twenty-first century. The increasingly reduced physical activity along with a sedentary lifestyle also affects the adult population. And now, in the specific global health situation that has lasted for many

months, this problem is becoming more and more serious. The announced lockdown related to the increased number of COVID-19 infections and the declared pandemic significantly limited physical activity of all people. Therefore, one should take into account the increased morbidity and even mortality due to many non-communicable diseases NCD. This problem may particularly concern the youngest generation, in which habits favoring a healthy lifestyle should be formed. Staying in isolation for several months has a significant impact on the pro-health behaviour of children and adolescents. Lack of school activities, including physical education lessons, and no extracurricular physical education classes, remote learning and the related several hours of sitting at the computer have an impact on both the physical and mental health of children and adolescents. Lack of exercise, limitation of direct contacts between them is the limitation of their natural needs necessary for proper development. Announcing further bans on leaving the house is associated with very big restrictions, and their effects can be difficult to predict.

Physical Activity of Children and Adolescents in Poland—Observed Trends

Research on PA and PF in paediatric population has a long tradition in Poland.

The interest in this problem in Poland is presented in the pioneering work of Jan Mydlarski entitled "Physical fitness of young people in Poland" published in 1932, in which the author described the close relationship between the degree of development of somatic features and the level of general fitness [19]. Since then, research on the proper motor and somatic development of children and adolescents has been the subject of interest of many scientific institutes and public health units [20–22]. It should be emphasized, however, that despite many pro-health initiatives undertaken both at the governmental level and by many research centers, the physical activity of both children and adolescents as well as adult Poles is highly unsatisfactory [23]. The observed decline in the physical activity of the Polish population corresponds at the same time to the data indicating a rapid increase in the prevalence of overweight and obesity in the entire population.

Particularly disturbing data come from long-term international studies of children and adolescents. International research on health behavior in school-aged children HBSC (Health Behavior in School-aged Children) has been carried out cyclically every 4 years since 1982. Currently, the research covers 49 countries from Europe and North America [24]. Poland has been a member of the HBSC network since 1989.

According to the HBSC protocol, students in three age groups 11, 13 and 15 are cyclically tested. The proposed multidimensional research model allows for a better understanding of health behaviors of adolescents as well as analyzing trends in changes in individual health areas and international comparisons. The frequency

of undertaking both moderate—(MVPA) and intensive physical activity (VPA) by the surveyed students as recommended by WHO was also analysed [25].

The latest research results conducted in 2017/2018 of Polish youth showed that only 19.6% of boys and 14.8% of girls (on average 17.2%) achieve the recommended MVPA [26].

Compared to the previous research results (HBSC 2014), a statistically significant reduction in the percentage of adolescents meeting the WHO-MVPA recommendations was found from 24.2% in 2014 to 17.2% in 2018. Intensive physical activity in line with WHO- VPA recommendations (at least 4 times a week) is undertaken by 33.1% of Polish teenagers (38.2% of boys and 28.2% of girls). The percentage of adolescents meeting the recommendations in this respect decreases with age: 39.3% of 11-year-olds and over 10% less 15-year-olds (28.1%) meet the recommendations. Compared to the previous HBSC studies, the VPA level decreased statistically from 40.5% in 2014 to 33.1% ($p < 0.001$) in 2018. The decline in daily MVPA since 2014 observed among young people both from Poland and from many other European countries is deeply worrying [26].

The systematically declining PA and PF of the Polish pediatric population and the parallel growing problem of obesity are noticed and signaled by many other scientific and expert units [27, 28].

Interactive Tools Supporting the Assessment of Physical Fitness in Children and Adolescents—Own Experiences

Currently, great importance is attached to the proper assessment of the PF of children and adolescents. PF usually means the ability to perform various forms of movement, associated with a particular level of development of motor characteristics, and morphological, physiological as well as mental functions. PF as an objective measure of PA is an important element of health and quality of life and early NCD prevention.

In the recently promoted concept of Health-Related Fitness (H-RF), the results of individual fitness tests should primarily support changes in health-related behavior patterns, create a healthy lifestyle and not solely concentrate on their numerical values [29].

The physiological and medical components of H-RF (Morphological-, Cardiorespiratory-, Musculoskeletal- and Motor Fitness) and the system energy efficiency are both of great importance. PF reference systems have been developed in many countries, including various performance tests in the form of percentile tables or graphical distributions [30–32]. The percentile values of PF for Polish school age children and youths (7–19 y), according to EUROFIT test battery, the International Physical Fitness Test (IPFT) and Cooper Test of PF, were developed in 2015 at the University of Physical Education in Warsaw [33]. Recently, PF reference systems for Polish preschool children have also been developed [34].

European PF percentiles in children between the ages of 6 and 9 were obtained for the first time in the IDEFICS study (identification and prevention of dietary and lifestyle-induced health effects in children and infants) in 2014 [35].

Recently, PF norms (Alpha—Fit) have also been developed for European children and adolescents aged 5–18 [36, 37]. It should be emphasized that in practice, the H-RF components are evaluated using various tests which sometimes hinder comparative analysis.

Dynamically developing e-Health and m-Health sectors as well as many other newer technology solutions (e.g., Wearable Technology, Internet of Things: IoT, Videogames for health: G4H, Intelligent Technologies, smartwatches and many others) have a great potential for effective prophylaxis of many Non-Communicable Diseases (NCDs), including the prevention of obesity complications [38]. Interactive network tools in the form of dedicated calculators are currently very helpful in quick interpretation and assessment of the child's physical fitness level. They are often an integral part of many portals and websites of leading societies and scientific organizations or medical universities.

The authors developed several tools of this type supporting the PF assessment in children and adolescents, intended mainly for school staff.

PF Calculators Based on Standard Field Tests

As the PF reference systems, the results of population studies of children and adolescents according to the standards EUROFIT (nine tests), IPET (eight tests) and Cooper test, developed by researches of the Polish Academy of Physical Education in Warsaw were used Dobosz Stupnicki [39–41]. The absolute values of all PF tests are also presented in the percentile, the z-score and the T-score scales. Indyvidual test can be independently acivated and interpreted using typical, a five step grading system of test results (Low, Moderately Low, Medium, High and Excellent). The results of each test are present graphically in the form of colored bars, with the use of three „traffic light" colors.

The designed fitness calculators allow for an interpretation of the various tests, in terms of both the actual calendar- as and the morphological age. This approach enables relativization of the motor test results and may be useful in the progressive development (pubertal spurt) which is the largest somatic differentiation between pupils in the same calendar age.

In subsequent modifications of the EUROFIT calculator, we also used a simple fuzzy inference system to assess PF [42]. Fuzzy logic (FL) is a very attractive field of artificial intelligence because it is based on natural language and allows for the interpretation of imprecise data [43–45]. The FL system used in the developed calculator enables the classification of both the individual four H-RF components and the general PF using language variables: very low (VL, low (L), median (M), high (H), very high (VH).

The use of FL in relation to the morphological component of H-RF allows for a more in-depth analysis of the nutritional status of a child, including, for example, central obesity [46–48].

A Calculator of Zuchora Index of Physical Efficiency (IPE)

Parents are crucial for shaping their children's behaviors, but many lack the knowledge and skills to provide optimal support for PA. In Poland, a popular test intended for both children and adults is the test developed by K. Zuchora [49].

It allows one, also at home conditions, to evaluate six basic motor abilities:

- Speed (10 s speeding run in a place with the lifted knees accompanied by clapping under each rised leg; the total number of claps is counted)
- Explosive strength (long jump from place; the jump distance is measured by the number of the own feet)
- Streng of arms (free overhang on a bar or on the tree branch in different configurations)
- Suppleness (standing forward bend without bending the knees)
- Abdominal muscles strength (lying on one's back, doing transverse leg shears as long as possible) and
- Endurance (maximum running time in a place at rate of 120 steps per minute or maximum distance running).

The results of each test is evaluated in a 6-point scale:

Minimum—1 point, sufficient—2 points, good—3 points, very good—4 points, high—5 points and an excellent—6 points.

In the end, the total number of points collected in all the tests performed allowed one to determine the Index of Physical Efficiency (IPE) as an average measure of PF with respect to age category.

The IPE is objectively comparable with the results obtained in different period of life, other people, and adults and children.

The developed calculator includes a detailed description of each test, the rules of score and additional accessories (virtual stopwatch and metronome) which can be used in the implementation of various tests. The results of all six tests are presented in a single window, both in numerical and graphic form, enabling an assessment of the fitness profile.

An example of a screenshot of an internet calculator is shown in Fig. 6.2.

Summary

The widely conducted activities promoting pro-health behavior are, among others, aimed at increasing physical activity. The current epidemiological situation overlaps with the already existing unfavourable trend favouring a further reduction in physical

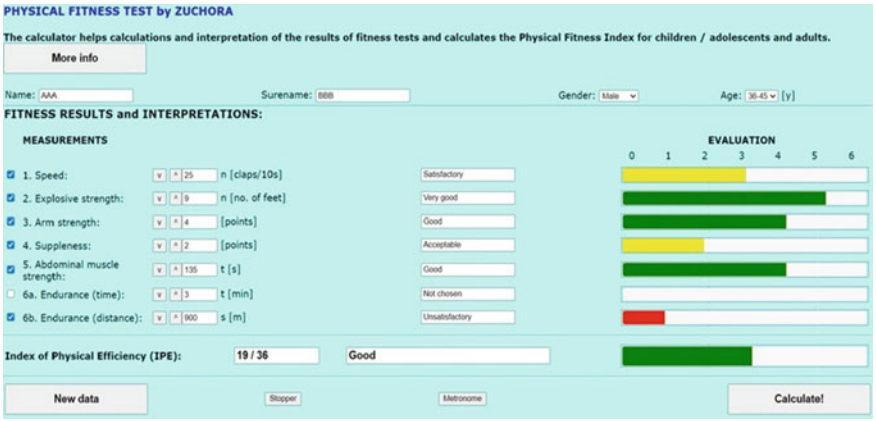

Fig. 6.2 An example of a screenshot of an internet calculator page with Zuchora's test

activity. There is a decrease in activity in the entire population. This unfavourable tendency, which has been perceived for many years in Poland and other countries, is particularly disturbing because it concerns children and adolescents. HBSC research conducted in Poland among adolescents showed a significant reduction in daily physical activity from 24.2% and in 2014 to 17.2% and in 2018. This is related to the unsatisfactory health condition of the developmental age population. This includes declining physical performance. Low physical activity and often concomitant obesity are factors that increase the risk of developing chronic non-communicable diseases.

In order to effectively change the behavior related to low physical activity of children and adolescents, multidirectional projects should be implemented. Parents, teachers (not just physical education teachers), health promoters and medical staff should participate in these activities. Children, adolescents and their parents should be encouraged to increase their daily physical activity and its beneficial influence on health should be emphasized.

An important element supporting pro-health behaviors, including physical activity, are new digital technologies, which are attractive to children and adolescents and may constitute.

The implementation of environmental and political activities means creating places for physical activity with increased access, without incurring financial costs for parents. Other implemented activities in the field of public health include: health education, education in schools and universities, social support for families and social campaigns in the mass media, but the effects of their impact are diverse and difficult to assess.

"*Movement will replace almost any drug, while no drug will replace exercise*

— Wojciech Oczko (1537–1599)

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Chapter 7
Exercise, Health, Longevity and Social Media: A Discourse

Dabota Yvonne Buowari and Kehinde Kazeem Kanmodi

Lack of activity destroys the good condition of every human being while movement and methodical physical exercise save it and preserve it.
— Plato (427-347BC)

Abstract Exercise is an activity carried out by all human beings from cradle to old age. It is a necessity for healthy living especially in the practice of lifestyle medicine. There are different types of exercise; they can be classified based on their intensity and effect on the body. Exercise plays a very crucial role in the development and maintenance of good health irrespective of the age of the individuals involved. Also, regular engagement in physical exercise helps in improving one's quality of life and also in prolonging one's life. In this chapter, we discussed the importance of exercise on health and longevity. Alongside, we discussed the impact of social media on exercise, health and longevity.

Keywords Physical activity · Aerobic · Anaerobic · Lifestyle · Well-being · Endurance · Strength

Introduction

Exercise is an activity carried out by all human beings from cradle to old age. It is a necessity for healthy living especially as it is one of the seven pillars of lifestyle medicine. Lifestyle medicine is a branch of medicine that uses modification of lifestyle in the management and treatment of illnesses especially non-communicable

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diseases (NCD). Non-communicable diseases have been on the rise due to sedentary and unhealthy lifestyle. Exercise plays an important role in the prevention of non-communicable diseases such as diabetes mellitus, hypertension, stroke, heart attack, coronary heart disease, certain cancers and osteoarthritis [1–4]. This in the long run increases longevity and reduces disability caused by some of these illnesses such as stroke which can lead to hemiparesis and paraplegia, osteoarthritis which can make the person dependent on others in carrying out the activities of daily living. Exercise is important for the human body irrespective of the age whether a child, adolescents, teenager, young adults, middle age, older adults and even the oldest old [1]. several studies conducted have revealed that physical activity in which exercise is a subcategory has effects that are beneficial to the health and wellbeing of all human beings hence it has a positive effect on older persons [5]. Good health and longevity is associated and has a positive relationship with non-sedentary lifestyle which includes physical activity [3, 6, 7]. The effects of exercise are not confined only to the physical and physiological impact of exercise on the body but it also extends to cognitive and mental domains [7].

What is Exercise?

Exercise is a movement that affects the body. Exercise can be defined as bodily movements and activities that are purposeful which involves generating forces by active skeletal muscles for the aim of fitness and training and not just as a routine [8–12]. Exercise is closely linked to physical activity but there are a difference between exercise and physical activity. The World Health Organization defines exercise as a planned, structure, repetitive and aims to improve or maintain one or more components of physical fitness and physical activity as any body movement produced by the skeletal muscles that require energy expenditure [13]. Physical inactivity has been identified as the fourth leading risk factor of death globally by the World Health Organization [14]. Hence exercise is a category of physical activity [10]. Exercise is structured and done specifically to be healthy and physically fit. Exercise done for competitive purpose becomes sports in which rewards may be given to the winners. Warm-up exercises are carried out before sports are done to reduce muscle soreness and strain. Physical activities related to occupational activities are not considered as exercise. Exercise is a planned scheduled while physical activity may sometimes be a spontaneous activity [10]. The performer of an exercise plans ahead of the time to carryout activities what type and duration of exercise. Meanwhile physical activity which also includes exercise is not always planned. Sports involve both exercise and physical activity, it is guided by a set of rules and regulations and the performer has to train over a period of time to master the sport. A similarity between physical exercises is that the body is made to work harder as energy expenditure takes place.

Types of Exercises

There are different types of exercises. Exercises can be classified using several criteria such as the intensity of the exercise, effect on the body etc.

Types of Exercises Based on Energy Exerted

Exercises can be divided as endurance, strength, balance and flexibility depending on the energy exerted [1].

- **Endurance**: Endurance exercises are exercises that involve endurance to conduct such activities that improve the health of the various body organs such as the heart, lungs and circulatory system. Carrying endurance exercise enables the performer to be able to carry out other physical activities that are not exercise some of which may include house hold chores such as mowing the lawn and climbing a flight of stairs. Endurance exercises causes increased respiratory rate as they cause increased breathing. There is also increased heart rate. Examples of endurance exercise are brisk walking, jogging and dancing.
- **Strength Exercise**: Strength exercises are exercises that make the muscles stronger hence they increase strength. They increase muscle strength, examples of strength exercises are lifting weights.
- **Balance Exercise**: Balance exercises are necessary for maintaining balance and helps prevents falls which is one of the geriatric giants. Fall is serious public health problem in the elderly. Balance exercises also help walking on uneven surfaces. Examples of balance exercises are standing on one foot, and standing on the toes.
- **Flexibility**: Flexibility exercises strengthen the muscles and make the body flexible. These are exercises that involve stretching.

Classification of Exercises Based on the Exercise Intensity

Exercise can be classified based on the exercise intensity as light, moderate and vigorous exercises [1, 11]:

1. **Light Exercise**: Light exercises are exercises in which the performer can engage in a conversation during the exercise activity, there is no change in the breathing pattern and do not cause sweating. An example of a light exercise is going for a walk.
2. **Moderate Exercise**: Moderate exercise is exercise in which although the performer feels out of breath, the performer can still talk. In moderate exercise, there is increased heart rate, and respiratory rate. The sweating starts 10 min after commencing the exercise [1]. Examples of moderate exercise are brisk walking, moderate cycling and walking uphill.

3. **Vigorous Exercise**: In vigorous exercise, the performer is panting and cannot engage in a conversation while performing the exercise or immediately after the exercise but make say few phrases. The performer breaths harder leading to increased respiratory rate and heart rate. The performer is hot and begins to sweat after three to five minutes [1]. The performer breaths deeply and cannot engage fluently in a conversation but can say few phrases [1].

Classification of Exercise Based on the Effect on the Body

Based on the effect on the body, exercise can also be classified as aerobic and anaerobic exercises [1].

1. **Aerobic Exercises**: This is due to metabolic pathway in the energy expended during the exercise [2]. Aerobic exercises are exercises in which large group of muscles are involved therefore the body uses more oxygen more than when it is in the resting state. An example of aerobic exercise is brisk walking. Blood flow is promoted by aerobic exercises [15].
2. **Anaerobic Exercise**: Anaerobic exercise involves strength and resistance training, they cause firmness and tones the muscles, improves bone strength, improves balance and coordination. An example of anaerobic exercise is push up.

Exercise Physiology

Exercise physiology is the scientific response of the body functions during exercise and adaptation of the body following exercise training and it includes the knowledge energy systems, physical fitness and energy intake [15, 16]. It also involves the acute and chronic adaptation of the human body to exercise. During exercise, several systems in the body undergo changes and adaptation during exercise. The effect of exercise may be acute following a single episode of exercise or chronic following a period of training. The respiratory and cardiovascular systems are the most immediately response to exercise. During exercise, the heart, blood vessels and lungs begins to work harder to deliver oxygen to the vital organs in the body. The body delivers oxygen quickly and efficiently in order to produce enough adenosine triphosphate (ATP) necessary for the muscles to function properly due to the muscle contraction and relaxation. Some of the cardiovascular responses to exercise are increased heart rate, stroke volume, cardiac output, blood pressure, blood flow and reduced blood plasma volume. Increased stroke volume results from the forceful contraction of the heart muscle which results in complete emptying of the ventricles. This increased stroke volume leads to increased cardiac output. Biomechanics, motor control, kinesiology and psychology are various aspects of exercise physiology [16]. Acute adaptation refers to a single session of exercise while chronic refers to series of training done overtime [15].

The response of the respiratory system to exercise is increased respiratory rate, tidal volume, ventilation and oxygen uptake. There is rapid expiration of carbon dioxide during exercise. This therefore triggers the respiratory centre in the brain leading to increased respiratory rate. Adequate hydration is promoted during exercise due to the sweating and increase in body temperature that follows. There is increased thirst to prevent dehydration, impairment in muscular power and strength [2].

Effect of Exercise on the Body Systems

1. **Cardiovascular System**: Exercise is very beneficial to the heart and the cardiovascular system [4]. Various parameters of the cardiovascular system are elevated during exercise such as the blood pressure, heart rate, blood flow, and coronary circulation. The systolic blood pressure increases during exercise; this reaches a peak of 200 to 240 mm of mercury. This then reduces at the end of the exercise which helps in the prevention of hypertension [17]. There is also an increase in the mean arterial pressure and cardiac output. The resultant effect is a decrease in the total peripheral resistance. This is desirable in the prevention of emboli and thrombi.

$$\text{Cardiac output} = \text{Heart rate} \times \text{Stroke volume}$$

The amount of blood pumped by the heart ventricles per minute is known as cardiac output and prevention of coronary heart disease. Coronary vasodilation and increased pressure of the coronary arterial during exercise results in increase coronary blood flow which is beneficial in hypertension. The acute changes in by after an exercise may be an important aspect of the role of physical activity in helping control blood pressure in hypertensive patients.

Oxygen Extraction

There is increased oxygen extraction from arterial blood as it passes through exercising muscles.

Coronary Circulation

The coronary arteries supply the myocardium with blood and nutrients. Capillary density of the ventricular myocardium can be increased by endurance exercise training.

During vigorous exercise, all three major determinants of myocardial oxygen requirements increase above their resting levels which are heart rate, myocardial contractility and the myocardial wall stress. Changes occur in blood flow during exercise. During rest, 20% of the cardiac output is supplied to the skin and skeletal muscles. During exercise, more blood is supplied to the skin and skeletal muscles. This is because the skeletal muscles become very active during the exercise session contracting and relaxing. Also increase body temperature causes increase blood flow

to the skin [17]. More oxygen is extracted from the blood as the arterial blood passes through the muscles involved in the exercise. This increase blood flow also affects coronary circulation. Endurance exercises increases the capillary density of the myocardium of the ventricles [17].

2. **Respiratory System**: The respiratory system is affected by exercise. The respiratory rate is increased when exercising. This normalizes post exercise.

Benefits of Exercise

Exercise has a lot of benefits which are physical and psychological. The psychological benefits of exercise are improvement in self-esteem, and prevention of depression. Exercise can be done as a form of relaxation.

Physical Benefits of Exercise

1. **Cardiovascular Conditioning**: Exercise results in conditioning of the cardiovascular system. This leads to the risk of illnesses of the cardiovascular system such as coronary heart disease, stroke, (cardiovascular accident) hypercholesterolemia, and hypertension [11]. Following regular exercise, the level of high-density lipoprotein (HDL) which is the good cholesterol increases.
2. **Muscle Strengthening and Resistance**: Exercise causes good muscle and bone strength which is a preventive measure to falls. It is also useful in preventing osteoporosis in post-menopausal women. This muscle strengthening also helps to strengthen the muscles of the heart to pump blood effectively [11]. Exercise also increases endurance [1].
3. **Weight Reduction**: Exercise results in burring off of subcutaneous fat and all the excess fat in the body to meet the increase energy demands necessary for exercise. This helps in the management of obesity. Obesity itself is a risk factor for non-communicable diseases such as coronary heart disease, hypertension, diabetes, certain cancers, stroke and heart attack.

There are several advantages of engaging in exercise. Globally, 3.2 million deaths occur annually are attributed to physical inactivity [11]. Research has revealed that partaking in aerobic, muscle and bone strengthening exercises slows down bone loss associated with aging.

Psychological Impact of Exercise

Exercise can be done as a form of relaxation hence it can be carried out to prevent depression. Amputees and persons with spinal cord injury should be involved in exercise to strengthen their muscles especially the skeletal muscles. Involvement in wheel chair sports provides psychological happiness for them as it helps them to forget about the accident that has led to their new way of life. Spinal cord injury caused by trauma leads to a drastic lifestyle changes with decrease in physical activity as the individual can no longer walk, some may be lucky to be able to sit down [18]. Wheel chair sports as wheel chair basketball and road racers can serve as a form of rehabilitation for this group of people. Wheel chair exercises are very beneficial to patients with spinal cord injury and amputees irrespective of their age, gender and duration of the injury [18].

Exercise Recommendation by Age

The exercise recommendations by the World Health Organization are [14]:

- **5–17 years**: 600 min of moderate to vigorous intensity of exercise weekly. Also physical activity including exercise of more than 60 min daily provides added benefits.
- **18-64 years**: 150 min of moderate intensity weekly or 75 min of vigorous activity
- **65 years and above**: 150 min of exercise weekly is necessary for healthy living. In older persons exercise should be done with caution to prevent fractures and dislocations.

Exercise Prescription

Prescription on the duration and type of exercise is individualistic; this means that regarding the exercise recommendations by the world health organization, prescription for exercise by a healthcare professional for example a physician or physiotherapist. The exercise is prescribed for the individual needs and target for the patient or client. Patients with diseases of the cardiovascular system such as severe hypertension and coronary heart disease should get an exercise electrocardiogram done before engaging in intense rigorous exercise. Although exercise is a non-pharmacological treatment for most diseases cardiovascular system, it may also be detrimental to their health. Choice of activities, intensity, duration and frequency of exercise sessions affects exercise prescription [18]. There are several factors that affect exercise prescription. This includes access to facilities available financial resources to purchase exercise and sporting equipment physical fitness and objectives of the exercise programme [18]. If the activity can be done as a group for instance if

it can be done together by a family, if the client has any underlying illness that can affect the joint. For instance, patients with any previous injury to the back should not be involved in any exercise involving lifting of weights and hyperextension of the back. Hemophiliacs should not be involved in exercise that can trigger joint bleeds. Patients with target joints should not be involved in exercises and sports that involve back and forth movement of the ankles such as tennis and badminton. Presence of medical diseases of the cardiovascular and respiratory system, reflexes and coordination, speed level and amount of contact when group sports is involved, cost of good protective gear and footwear.

The Relationship Between Exercise and Longevity

Longevity is affected by several factors. This include environment, health, social and occupational factors. Longevity is also affected by diseases especially some of the non-communicable diseases which is on the rise due to globalization, civilization and advancement in technology which has encouraged physical inactivity. Physical inactivity and sedentary lifestyle are risk factors for most non-communicable diseases. The effects of aging can be retarded following a well-balanced exercise program [1]. Exercise is required for the improvement of physical fitness [10]. When an individual is mentally and physically fit, free from illness, long life is then guaranteed.

There are various exercises that can be done to improve health and longevity. All exercises do not need to be done in a gymnasium. Exercises can be done at home no matter the available space. Dance is also considered to be a form of exercise. This is because though it is an art which is technical and rhythmic, the high physiological capacity involved in dance makes it to be qualified as an exercise [16]. Exercise which is a subcategory of physical activity takes various forms.

The process of aging can be reversed by regular engaging in exercise, the aging effect of physiological functions is reserved in the elderly if they engage in exercise [12].

In a study conducted by Lee and Paffenbarger on the associations of light, moderate and vigorous intensity physical activity with longevity, the data generated from the study revealed that increased longevity is associated with greater energy [6]. This means that an individual needs to be expending much energy. During exercise and physical activity, energy is expended while activities that promote sedentary lifestyle such as sitting down for long hours, no energy are expended. Hence the result from this study supports the science that to some extent, longevity is negatively affected by overweight and physical inactivity. Being involved in exercise regularly improves the quality of life by the various effects it has on the body including the physiological and psychological impact on the aging process therefore promoting longevity [3]. Exercise promotes cognitive, emotional, learning and various neurophysiological domains [19]. Happiness is necessary for a fulfilled long life. Exercise helps to reduce stress, allay anxiety and prevent depression. Moderate exercise is enough to provide the benefits of exercise but individuals involved in exercise more

than the recommended guidelines have more benefits [19]. The intensity, duration and frequency of exercise affect the physiological response of exercise [20]. Exercise improves insulin sensitivity hence it helps in the prevention of diabetes mellitus.

Demerits of Exercise

Exercise promotes longevity by the prevention and management of non-communicable diseases, healthy living and good psychological wellbeing. There are also some risks associated with exercise; these include bleeding into the joint or muscle and other injuries from body collision, contact and unpredicted injuries.

1. **Joint Bleed**: People can bleed into the joints during exercise. This is common in hemophiliacs. It also results following injury to the synovial membrane. Predisposing factors to joint bleed during exercise are exercise that involves putting weight and stress on the joints and forceful movements such as kicking and throwing.
2. **Muscle Bleed**: Bleeding into the muscles can occur during exercise. This occurs when the muscle is strained or over stretched.
3. **Soreness of the Muscles**: Soreness of the muscles can occur following exercise.
4. **Damage to the Joints**: Injury can occur to the cartilage. This is worst if the individual has osteoarthritis or a target joint. A target joint that has had recurrent and repeated bleeds in a hemophiliac.
5. **Body Collision**: Exercise done collectively as a group can result in body contact and collision. It can also occur in group sports. This can lead to bruises and cuts, severe injuries can also occur if the injuries affect the head, neck and chest. Traumatic brain injury, blunt chest and abdominal injury can occur. Factors that can affect this kind of injuries are the velocity, speed and force of the impact, aped and if the exercise involves falling from a height.
6. **Unpredicted Injuries**: Some unpredicted injuries can result following exercise. For instance, a person can fall off a treadmill if he cannot maintain the speed of the treadmill or has problems with vision and coordination which can result in very serious life threatening injuries such as traumatic brain injury.

Impact of Social Media on Exercise, Health and Longevity

Social media has been a way of communication connecting people together despite their geographic locations and times zones. Several studies have been conducted on the relationship between social media and health and also between social media and longevity. There are several positive and negative factors. Little is known about social media networking even though it is becoming popular in several populations and age groups [21]. Social media includes several platforms such as Facebook, YouTube, WhatsApp, snapchat and several others. Also the use of video conferencing

apps is becoming popular especially among teenagers and young adults. Some of the important and positive impact of social media on exercise and health is that it allows the joining of support groups to encourage one another in carrying out exercises together. For instance there are various support groups in which people can share their experiences on how exercise has helped them in keeping fit and achieving weight control. This will help and others battling with weight control. An example if the lifestyle medicine Nigerian WhatsApp support in which people share videos and pictures of their daily exercises, and meals depicting portion control hence encouraging others in the group that it is easy make out time for exercise as time is always available for wherever your heart is. The negative effect of social media and increased screen time on exercise and health is addiction. Uncontrolled and undisciplined use of social media can lead to addiction in which several hours are spent on social media. This will lead to lack of time available for meaningful activities including exercises. Content posted on social media are not regulated as the social media seems to be a dumping group for anyone that wishes to post anything. It leads to misinformation and exposure to wrong information that can affect the health. Increased screen time also have some effects on the body as it can lead to distress, and digital eye strain. Digital eye strain can be relieved by screen therefore the 20–20–20 rule should be applied. This means that every 20 s, look at an object 20 m away for 20 s. Other physical problems that may arise from increased screen time is positioning if bad posture is maintained while using social media can lead to low back pain, neck pain and shoulder pain. As the physical health and quality of life can be affected positively by social media through networking, tit is also possible that long term negative effects can also occur [2].

Conclusion

Every human being wants to live long to achieve their various aims and dreams in life. Longevity is a topic that has been studied from time immemorial. Longevity is affected by various factors, one of which is physical activity. Exercise is a subcategory of physical activity and important for the prevention and management of non-communicable diseases (NCD) such as diabetes mellitus, hypertension, coronary heart disease, stroke, and certain cancers. It also helps in the prevention of heart attack. Physical inactivity and lack of exercise is a risk factor for most of these illnesses. During exercise, the heart rate, myocardial contractility and the myocardial wall stress increases which all determine the oxygen requirements of the myocardium. The benefits of exercise are enormous and include conditioning of the cardiovascular system, improvement in the strength of the muscles and bone, weight control, treatment and management of obesity and non-communicable diseases. Exercise can be carried out by any human being irrespective of the age. When the recommendations by the World Health Organization on exercise if followed and adhered to, the risk of death besides from accident is reduced hence longevity is enhanced. It also reduces

the risk of certain cancers, hypertension and in older women, it reduces the risk of osteoporosis.

Quote

Any day other I stop exercising

I start growing old.

— Dabota Yvonne Buowari, 2020

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Chapter 8
Life-Course Effects of Sleep on Health Promotion and Disease Prevention

Negin Badihian, Shervin Badihian, Parnian Poursafa, and Roya Kelishadi

"You're not healthy, unless your sleep is healthy."
William C. Dement

Abstract Almost all organisms have sleep time. In humans, about one third of life is spent in sleeping or trying to fall asleep. Obtaining the standard sleep in each of the life periods is of crucial importance. Adequate duration, good quality, appropriate timing and regularity, along with absence of any associated sleep disorders are the main features of a standard sleep. Genes, gender, and age mainly determine the sleep needs. Sleep is essential for the proper functioning of multiple body organs and systems; thus, its problems will adversely affect nearly all body organs. These adverse health consequences depend on the chronicity of the problem, age, and type of the sleep disturbance. It seems that the adverse effects following sleep disturbances are more prominent in the brain in younger population, i.e., children and adolescents, while adults and older ages experience more chronic diseases. In addition to increasing mortality, sleep problems have short- and long-term impact on increasing the risk of several chronic disorders including cardiovascular diseases, metabolic syndrome, obesity, type 2 diabetes, hormonal imbalances, cognitive and mental health problems, cancer, osteoporosis, and stroke. In the present chapter, we will first briefly explain the mechanisms of sleep regulation and the characteristics of a standard sleep. Then, we will summarize the importance and benefits of a life-course healthy sleep, as well as acute and chronic adverse health effects of sleep disturbances.

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The Mechanisms of Sleep Regulation

Sleep regulation is a very complex process; the exact physiological and molecular basis of sleep drive and homeostatic regulation are largely unknown [1]. Sleep scientists have proposed various models to explain the hemostatic regulation of sleep components hitherto. Most popular models include flip-flop binary (mutual inhibition) model, two-process model, integrator circuit model, and reciprocal interaction model [1, 2]. It is suggested that interactions between the homeostatic and circadian systems, activation and inhibition of multiple neural circuits in the brain, release of significant neurotransmitters and neuromodulators, and changes in the concentration of ions such as potassium and calcium in the brain are involved in sleep–wake cycle regulation [2, 3]. Interactions between subcortical neurons of brainstem, midbrain, hypothalamus, basal region of the forebrain, thalamus, and brain cortex determine sleep and wakefulness states and their associated behavioral and physiological features [2, 3]. Many factors may affect the sleep–wake cycle and the circadian rhythm and cause different patterns among individuals. Internal needs, environmental stimuli (e.g., temperature, and noise), age, gender, mental and emotional status, season, nutrition, usual mealtime, autonomic function, bedtime routine, health and immune system status (e.g., presence of pain or inflammation), used medications, and pattern of breathing are among the most important ones [4, 5]. Moreover, sleep researchers have shown important direct and indirect links of epigenetic mechanisms, i.e., DNA methylation, histone posttranslational modifications and chromatin remodeling, and non-coding RNA regulation with the circadian clock [6, 7]. Interactions between different factors and mechanisms ultimately would lead to a scheduled sleep and wakefulness cycle.

Generally, the first signs of sleep are the associated gross physiological presentations and vary between the two components of sleep, non-rapid eye movement (NREM) and REM sleeps [8]. Low postural muscle tone, increased muscle blood flow, decreased eye movements, rhythmic and slow breathing, reduced heart rate, energy restoration, hormone secretion, and tissue repairment mainly happen during the NREM period [9, 10]. The REM sleep is called paradoxical sleep; it is determined by significant brain activity associated with complete loss of axial postural muscle tone. Dreaming and accompanying facial and vocal expressions take place in the REM sleep. Muscle twitching and irregularities in heart rate and breathing occur during this period as well [2, 11]. Brain wave alterations are the other important characteristics of sleep. These waves are the result of the ionic current changes that occur in the neural and glial cells. Electroencephalogram (EEG) recordings have shown the presence of delta frequency and sleep spindles during the NREM sleep, and theta and gamma waves during REM sleep [8, 12]. The duration of REM and NREM sleeps, and brain wave presentations change by the individual age and health status [3].

Normal Sleep Characteristics During Life Stages

Adequate duration, good quality, appropriate timing and regularity, and absence of any associated sleep disorders are the main features of a standard sleep [13]. The main determinants of the sleep need are the genes, gender, and age. Sleep–wake cycle development requires time. The cycle development starts around 2 months of age. A regular cycle containig REM and NREM sleeps usually could be seen as the child gets to 6 months of age [14]. An inverse relationship exists between sleep need and age. Infants have the maximum duration of sleep, and the duration reduces as the child grows up. Normal expected duration of sleep highly differs among infants less than 4 months and is around 12–16 h/d from 4–12 months of age. As the child gets to 6–9 months, nighttime feeding would be no more required for sleep maintenance [15]. When the child becomes 1–2-year-old, 11 to 14 h/d of sleep is needed. The needed sleep duration would decrease to 10–13 h/d among children aged 3 to 5 years, 9–12 h/d in preschool ages, and 8–10 h/d by adolescence. During adulthood, the sleep need is around 7–8 h/d. By older ages, the sleep duration and quality are both reduced. It is suggested that the reduced sleep duration is the result of both reduced sleep need, and the ability to get the needed sleep [16]. Moreover, increased sleep fragmentation, earlier sleep timing, involuntary awaking during sleep, and reduced sleep–wake rhythm amplitude could be seen in older ages. The other factor normally affected by life stages is the sleep onset. While newborns' sleep onset is via REM sleep, children experience transitions between REM and NREM sleep. During adulthood and older ages, sleep onset occurs via NREM sleep [17]. Moreover, by growing up the REM-NREM sleep cycling duration increases throughout the night. Normal sleep cycling in newborn happens around every 50–60 min and will get to every 60–90 min during childhood. Among young and older adults, the cycling happens every 90–110 min [18].

The other determinant of a normal sleep is gender. Studies suggest that sleep quality and efficiency are higher among women compared to men, and they experience shorter sleep-onset latency [17]. In addition, sleep duration is longer in women and they generally sleep 20 min more than men. Such sleep differences between genders usually present after puberty. Moreover, Sleep patterns undergo changes during menstruation, pregnancy, and menopause. Sleep alterations associated with physiological and hormonal changes mainly occur among women, whereas in men sleep is not affected by such changes [19]. Another normal feature of sleep among women is that they usually experience lighter sleep and are more susceptible to sleep disruptions, insomnia, obstructive sleep apnea, and disorders like restless legs syndrome [4].

Importance and Benefits of Normal Sleep

Studies suggest that about one third of human's life is spent in sleeping or trying to fall asleep. This is even more in children, with 40% of the life being spent in sleep. Maintaining the standard sleep in each life period is of great importance. Generally, sleep has significant roles in energy metabolism and restoration, controlling inflammation, and improved neural plasticity [11]. During sleep, energy expenditure decreases and glycogen stores of the brain refill. Also, adequate sleep is known to boost the immune system, increase the ability to fight with and recover from infections, and improve vaccination efficiency [20]. In addition, some of the immunological factors have circadian rhythmicity, highlighting the importance of a standard circadian rhythm and sleep–wake cycle [4]. Regarding neural plasticity, there are associations between sleep and the synaptic homeostasis underlying memory consolidation, cognition, attention, and learning. Getting the required sleep would lead to emotional stabilization, improved mental health, crystalized intelligence, and behavioral regulation [3]. Moreover, clearance of noxious substances produced as molecular wastes during brain activity via perivascular channels of the brain is known to be augmented during sleep [3]. The main goal of sleep is suggested to be the process of brain development, especially in younger ages [21]. For instance, studies conducted among children and adolescents showed that sleep can affect the intelligence quotient (IQ) [22]. Another significant aspect of sleep is its role in myelin maturation, brain morphology, gray matter volume of specific brain regions, and white matter integrity, which are of crucial importance in children and adolescents [14, 23, 24]. Sleep also has direct and indirect relationships with glucose metabolism and the level of insulin and ghrelin hormones [25]. Cardiovascular and gastrointestinal systems are other systems affected by sleep [26]. Hence, sleep is essential for survival and proper functioning of the body in all stages of life.

Acute and Chronic Effects of Sleep Disturbances on Health

Sleep disturbances are reported to affect a wide range of 1.6% to 56.0% of the individuals worldwide, with increasing trend in some countries [27]. The prevalence of sleep disturbances in preschool children is reported to be 25–50% [8].

Disruption of sleep might affect almost all body organs and systems (Fig. 8.1). It significantly affects quality of life, mental health, physical health, and brings short- and long- term adverse effects [28]. Besides, sleep problems are associated with social and economic burden. Studies report that almost 20% of severe injuries following car accidents were associated with sleepiness of the driver [27]. The main presentations of sleep disturbances include improper sleep duration (shorter or longer than the recommended duration for the age), low sleep quality, lack of sleep continuity, inconsistent sleep/wake pattern, and sleep related complains, including sleep apnea,

Fig. 8.1 Acute and chronic effect of sleep problems on body

restless leg syndrome, etc. [13]. Here, we would discuss some of the most important adverse outcomes associated with sleep disturbances.

A. **Mortality**: Different studies have assessed the relationship between sleep duration and mortality. Increased mortality associated with short or long sleep duration have been reported by most of the previous studies, although there are some heterogeneous reports considering the methods used for assessing the sleep duration and the definitions used for short- and long- sleep terms. In a study on 444 women with mean age of 67.6 years, after adjustment for chronic underlying diseases, 61% and 78% survival rates were reported for those with less than 5 h/d and more than 6.5 h/d of sleep, respectively. Moreover, the survival rate after 10 years of follow up was 90% for those who slept 5–6.5 h/d, based on the one-week actigraphic recordings. This study also reported sleep efficiency, and the timing of melatonin metabolite excretion as other factors with statistically significant association with mortality [29]. Results from two meta-analyses reported an increased risk of mortality associated with short or long sleep durations, as well [30, 31]. Hence increased duration of sleep is suggested for those suffering from sleep deprivation, whereas sleep restriction should be recommended for long-sleepers. Besides decreasing the mortality risk, acute sleep restriction can improve the mood by its antidepressant effects, and the chronic restriction can effectively improve primary insomnia among long-sleepers [32].
B. **Cardiovascular diseases (CVD)**: CVDs are reported as the main cause of mortality in the world [33]. Sleep deprivation is reported to be associated with an increased risk of CVD and related events. Insomnia and insufficient sleep can contribute to an elevated incidence of CVD through different mechanisms. Autonomous nervous system (ANS) dysregulations have been reported in individuals suffering sleep inadequacy. ANS dysregulations present as increased sympathetic tone, decreased parasympathetic tone, changes in the heart rate variability, and increased norepinephrine secretion [33]. Moreover, the expected decrease in systolic blood pressure during a normal sleep, would be blunted in short-sleepers and they would experience a higher level of nighttime systolic

blood pressure [34]. In addition, the results of a meta-analysis revealed that sleep-deprivation and insomnia were associated with an increased risk of hypertension incidence, while such an association was not observed in long-sleepers [35]. The relationship between long sleep duration and risk of hypertension was suggested by another meta- analysis as well. The authors reported a relationship between long sleep duration and the risk of prevalent hypertension especially in those age under 65 [36].

Another underlying mechanism, linking inadequate sleep and insomnia with CVD occurrence, is the metabolic syndrome [33]. Considering the known relationship between metabolic syndrome and CVD, and increased risk of metabolic syndrome following inadequate sleep, the link between sleep and CVD could be drawn. Moreover, sleep insufficiency is suggested to increase hypercholesterolemia risk, increased level of LDL, and decreased level of HDL, by affecting appetite, physical activity level, and lipolysis following catecholamine secretion [37, 38]. Results of a longitudinal study assessing the relationship between the sleep duration during adolescence and future risk of hypercholesterolemia in adulthood showed a statistically significant relationship between inadequate sleep and future risk of the disease in females, although such an association was not found for males [37]. Many other cross-sectional studies have also shown the negative effects of inadequate sleep on lipid profile. However, it should be mentioned that results of a meta-analysis of 13 studies did not confirm a definite association between sleep insufficiency and dyslipidemia [39].

Atrial fibrillation (AF) is the other condition related to sleep disturbances [40]. There are evidence that sleep deprivation, recurrent awakenings during the night, early morning awakening, long sleep latency, and insomnia are associated with an increased incidence of AF among adult population [33, 40]. Although some previous studies using the subjective report of sleep duration did not find a statistically significant relationship between sleep duration and AF, objective assessments support such an association [41].

The associations between sleep disturbances and myocardial infarction (MI) are shown previously. A study conducted among 52,610 men and women reported a moderate dose-dependent relationship between insomnia and the risk of myocardial infarction after 11.5 years of follow up [42]. Another study on 461,347 participants reported 20% and 34% higher risk of MI incidence among those with an average sleep duration of < 6 h/d and > 9 h/d, respectively, independent of other sleep features. The authors reported that having standard sleep duration was associated with a decreased risk of MI among participants with high genetic liability [43]. Sleep duration can be related with adverse outcomes of CVD as well. Results of a meta-analysis showed higher risk of mortality and morbidity following coronary heart diseases and stroke among both short and long sleepers [44]. Stroke is the other problem known to be associated with sleep disturbances [45]. Considering the adverse effects of sleep problems on cardiovascular system and glucose and lipid metabolism, it can be expected to observe an increased risk of stroke in patients suffering sleep

problems. In a study evaluating 23,620 adults, short sleep duration of < 6 h/d was associated with twofold increased risk of stroke during the mean 7.8 years of study follow up [46].

C. **Metabolic syndrome and obesity**: Abdominal obesity, insulin resistance, dyslipidemia and elevated blood pressure, the main components of metabolic syndrome, are the major underlying causes of many cerebrovascular and cardiovascular diseases, diabetes, and many other chronic diseases. The relationship of sleep duration, quality, and disorders with metabolic syndrome have been evaluated before. Sleep disturbances are suggested to be one of the leading causes of insulin resistance [47]. Results of a meta-analysis of 22 studies showed significant association between overall sleep quality and metabolic syndrome. Moreover, difficulty in initiating and maintaining sleep and inadequate sleep were associated with higher risk of metabolic syndrome [48]. Another meta-analysis of 18 studies found a dose response relationship between sleep inadequacy and metabolic syndrome. The risk was highest among those with < 5 h/d of sleep. This meta-analysis reported that no statistically significant relationship was observed between long sleep duration and metabolic syndrome, although some studies have reported such a relationship [49]. In addition, a study on 1344 participants reported that objective short sleep duration among patients with metabolic syndrome was associated with greater mortality after following up for 16.6 ± 4.2 years. The authors discussed that the observed effect modification was mainly determined by the elevated blood pressure and impaired glucose metabolism [50]. Obstructive sleep apnea is another important sleep disorder associated with metabolic syndrome. Obstructive sleep apnea is known to increase the risk of all of the metabolic syndrome components, including insulin resistance, abdominal obesity, hypertension, dyslipidemia, inflammation, oxidative stress, endothelial dysfunction, and hypercoagulability [50]. Regarding obesity, there are evidence that short sleep duration would lead to increased food craving and food consumption, especially fat and carbohydrate rich food. This association is due to the body's efforts to compensate the lack of energy caused by lack of sleep through food consumption to sustain additional wakefulness, the increased production of ghrelin (the hormone that stimulates appetite), and decreased level of leptin (the satiety hormone) [25, 28]. Sleep insufficiency is suggested to be associated with an almost 20% increase of the daily calorie intake [25]. Furthermore, circadian misalignment has been shown to alter energy expenditure, causes hormonal imbalance and insulin resistance, impair glucose metabolism, activate inflammatory cascade, and finally cause obesity and metabolic syndrome in both animal models and humans [25, 33, 51].

D. **Hormonal imbalances**: The secretion level of many hormones shows oscillations with sleep. Studies have reported changes in the level of hormones such as growth hormone, sex hormones, and thyroid hormones during the night indicating a close link with the circadian system. The relationship between hormones and sleep is bidirectional and changes in any of them would affect the other one [19, 52]. Growth hormone levels are known to be increased during

sleep, with a maximum level following the sleep onset [52]. In addition to the duration of sleep, the quality of sleep and its stages affect secretion of growth hormone. Studies have reported significant increase in the level of this hormone in slow-wave sleep compared to other stages of sleep, indicating the intermittent secretion of this hormone during sleep, and the importance of having a standard sleep architecture [52, 53]. Regarding sex hormones, testosterone is known to have a circadian oscillation. The maximum level of testosterone secretion occurs during sleep and the level increases by late afternoon [54, 55]. Having at least 3 h of normal sleep is essential for a normal level of testosterone. Any disturbances in the duration or quality of sleep, or presence of sleep related disorders such as obstructive sleep apnea, would be associated with reduced level of testosterone [54]. In women, the relationship between sex hormones and sleep are more complex with close interrelationships. There are evidence that the secretion of these hormones in teenage girls and in women of fertile ages is influenced by sleep [19, 55]. Follicle-stimulating hormone (FSH) is reported to be higher among women sleeping longer compared to short sleepers. Moreover, gonadotropin, prolactin, and luteinizing hormone (LH) levels are shown to be related with the duration of sleep in women [56, 57]. Besides duration of sleep, its quality is known to affect the level of sex hormones in women as well. Poor sleep quality is reported to be associated with decreased level of estradiol and increased level of FSH [56, 57]. Thyroid hormones are the other hormones that undergo changes during sleep and are influenced by sleep disorders and circadian dysregulations [58]. The function of hypothalamic-pituitary-thyroid axis is increased following sleep loss. Acute sleep deprivation is associated with increase in the level of thyroid stimulating hormone (TSH), T3 and T4 in human, but not rodents [59]. A study found that both sleep deprivation and long sleep duration are associated with increased risk of subclinical thyroid dysfunction [60]. Moreover, there is a relationship between sleep duration and autoimmunity, i.e., an important cause of thyroid disorders [60, 61].

E. **Diabetes**: Plasma glucose, free fatty acids, and triglycerides levels have obvious circadian oscillations. The level of glucose in the plasma gradually increases during sleep and reaches its maximum level in the early morning. These changes do not depend on the levels of circulating insulin or glucagon [26, 38]. The levels of free fatty acids and triglycerides in the plasma progressively decrease during sleep [25]. Sleep insufficiency, decreased sleep quality, sleep disorders including obstructive sleep apnea, and circadian dysregulations are all known to be individually associated with impaired glucose metabolism, pancreatic β-cell dysfunction, and insulin resistance [13, 25]. Various mechanisms are suggested as the underlying causes of the observed changes following abnormal sleep. Studies suggest activation of the sympathetic nervous system, alterations in the hypothalamic–pituitary–adrenal axis activity, oxidative stress, activation of multiple inflammatory pathways, and changes in the level of adipokins release, as the main mediators [25, 52]. In individuals suffering chronic sleep disturbances, these mechanisms will eventually lead to the development of type 2 diabetes mellitus. A meta-analysis evaluating the relationship between sleep

duration and risk of type 2 diabetes mellitus based on prospective studies reported a U-shaped relationship. The lowest risk of diabetes was observed among those with a normal duration of sleep per night (7–8 h). Sleep inadequacy and long sleep duration were both associated with an increased risk of diabetes and the risk increased in a dose-dependent manner based on the number of inadequate/excessive sleep hours [62]. Moreover, studies have shown higher prevalence of impaired glycemic control among those diabetic patients who suffered from short sleep duration or decreased sleep quality, emphasizing the importance of sleep in glucose metabolism and the related mechanisms [63, 64].

F. **Cognitive problems**: Having standard sleep is essential for neurocognitive function. Sleep problems will affect the cognition in all ages, but the effect is more prominent in children who are in the period of brain development [22, 65]. It is documented that an association exists between chronic inadequate sleep and an increased risk of impulsivity, risk-taking behaviors, and immature reasoning as well as decision making [27, 28]. Chronic sleep deprivation might have persistent effects. In a study, short sleep duration during early childhood was related to diminished cognitive performances during school ages [66]. Also, a meta-analysis of cross-sectional and prospective studies conducted among older adults demonstrated adverse effects of both short- and long- sleep duration on various aspects of cognition, including executive functioning, verbal and working memory, and multiple-domain performance [67]. The effect of sleep quality on cognition among adults is controversial; while some studies report a direct association between low sleep quality and diminished cognitive performance, others do not support such an association. The observed differences are mostly due to the methodological differences among these studies [68]. However, a systematic review and meta-analysis of 51 cohort studies on adults demonstrated that all kinds of sleep disturbances, including sleep duration problems, low quality sleep, and sleep disorders, are associated with an increased risk of developing cognitive disorders and dementia in the future. The study found a U-shaped relationship between sleep duration and future risk of cognitive dysfunction, with highest risks among those with < 4 h or > 10 h of sleep per night [69]. Another study conducted among elementary school children showed that performance of the children in the morning could be predicted by the quality of sleep [70].

G. **Mental health disorders**: The effects of sleep on mental health have been largely studied. Sleep disturbances are known to affect psychological status throughout all stages of life. Various psychological problems, including emotional distress, impaired memory, mood swings, diminished performance, depression, anxiety, risky behaviors, drug and alcohol abuse, suicidal and self-harm behaviors, and psychosomatic complaints, have been reported following sleep problems [13, 51]. Moreover, sleep disturbances could be seen among the diagnostic criteria of many psychiatric diseases. Many longitudinal studies have suggested sleep problems as an independent risk factor for depression development. The adverse effects of sleep disturbances on neuroendocrine stress system, sympathetic nervous system activation, impairments in the serotonergic

neurotransmission system, and disturbances in the underlying mechanisms of neural plasticity and neurogenesis are suggested as the mechanisms involved in depression onset [71]. A recent review concluded that not only there is a bidirectional relationship between mental health conditions and sleep disturbances; evidence are stronger for the pathway that considers sleep as the causal factor for psychological problems. This review suggested that treating sleep problems could be considered as an early preventive strategy for the development of further psychiatric complaints [72].

H. **Cancer**: There are evidence suggesting an association between sleep disturbances, especially short sleep duration, and increased risk of cancer. The underlying mechanisms for this relationship are very complex and many of them are still unknown. Dysregulations of the autonomic nervous system, development of an inflammatory state, suppression of the immune system, and changes in the level of melatonin are among the suggested mechanisms [46, 61]. Chronic sleep insufficiency is reported to cause systemic low-grade inflammation in the body, which is one of the known provocatory factors for malignancy and cancer [61]. Also, melatonin which is known to decrease cancer development, particularly breast cancer, is suppressed in short sleepers [73]. A study conducted on 23,620 middle-aged participants showed an increased risk of cancer onset by almost 43% after a mean follow up of 7.8 years in those suffering from sleep insufficiency (<6 h/d) [46]. Another study evaluating 23,995 Japanese women, reported a significant increased risk of breast cancer among those with a mean sleep duration of ≤6 h/d [74]. Also, a systematic review and meta-analysis assessing the relationship between sleep duration and cancer risk reported an association between short sleep duration and increased risk of cancer among Asians. A statistically significant association was observed for long sleep duration and risk of colorectal cancer in the subgroup analysis, as well. However, the results did not demonstrate a dose-dependent relationship between sleep duration and cancer, and in the categorical meta-analysis, no associations were observed [75].

I. **Other disorders**: Many other body organs and systems are also suggested to be affected by sleep disturbances. For example, bones are vulnerable to sleep problems. Studies have suggested an increased risk of osteoporosis among those suffering sleep inadequacy, low sleep quality, late sleep onset, and obstructive sleep apnea [76, 77]. Also, sleep and gastrointestinal system have a bidirectional relationship and any problems in each of them will consequently affect the other one. There are evidence suggesting associations between sleep disturbances and inflammatory bowel disease, irritable bowel syndrome, peptic ulcer disease, functional dyspepsia, gastro esophageal reflux disease, gastritis, liver problems and colorectal cancer. Moreover, sleep disturbances are associated with functional gastrointestinal disorders among children and adults. The systemic inflammatory state, autonomic nervous system dysfunction, and immune system imbalance caused by sleep problems have been considered as the most important mechanisms [78, 79]. Skeletal muscles are the other body

organs undergoing changes following sleep problems. Considering the essential role of sleep for muscle recovery, sleep deprivation is suggested to impair the maximum strength of the muscle in especial movements [80].

Conclusion

Sleep has fundamental roles in the body, and having a standard sleep is essential for the proper working of multiple body organs and systems. Nearly, all systems in the body show changes during sleep disruptions, although the severity of these effects differs by the chronicity of sleep problem [28, 51]. It seems that the adverse effects following sleep disturbances are more prominent in the brain in younger population (children and adolescents), while adults and older ages experience more chronic diseases, such as cardiovascular and metabolism problems [26, 65]. Considering the rising prevalence of sleep problems among all ages, increasing use of computer and smartphones during the late afternoon, and higher engagement of young adults in shift-works, more attention should be paid to sleep schedule by societies in order to prevent future development of chronic diseases. Further longitudinal studies evaluating the effects of sleep disturbances on the development of chronic diseases are needed.

Sleep is essential for proper brain and body functioning and living a long healthy life.

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Chapter 9
Prevention and Control of Tobacco Use as a Major Risk Factor for Non-communicable Diseases (NCDS): A Lifecourse Approach

Aastha Chugh, Neha Jain, and Monika Arora

Abstract Tobacco use is responsible for approximately 8.7 million (6.5 million in men and 2.1 million in women) deaths across the world in 2019, majority of which occurr prematurely. In spite of such high death rates, there are more than 1.3 billion tobacco users (age 15 years and above) in the world, of which 80% reside in the LMICs. It is also estimated that 24 million children (between the ages of 13–15 years) smoke and 13 million use smokeless tobacco, globally. The behaviour of tobacco uptake and consumption is encompassed within various social, environmental, cultural and economic factors and impact people in all age groups. Factors, including sex, age, education and income are important predictors of all forms of tobacco use. This chapter explores the impact of tobacco on various non-communicable diseases such as cardiovascular diseases, respiratory diseases, cancers, oral health diseases and also comments on the implication of tobacco use in COVID-19 pandemic in all age groups. It further discusses the physiology of nicotine addiction and comments on the evidence available on the uptake of tobacco use. The chapter elaborates on various tobacco control measures that are available currently while also raising concerns brought on by introduction of new electronic nicotine delivery devices in the recent years. It is an overview of the tobacco epidemic presented through the lens of the prevalence of non-communicable diseases.

Keywords Adolescent tobacco use · Smokeless tobacco · Nicotine addiction · Second hand smoke · Electronic nicotine delivery system (ENDS)

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Introduction

"*Tobacco use is the number-one agent of preventable death. More than seven million people every year die from tobacco use. If a communicable disease was killing that many people each year, every government would be racing to cure it!"*—Michael Bloomberg during his 2018 Keynote Speech to the United Nations High Level Meeting on Non-Communicable Diseases.

Non-Communicable Diseases (NCDs), including cardiovascular diseases, chronic respiratory diseases, cancer, diabetes and stroke impose a major public health challenge taking approximately 41 million lives (71% of total deaths) every year worldwide [1]. NCDs can affect people at any age group but evidence shows that 15 million of all NCD-related deaths occur prematurely between the ages of 30–69 years [2]. Of these premature deaths, majority (more than 85%) occur in low and middle-income countries and impact the lives of people due to the vulnerability contributed by the NCD risk factors (unhealthy diet, tobacco use, alcohol use, physical inactivity) [2]. Of all the NCD risk factors, tobacco use, which accounts for one in five of all NCD deaths, is the most preventable cause of NCDs [3].

Indeed, it's a fact that tobacco is a taboo in the new era of this twenty-first century. Tobacco products are broadly categorised as smoking (such as cigarettes, bidi, cigar, pipe tobacco etc.) and smokeless tobacco products (such as gutkha, khaini, zarda, snus etc.). Tobacco use is responsible for approximately 8.7 million (6.5 million in men and 2.1 million in women) deaths across the world in 2019, majority of which occurr prematurely [4]. Most of these deaths are attributed to cigarette smoking [4]. Use of smokeless tobacco products also exerts a significant mortality and mobility burden, with 0.65 million deaths and with South-east Asia Region bearing 88% of burden of these smokeless tobacco-related deaths. In spite of such high death rates, there are more than 1.3 billion tobacco users (age 15 years and above) in the world, of which 80% reside in the LMICs [5]. It is also estimated that 24 million children (between the ages of 13–15 years) smoke and 13 million use smokeless tobacco globally [6]. Despite a 15% relative reduction in smoking rates (between 2007 and 2017) [6], the economic burden caused by tobacco-related diseases is indispensable.

Smoking attributable diseases alone caused a healthcare expenditure of $467 billion (US $422 billion) in 2012, which equals to about 1.8% of world's annual gross domestic product (GDP) [7]. The social costs of NCDs attributable to tobacco use, due to premature deaths and prolonged disability, cause loss of employability, productivity, family income and have cascading effects on overall life [8].

Due to the compromised immune system, tobacco users are also more vulnerable to get affected in case of public health emergencies, such as the COVID-19 pandemic [9]. Previous literature shows that smokers are twice more likely than non-smokers to get infected with influenza virus and have more severe symptoms. In addition, studies have shown that morbidity and mortality of COVID-19 is more in tobacco smokers than non-smokers, making them more vulnerable to COVID-19 complications. Thus, it is vital to promote awareness about ill-health effects of tobacco use from early on

in childhood to adulthood to reduce the overall impact of tobacco on human kind, even during public health emergencies like COVID-19.

Box 1 Implications of Tobacco Use During COVID-19

The COVID-19 infection, SARS CoV-2 (Severe Respiratory Syndrome Corona Virus -2) reported as a pandemic by the World Health Organization is reported to affect the respiratory system. The interlinkages between the severity of COVID-19 and NCDs is being widely recognised, with evidence which suggest that tobacco users are more prone to getting infected by COVID-19 or suffer complications. Thus, many countries across the world imposed stringent measures, including ban on sale of tobacco products, ban on production, supply and marketing; restricted availability etc., to control the use of tobacco during COVID-19 public health emergency. Measures such suspending and banning production, supply, marketing and sale of tobacco products were taken in countries including Bangladesh, South Africa, Egypt, UAE, Iran, Kuwait, Pakistan, Qatar, Saudi Arabia, Israel, Botswana and India. The impact of such measures on tobacco consumption is under-researched but early evaluations have shown that these measures have been effective to reduce tobacco consumption and motivate people to quit tobacco.

Physiology of Nicotine Addiction

Tobacco is one of most persistent and widespread addictions. Similar to any other addiction, tobacco addiction comprises of a nexus of genetics, pharmacology, conditioned factors; social and environmental factors (like marketing strategies) [10]. Nicotine—a toxic colourless (or yellowish) greasy liquid is the major pharmacoactive component of tobacco [11]. Smoking or chewing tobacco products releases nicotine into the body of the user. As a result, nicotine stimulates dopamine release from neurons in the part of the brain that controls pleasure and motivation. Nicotine stimulates its molecular targets (nicotine acetylcholine receptors [nAChRs]) in the brain [12]. This brings about a gratifying sensation to the physical and mental functions of the tobacco user and thus, results in tobacco addiction, making it difficult to quit (Fig. 9.1).

Nicotine initially enhances the metabolism of the body and reduces appetite, thereby, leading to weight loss. Nicotine also stimulates secretion of adrenaline hormone, which results in increased heart rate and respiratory rate of tobacco users. The fast action of nicotine on the brain cells can be another reason attributed to its addiction. The nicotine delivered by a single puff of cigarette can reportedly reach the brain within 7 seconds [14]. Contrary to its quick mode of action, its elimination half-life is reported between 2–3 h [15]. While, the above-mentioned fact works for

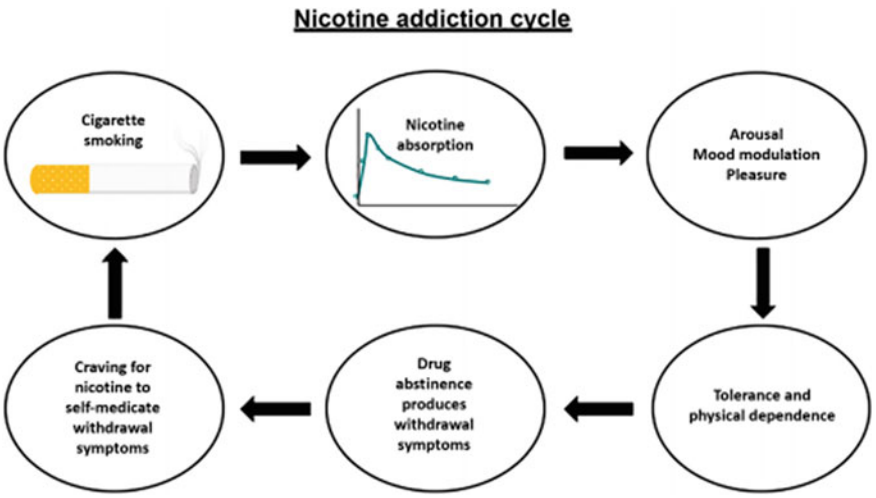

Fig. 9.1 Nicotine addiction cycle [13]

smoking tobacco, the mode of nicotine absorption and elimination is completely different for chewing tobacco. The chewing tobacco absorption is slow in comparison to smoking tobacco and its bio-availability is enhanced due to its increased absorption in the gut owning to its alkaloid pH [15].

The tobacco users are trapped in nicotine addiction to the extent, that out of 80% of the users who attempt to quit smoking, only 3% are able to maintain their abstinence while others relapse within a month [16]. Due to the pharmacokinetics of nicotine, abstinence from tobacco even for few hours can cause mental distress among the tobacco users [17]. Existing literature also suggest an association between mental health illness and tobacco use due to its addiction. A study conducted among 8213 current smokers in U.S also reported that the withdrawal symptoms become more profound among users with daily current mood disorders [18]. In fact, tobacco users who suffer from mental health issues are less likely to quit tobacco due to increased risk of depression and therefore, are more likely to relapse [19, 20].

Uptake and Use of Tobacco

The use of tobacco usually begins in adolescence phase. The prevalence of tobacco use among 12–15 year old was estimated in 68 countries from analysis of data from the Global School-based Student Health Survey (2006–13) and China Global Youth Tobacco Survey (2013). It was found that percentage of current tobacco use ranged between 2.8% in Tajikistan to 44.7% in Samoa [21]. Further, current use of tobacco products other than cigarettes was between 2.2% in China to 38.6% in Samoa. It was found that a large percentage of this age group reported that they used their first

cigarette before 11 years of age. In 42 of the countries, it was found that more than 50% of the smokers in this age group had in fact tried their first cigarette before the age of 11 years. The proportion ranged from 23.1% in Macedonia to as high as 82.1% in Ghana. Although, it could be argued that many of such young adolescents would have only smoked as an experiment and that not all such young adolescents would grow up to become regular smokers. However, studies, on the other hand, do show that a significant proportion of young experimenters become weekly smokers over 1 year of follow-up [22]. A study on American youth also found that nicotine dependence was higher among those tobacco users who had initiated the use before 13 years of age [23]. Furthermore, many other studies from lower and middle income countries have reported equally staggering figures. The age of smoking initiation was found as early as 7 years in a study done on African countries. The prevalence of tobacco use among 10–11 year old was estimated to be 0.7% in Ghana to 9.6% in Cote d'lvoire at 12–13 years of age [24].

The behaviour of tobacco uptake and consumption is encompassed within various social, environmental, cultural and economic factors. The use of tobacco can be classified to occur in stages which includes no use of tobacco, to low level of use, to high dependence and high use of tobacco [25]. Some researchers believe that social and environmental factors such as socio-economic status (SES) and availability of tobacco products, respectively, may be more likely the aetiology in the early stages of tobacco use with low level tobacco consumption. Intrapersonal factors such as self-esteem and personality might have a role in high dependence. [26, 27] However, there is also evidence that these distinct factors are attributable in all the stages of tobacco use. [28] Regardless, tobacco addiction is not merely a consequence of a social habit and is often envisaged within factors that may be beyond an individual's control.

Factors, including sex, age, education and income are important predictors of all forms of tobacco use. The impact of parents' tobacco use status also has an impact on their child's tobacco use habits. Relatively speaking, the strength of association is stronger with maternal tobacco use than paternal tobacco use [21]. Tobacco use is also found to be higher in males than females [21, 29]. In adults, it was found that a presence of college degree was associated with lower odds of initiating cigarette smoking and that higher age was also inversely proportional to risk of tobacco initiation [29]. In addition, unhealthy environment due to tobacco industry promotions and targeting youth in tobacco marketing are also found to be significant correlates of tobacco use [24].

The use of tobacco has also been known to be influenced by cultural practices native to an individual's place of living. Unfortunately, the cultural practices often have a way of making the practice of tobacco consumption socially acceptable and hence promotes its use. For example, smokeless tobacco use is widely accepted in India because of its association with socialising, sharing and family tradition [30]. Many families in different parts of India indulge in *Hookah* consumption and often share the same pipes between different members of the family or friends while socialising. In China, cigarettes are offered to guests as gifts and its refusal is often considered impolite [31]. In addition to cultural influences, the impact of a social

group on tobacco consumption has also been documented in various cross-sectional as well as longitudinal studies, with the latter being a more reliable source to understand the causality. Having friends who consume tobacco increases the risk of uptake of tobacco consumption or leads to increased consumption that usual [32–35].

Health Impact of Tobacco Consumption

Tobacco has been known to be around since the last 10,000 years. However, its use only became popular in the last 500 years due to ease in productions, which improved in the late 1800s due to advancement in mechanisation, transportation and technology [36]. However, knowledge about the harmful effects of tobacco were only brought to the surface as late as the mid-twentieth century. By this time, tobacco had already gained massive popularity and was commonly used across the world in various forms. The use of tobacco in any form has massive consequences on an individual and the society as a whole. Cigarette smoking has been known to harm every single organ in the human body [37]. A cigarette consists of more than 7000 chemicals, most of which are also used in industrial grade pesticides, burners, detergent and construction materials [38]. The use of smokeless tobacco was limited to few regions in the world and hence was not given the same importance as smoking forms of tobacco. However, ample evidence is available that links even smokeless tobacco to both short-term and long-term impact on the human body. Smokeless tobacco, like smoking tobacco has been attributed in a range of cancers, cardiovascular diseases and oral diseases. Tobacco effects the immune system of the body and causes an inflammatory response, which attributes it in pathophysiology of various diseases in the body [39]. As mentioned above, the use of tobacco is one of the four modifiable risk behaviours that lead to non-communicable diseases.

Tobacco and Cardiovascular Diseases

Tobacco is the single largest preventable cause of cardiovascular diseases [40] as well as the leading cause of premature death from cardiovascular disease. Tobacco was attributed in the deaths of 3 million people who died of cardiovascular diseases (Global Burden of Diseases 2019) [4]. Smoking tobacco contains carbon monoxide, which is absorbed in the blood and increases the concentration of carboxyhaemoglobin which reduces the systemic transportation of oxygen in the body [41]. Tobacco also consists of other toxic chemicals such as polycyclic aromatic hydrocarbons, heavy metals and their oxides which impact the vascular endothelium, blood lipids and clotting factors, hence causing atherosclerosis [40]. The main pathways by which tobacco smoking effects human physiology include inflammation, endothelial dysfunction, prothrombosis, altered lipid mechanism, insulin resistance and decreased supply of myocardial oxygen and blood. Smokeless tobacco is

also associated with cardiovascular diseases, with a 13% higher risk of fatal heart attack and 40% higher risk of fatal stroke in tobacco consumers as compared to non-consumers [42]. Furthermore, evidence is also available of a dose–response relationship between smokeless tobacco and cardiovascular diseases.

Tobacco and Respiratory Diseases

The act of tobacco smoking introduces a range of harmful substances into the respiratory system of the smoker. These chemicals and toxins impact the structure and function of the peripheral bronchi, alveoli and capillaries [41]. There is eventual loss of normal histology and physiology of the respiratory systems. Smoking causes Chronic Obstructive Pulmonary Disease (COPD), which includes emphysema and chronic bronchitis, aggravates asthma, and causes lung cancer in the long term [37]. Smoking is also found to have a dose response relationship with forced expiratory volume (FEV) in one second (FEV1)[1] of the lungs. Current smokers usually have a lower FEV1 [41]. The lung function begins to decline at a younger age in smokers and age-related decline also occurs at a faster rate in such population [37]. Due to the impact of smoking on immunity, smokers are more prone to acute infectious respiratory illness such as pneumonia [43], and very recently the COVID-19 [44]. As per Global Burden of Disease Data, 2017—smoking was the leading risk factor for chronic respiratory disease related disability globally for men [45]. Furthermore, tobacco smoking is the leading cause for lung cancer and is attributable in more than two-thirds of lung cancer deaths globally [46]. As compared to non-smokers, men who smoke tobacco are 23 times and smoking women are 13 times more likely to develop lung cancer [37].

Tobacco and Cancer

The use of tobacco is one of the leading risk factors for developing cancer in the life-course of an individual. Both smoke and smokeless form of tobacco are responsible for various cancers in the body. Moreover, even those individuals who are regularly in the contact of second-hand smoke have an increased risk of developing cancer (see section on ‘Passive Use of Tobacco’). The use of tobacco has been attributed in cancers such as those of lung, larynx, oral cavity, oesophagus, throat, bladder, kidney, liver, stomach, pancreas, colon, rectum and cervix, among others.

Cigarette smoke has more than 7000 toxic compounds, at least 60 of them are carcinogenic in nature [38]. Tobacco in unburnt form consists of 16 carcinogens.

[1] FEV measures the amount of air that a person exhales through a forced breath. It is a lung function test to diagnose obstructive diseases of the lungs such as COPD. A person with COPD would usually have lower FEV1 result than a healthy person.

These carcinogens are responsible for altering the normal DNA in the body, thereafter leading to mutations and abnormal cell growth leading to cancer. Past research has also indicated that in addition to promoting abnormal cell growth, the compounds found in tobacco also alter the tumour suppressor genes, hence interfering with in-built disease fighting physiology of the human body [47].

Data from Global Burden of Diseases, 2019, indicate that more than 2.5 million people died due to tobacco-attributable cancer and nearly 60 million disability-adjusted life years were lost due to the same reasons. Tobacco smoking has a dose–response relationship with many cancers. It has been found that the risk of stomach cancer is 50–60% higher in smokers than in non-smokers (risk ratio = 1.5–1.6). Several studies have also found that the relative risk of stomach cancer is more than twice greater in smokers than in non-smokers [48, 49]. Tobacco smoking also increase the relative risk of liver cancer by 1.5–2.5 times in smokers [48]. However, the increased risk could be attributed to concurrent use of tobacco and alcohol. Hence, in subsequent studies, the use of alcohol was adjusted in statistical analysis and it was found that in individuals who smoke but do not drink alcohol also have an increased risk of liver cancer [48]. Similarly, tobacco smoking has also been associated with certain types of cancer in the kidney. Apart from cigarette smoking, bidi smoking has also been linked with cancers of the respiratory and digestive systems. Cigar and pipe smoking are also causally associated with the cancers of the oral cavity, oropharynx, larynx, oesophagus and lungs. A recent study estimated the burden of various cancers caused due to tobacco smoking in South-East Asian countries [50]. The study found that tobacco smoking was most strongly associated with lung cancer. This was followed by cancers of the liver and nasopharynx in males and cancers of the reproductive system in the females. Furthermore, in males the tobacco attributable cancer incidence was highest in Indonesia, then Viet Nam, and Thailand. For females, the incidence was highest in Indonesia, Philippines and in Myanmar.

The use of smokeless tobacco is prevalent in 127 countries with the highest use in South and South-East Asian countries. In 2017, at least 2.5 million DALYs were lost and 90,791 people died due to oral, pharyngeal and oesophageal cancer attributed to the use of smokeless tobacco [51]. A systematic review found significant association between the use of smokeless tobacco products and oral cancer [52]. It was found that the risk was highest among South East Asian Region (RR = 4.4, 95% CI = 3.51–5.61). Eastern Mediterranean Region had a risk ratio of 1.28; 95% CI = 1.04 − 1.56. The risk of developing oral cancer from the use of gutkha was the highest, followed by pan tobacco/betel liquid, oral snuff, Manipuri tobacco and then snus.

Tobacco and Diabetes

The evidence of association between diabetes and tobacco use is relatively recent as compared to other tobacco-attributed diseases. It has now been established that tobacco users are 30–40% more likely to developed Type-2 Diabetes Mellitus as compared to non-users [37]. A recent meta-analysis conducted in 2017, showed that

the current smokers were at 1.38 times risk and former smokers were at 1.19 times risk of developing Type-2 Diabetes Mellitus as compared to non-smokers [53]. It further concluded that 18.8% of Type-2 Diabetes Mellitus cases in men and 5.4% cases in women were due to smoking. Furthermore, people with diabetes who smoke will have more difficulty in controlling their disease [54], have greater insulin needs [55], increased insulin resistance [56] and increased risk of hypoglycaemia [57]. As with others, the relationship between tobacco and diabetes is dose-dependent. The complications from diabetes are also more likely and more severe in tobacco smokers [38].

Tobacco and Oral Diseases

Regardless of whether tobacco is smoked or chewed, the first point of contact of the tobacco product is with the oral cavity. Tobacco has been attributed in various pathology in the oral cavity. Apart from its associated risk in oral cancer, tobacco has also been shown to be associated with oral mucous lesions such as Oral Submucous Fibrosis, periodontal diseases, gingival recessions, dental caries and poor success rate after periodontal surgery and orthodontic treatments. Through a systematic review, it was found that in ten out of eleven studies in the review, a positive association was found between tobacco smoking and dental caries [58]. However, the strength of the studies found was not very strong. Other studies have also shown that tobacco smokers had significantly higher number of dental caries [59]. Chewing tobacco was also found to be attributed in root caries as well as coronal caries due to its high sugar content, impact on gingival recession and increased collagenase activity [60].

The Surgeon General's report in the USA also concluded that tobacco use had a dose-respondent relationship with periodontitis [37]. Further, 50% of all periodontitis cases in the United States were due to tobacco smoking. Another systematic review also showed that individuals with diseases of the oral cavity had worse orofacial pain if they used smoked or smokeless form of tobacco [61].

Passive Use of Tobacco

The act of tobacco smoking is not only harmful to the smoker but also to those who are exposed to the smoke in the environment. This smoke, known as second-hand smoke (SHS) is attributed in a range of diseases in the non-tobacco users. SHS is a combination of smoke from the cigarette and the smoke exhaled out by the smokers. SHS also contains more than 7000 chemicals, many of which are toxic and approximately 70 of them are carcinogenic [37]. The act of inhaling SHS is known as passive smoking.

SHS is responsible for increased oxidative damage to the DNA and lipids. Relative to individuals not exposed to the smoke from tobacco, those non-smokers who are

exposed have lower concentrations of Vitamin C and provitamin A carotenoid. SHS can cause diseases of the cardiovascular system and respiratory system apart from having impact on foetuses. As per the Surgeon General's report, United States, SHS is responsible for 34,000 premature deaths due to heart diseases. Moreover, non-smokers are 25–30% more likely to develop heart diseases and 20–30% more likely to have stroke due to SHS. Additionally, a person exposed to SHS at work or at home is 20–30% more likely to develop lung cancer. More than 7000 non-smoking individuals die from lung cancer due to SHS in United States each year. SHS also is responsible for worse outcomes in patients with asthma [62].

The impact of SHS in children is severe. Parents who smoke tobacco are very likely to expose their children to SHS, causing serious health problems. Furthermore, it is possible that children are less likely to prevent their own exposure. Health impacts of SHS in children include respiratory tract infections, asthma, otitis media and sudden infant death syndrome [63, 64]. Children with exposure to SHS have reported more number of days of restricted activities, more days of bed confinement and increased school absenteeism than those children not exposed to SHS [65]. As a matter of concern, parents who smoke with children present inside the cars are exposing them to a lot higher amount of toxicity than in home [66]. This is due to the confined space within the cars.

Sufficient evidence also confirms that smoking during pregnancy has dire consequences on the health of the unborn child. Additionally, exposure to SHS during pregnancy has also been recognized as a risk factor for poor developmental outcomes in the children. Smoking during pregnancy has been linked with placental abruption, premature rupture of membranes, poor infant outcomes such as low birth weight infants, asthma or wheeze [67–70].

Exposure to SHS is also a significant risk factor for Sudden Infant Death Syndrome (SIDS) in children. SIDS is the sudden, unexplained and unexpected death of an infant in the first year of their life [71]. Smoking by women during pregnancy and exposure of infant to SHS increases the risk for SIDS. Infants whose mother smoked during pregnancy had a 4.09 times greater risk of death than those whose mothers did not smoke. Postnatal smoking was also significantly associated with increased risk of SIDS [72]. Furthermore, smoking by father or other members of the household also increased the risk of SIDS.

The presence of third hand smoke (THS) is another form of passive smoking. Third hand smoke is the residue from SHS that persists in and adheres to indoor surfaces such as curtains, sofas, clothes, etc. and also reemits into air [73]. Just as SHS, the presence of THS is a hazard for non-smokers, especially children and infants. Even in smoking households wherein indoor smoking is banned, children have 5–7 times greater nicotine exposure than children from non-smoking households. When THS is left in indoor surfaces, children and infants may unknowingly ingest, inhale or dermally absorb the harmful substances. Recent reviews also suggest that THS may in fact be more harmful than SHS [74]. One of the concerns of THS is that the components in the residual smoke can interact with other compounds present in the environment to form new toxic substances. For instance, residual nicotine can combine with nitrous oxide (a common indoor pollutant) to form the carcinogenic tobacco-specific nitrosamines [75].

Benefits of Quitting

Contrary to popular beliefs, quitting tobacco has immediate as well as long term benefits. Quitting tobacco is beneficial to not just the tobacco user, but to the family of the user and the society as a whole. Tobacco cessation improves health but also benefits a person socially and economically. The prevalence of SHS and THS also declines considerably. Some of the health benefits of quitting tobacco includes [76]:

- Improvement in health and quality of life
- Increased life expectancy and reduction in premature death
- Reduces the risk of poor reproductive health outcomes, cardiovascular diseases, respiratory diseases and cancer.

The benefits of quitting begin as early as two minutes of quitting and last for a lifetime. Figures 9.2 and 9.3 enumerate the short and long term benefits of tobacco cessation.

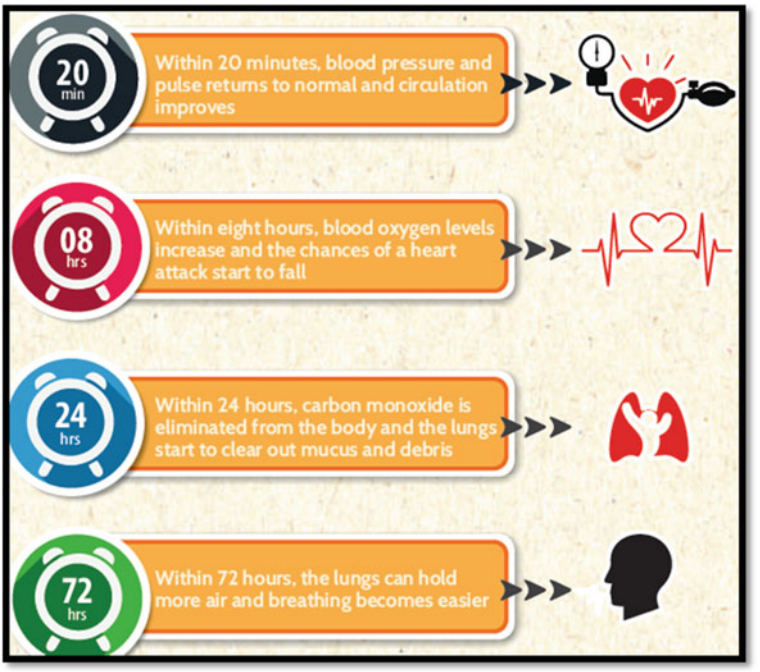

Fig. 9.2 Short term benefits of tobacco cessation

Fig. 9.3 Long term benefits of tobacco cessation

Tobacco Cessation Methods

Tobacco cessation interventions are considered as one of the most cost-effective tobacco control measures and thus, the World Health Organization recommends member states to adopt Article 14 of Framework convention for tobacco control (FCTC) in order to prioritise "demand reduction measures concerning tobacco dependence and cessation" [77]. According to Global Epidemic Tobacco Report 2019, only 26% of the world's population is protected by comprehensive cessation support programmes since 2017 and are available to 2.4 billion people in 23 countries [6]. Two types of cessation methods can be adopted to promote tobacco users quit. The first one is pharmacological methods including Nicotine Replacement Therapy (NRT) and other medicines; and the second one is non-pharmacological methods including behavioural counselling.

(a) Behavioural Interventions: Tobacco cessation interventions are commonly influenced by the theories of behavioural change, including the Trans theoretical model, Health Belief Model and/or Social cognitive/Learning Theory. Key aspects of these models focus on the importance of motivation, self-efficacy, consideration of barriers and benefits to change, subjective norms, attitudes and cues to actions. Tobacco cessation through non-pharmacological interventions are an important pathway offered at an individual level. Type of behavioural or non-pharmacological interventions are:

(i) Cognitive Behavioural Therapy (CBT)
A variety of behaviour therapies, ranging in complexity from simple advice offered by a physician or other health care provider or much more extensive therapy offered by counsellors, have been shown efficacious for tobacco cessation. It is one of the most effective non-pharmacological interventions for tobacco users which motivates them to quit tobacco by behaviour change. To provide behavioural therapy clinicians should follow guidelines for tobacco cessation: 5 A's (Ask, Advise, Assess, Assist and Arrange) and 5 R's (Relevance, Risk, Rewards, Repetition and Roadblocks).

(ii) Self-help Manuals
Self-help manuals when distributed to individuals who have desire to quit, have shown increased quitting rates. The self-help manuals have instructions on how to initiate quitting and also how to overcome withdrawal symptoms and relapse.

(iii) Counselling
Counselling is usually done by healthcare professionals, including physicians and paramedics. The tobacco user is counselled about the ill health effects of using tobacco products and also motivated to quit. Counselling is usually done as a part of Cognitive behaviour therapy.

(iv) Quit lines
In some countries like India, Quitlines are telephone-based programs that have shown as higher success to provide support to the tobacco users for abstinence.

(v) Other alternative/supportive therapies
Other alternative therapies such as diet modification, psychiatric treatment, boosting confidence of patients and other required treatment have also been effective as non-pharmacological interventions for tobacco cessation at an individual level.

(b) Pharmacological Interventions:

(I) First line of drugs:

(i) Nicotine Replacement Therapy (NRT): is a pharmacological intervention, where nicotine is provided to the tobacco users to overcome addiction and withdrawal symptoms when quitting tobacco. It is a medically approved way to consume nicotine by means other than tobacco which eases transition from using tobacco to complete abstinence. Consequently, NRT is widely prescribed by doctors to help tobacco users (both smokers and smoke-less) to quit smoking or stop chewing tobacco. In fact, studies have shown that the chances of quitting tobacco increase by 50–70% when using NRT [78].
The main mode of action of NRT is through stimulation of nicotine receptors in the brain and subsequent release of dopamine in the body. This and other peripheral actions of nicotine

(through NRT) lead to reduction in nicotine withdrawal symptoms in tobacco users which abstain tobacco use. In fact, NRT also provides a coping mechanism which makes tobacco less rewarding to the user and thus, is a preferred treatment used for tobacco cessation. There are different forms of NRT including chewing gum, transdermal patches, oral and nasal sprays, inhalers and tablets/lozenges [79].

NRT is considered safe and long-term use of NRT does not expose users to any serious harmful effects. Concerns over the safety of NRT in circumstances in which nicotine might be harmful—such as in pregnancy, cardiovascular disease, or in adolescents—therefore need to be considered in relation to the safety of the likely alternative, which is continued intake of nicotine from cigarettes [80, 81]. The effectiveness of NRT in terms of the risk ratio appears to be largely independent of the intensity of additional support provided. Nonetheless, like other pharmacological interventions, NRT is an effective technique for tobacco cessation when used in conjunction with behavioural and other non-pharmacological techniques.

(ii) Bupropion

Bupropion (Zyban) with its dopaminergic activity significantly reduces withdrawal symptoms and nicotine craving and thus, is used as a first line of drug for cessation services. Bupropion is used to prevent relapse and attenuation of weight gain in abstinent tobacco users. Bupropion is an effective drug for delivering nicotine and has shown to double cessation rates when prescribed, same as that of NRT.

(iii) Varenicline

Varenicline is a newer drug in the market and is used especially for smoking. Varenicline works by reducing the strength of the smoker's urge to smoke and by relieving craving and withdrawal symptoms. Varenicline is highly absorbed through oral administration and doubled the odds of quitting smoking compared with placebo and is significantly better than bupropion. Varenicline can be prescribed for use to smokers, except those with renal impairment, pregnant and/or breastfeeding. A 2016 Cochrane review of 27 studies also found that the number of people stopping smoking with varenicline was higher than with bupropion or NRT [82].

(II) Second line of drugs: Nortryptiline and Clonidine are used as second line of drugs for tobacco cessation. Nortryptiline, a tricyclic antidepressant which has found to have similar quit rates as of bupropion. In addition, Clonidine, an alpha-2 adrenoceptor antagonist is also used to diminish some of the tobacco withdrawal symptoms.

(c) Combination therapies
In combination therapies long-term formulations (such as nicotine patch) is used in combination with the short-acting formulations (such as nicotine gum or lozenge). The long-acting formulation prevents onset of withdrawal symptoms, whereas the short-acting formulation is helpful to control withdrawal symptoms that occur during potential relapse conditions (for example, after meals, when stressed, or when around other tobacco users). NRT and sustained-released bupropion and NRT and nortriptyline are the two combinations mostly used in the therapy.

Global Best Practices for Tobacco Control

Burden of tobacco-related diseases and economic consequences makes its significant to comprehend tobacco control to prevent tobacco uptake and promote tobacco cessation. To help countries reinforce best practices for tobacco control, the WHO adopted the first global public health treaty—the Framework Convention on Tobacco Control (WHO FCTC) on 21st May 2003 [83]. The WHO FCTC was developed in response to the globalization of tobacco epidemic across the globe. WHO FCTC provides evidence-based guidelines to member states for initiating and accelerating tobacco control efforts. To help countries adopt WHO FCTC, MPOWER measures were introduced by the WHO. MPOWER package consist of six evidence-based cost-effective measures to assist countries in effective implementation of tobacco control programmes [6, 84]. The six categories under MPOWER include:

M—Monitor tobacco use and prevention policies
P—Protect people from tobacco smoke
O—Offer help to quit tobacco use
W—Warn about the dangers of tobacco
E—Enforce bans on tobacco advertising, promotion and sponsorship; and
R—Raise taxes on tobacco

As per WHO FCTC, tobacco control interventions can either be targeted to reduce demand of tobacco products (price and non-price measures) or to reduce supply of tobacco products.

(I) Effective tobacco control interventions to reduce demand of tobacco products:

(a) Price measures:
Taxation on tobacco products is one of the most cost-effective measure to reduce consumption of tobacco products. Tobacco use leads to considerable economic loss, in the form of healthcare expenditure to treat diseases caused by active or passive tobacco use. Therefore, a variety of taxes (such as excise duty, custom duty, value added tax, general sales or consumption tax and other county-specific taxes) can be applied

to tobacco and its various products. This results in reducing the affordability of tobacco products to its consumers and thereby, reduce demand. Studies have shown that a 10% increase in prices of tobacco products can reduce tobacco use by 5% and 4% on an average, in Low- and Middle-Income Countries (LMICs) and High Income Countries (HICs) respectively [85]. Moreover, young people, minorities, and low-income tobacco users are more likely to quit, reduce tobacco consumption and prevent youth from tobacco initiation in response to price increases [86].

(b) Non-price measures:

Various non-price measures have shown to be effective to reduce tobacco consumption. School-based tobacco prevention education programmes enforced in schools to educate youth have shown promising results in preventing initiation of tobacco use [87]. In addition ban on tobacco advertising, promotion and sponsorship (TAPS) in high-income countries have shown an average of 7 per cent reduction in tobacco consumption [88]. In fact, it is evident from the literature that youth become more susceptible to tobacco use due to tobacco imagery exposure in entertainment media, such as films, television or streaming platforms [89–91]. However, in countries like India where the Government has introduced stringent tobacco-free film rules related to the depiction of tobacco imagery in all films screened across the country, have proven to be effective in raising awareness about the ill-health effects of tobacco products. Comprehensive Smoke-free policies has also shown to reduce the social acceptability of smoking, help in smoking initiation by young adults, and increase smokers' efforts to quit smoking [92].

Health warnings on the tobacco packs is one of the most cost-effective way to educate tobacco and non-tobacco users regarding the ill-health effects of tobacco. In addition to large pictorial health warning, countries like Australia have introduced plain packaging on tobacco products, with all packets sold from 1 December 2012 being sold in logo-free, drab dark brown packaging. As a result of plain packaging the impact of health warnings on tobacco packs increase, which motivate tobacco users to quit [93].

Mass media campaigns (through television, newspapers etc.) and cessation programmes are also significant within tobacco control as non-price measures to reduce the demand of tobacco products.

(II) Interventions to reduce the supply of tobacco products:

Interventions to reduce the supply of tobacco products have also shown effectiveness in reducing tobacco consumption. Ban of sale of tobacco products to minors (below the age of 18 years) is one such measure, which has reduced tobacco initiation among young adults in many countries. Other ways are to eliminate illicit trade of tobacco products, crop substitution and elimination of government subsidies for tobacco farming.

New Nicotine Products and Its Impact on Youth

Despite making various attempts to curb nicotine use through tobacco control policies, new trends like ENDS (Electronic Nicotine Delivery Systems) are emerging worldwide. Electronic Nicotine Device Systems (ENDS) are battery-powered devices which typically have a cartridge filled with liquid that contains nicotine, flavourings, polyethylene glycol, and other chemicals. ENDS deliver the nicotine in the form of vapour along with other chemicals such as flavourings (diacetyl), volatile organic compounds, cancer-causing chemicals and heavy metals (nickel, tin and lead) into the respiratory tract [94].

These new nicotine products, ENDS have been gaining popularity among youth due to heavy industry advertising, promotion as a safer alternative to smoking and their availability in attractive flavours [95]. Research with school students, teachers, parents and college students has highlighted that ENDS are considered to be non-tobacco, non-nicotine products by students [96, 97].

Over the years, evidence has emerged on the health harms of ENDS products [98] and their potential to lead to conventional tobacco use among youth [99], while there has been a lack of evidence on the safety of these products for quitting tobacco. Despite being marketed as harm reduction products, evidence suggests that ENDS are not safe for youth, young adults and pregnant women [100]. The aerosol delivered through ENDS contains lesser toxic chemicals as compared to conventional cigarettes, however, it is not free from health harms. The major ingredient of ENDS is nicotine which is a highly addictive psychoactive substance [10]. Adolescence is the period when students generally get addicted to nicotine while the development of the brain also continues during this period [101]. As mentioned in previous section of this chapter, nicotine can exert neurotoxic effects hampering the development of the 'pre-frontal cortex' which can lead to psychiatric disorders and cognitive impairment later in life. Other chemicals present in ENDS are also associated with adverse health effects e.g. popcorn lung (Diacetyl), acute lung injury, chronic obstructive pulmonary disease (COPD), asthma and lung cancer (Acrolein and ultrafine particles), and exacerbation of respiratory diseases (Cinnamaldehyde) [102]. The e-cigarette liquid is cytotoxic, pro-inflammatory and inhibits phagocytosis in alveolar macrophages (increasing the chances of respiratory infections) [102]. It is therefore essential to protect the adolescents from these new nicotine products, ENDS initiation and continued use.

Conclusion

Decades of research has collated evidence on the burden of tobacco. Tobacco has been attributed in impacts on physical and mental health, social life and economic conditions of an individual. Tobacco is known as the only commodity that is responsible for deaths in almost half of its users. It has direct pathways of disease in

non-communicable diseases such as cardiovascular diseases, respiratory diseases, cancers, oral health conditions and even diseases of the reproductive systems. All forms of tobacco cause harm to the human body and equally affects non-smokers through second-hand and third-hand smoke. Its prevalence has been found across various socio-economic demographic groups and the use and burden of tobacco exhibits a social gradient, with the disadvantaged groups at higher risks.

The onset of the COVID-19 pandemic has only further established tobacco use in the aetiology of worse health outcomes, irrespective of it being due to communicable or non-communicable diseases. The COVID-19 pandemic again raises the important question—how far do we go before we realise the collective burden from tobacco use far outweighs any economic benefit that the country gets from tobacco production and distribution?

Marketing tactics by the tobacco industry have been responsible for making the use of tobacco synonymous with "being attractive", and hence have generated a young client base. Peer pressure, social acceptance and a tobacco friendly environment have been contributing to decrease in ages of initiation of tobacco use, thereby increasing the levels of nicotine addiction in adulthood. The various tobacco control measures have been successful in decreasing the tobacco use over the past two decades, yet a significant percentage of the global population remain addicted to tobacco use even now, hence signifying the need to equally strengthen tobacco cessation avenues in all countries. Moreover, tobacco industry interference in policy making continues to be one of the biggest challenges faced by tobacco control advocates.

Thus, the authors of this chapter emphasise on "*strengthening the tobacco monitoring mechanisms, especially in low and middle income countries, equally enveloping all forms of tobacco use in tobacco control measures, introducing novel tobacco cessation avenues and increasing transparency and accountability of the government are all need of the hour to ensure that the ongoing tobacco epidemic is addressed in its entirety*".

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Chapter 10
Shisha Smoking—Behaviour with Health and Social Implications, Affecting All Ages

Kehinde Kazeem Kanmodi, Dabota Yvonne Buowari, and Roya Kelishadi

"As the smoking of tobacco has taken very bad effect upon the health and mind of many persons, I ordered that no-one should practice the habit. My brother Shah Abbas also being aware of its evil effects, has issued a command against the use of it in Iran."
—Mogul Emperor of Hirdustan—Early 17th Century

Abstract Different behaviours are developed over time; some are learnt from childhood while some are learnt at adulthood. Some of these behaviours may or may not have adverse effects on our health. While some behaviour have adverse health effects, some people still practice it due to social influence. A popular example of a harmful social behaviour is shisha smoking. Shisha smoke contains so many harmful substances which can cut human life short. Most, if not all, of the scientific research works ever conducted on shisha were focused on young people; little to no attention on the exploration of shisha smoking practices (or exposures to shisha smoke) among people who are in the extreme ages (i.e. foetus and the elderly). Meanwhile, in reality, all are prone to the hazards associated with exposures to shisha smoke. In this chapter, we described how shisha works, and went further to discuss the historical and epidemiological aspects, socio-legal issues, and medical issues on shisha . We also

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pointed out the health implications of shisha on those in the extreme ages. Importantly, the existing policies, laws, and scientific information on shisha are largely inadequate. We recommended important strategies that can be effectively used to reduce the burden of shisha smoking across all ages.

Keywords Waterpipe · Hookah · Narghile · Hubble bubble · Tobacco · Lifestyle · Use · Paediatrics · Geriatrics

Introduction

The study of social and behavioural lifestyles of humans constitutes a major aspect of public health. From cradle to the grave, the behaviour of humans had been well-studied using various scientific research methods. Through scientific study, some human behaviours have been found harmful to health while some were found helpful. For instance, regular brushing of teeth is a behaviour that has many health benefits to the human body. Through regular tooth brushing, the oral cavity can maintain good sanitary conditions void of oral diseases [1]. However, on the other side, behaviours such as shisha smoking have virtually no health benefit to profit humans [2]. Through (passive or active) shisha smoking, one can develop chronic and debilitating health conditions which can affect the body [2]. Looking at shisha smoking, a popular social behaviour in our present day society, we will find that many biological and non-biological problematic issues are associated with the behaviour, affecting all age groups and races, bringing about significant social and public health implications [3]. In this chapter, we shall discuss on the above-mentioned themes with preference to social and public health understanding. However, to start with, it is highly recommended to first describe how shisha looks like and how it is being operated before discussing other issues of relevance.

Shisha: Description and How It Works

According to the Macmillan Dictionary, "shisha is a water-pipe, popular in many Arab countries, in which fruit-scented tobacco is burnt using coal, passed through an ornate water vessel and inhaled through a hose" [4]. The shisha has the following parts: head, body, bowl, hose, and mouthpiece [2].

Before discussing about the health implications of shisha use, it will be noteworthy to briefly describe how shisha works/is operated. This is how shisha works/is operated: (i) tobacco is loaded into the head of shisha; (ii) the head is covered with an aluminium foil; (iii) small punched holes are made on the aluminium foil; (iv) hot coals/charcoals are placed on the foil (the heat from the coals/charcoals heats up the tobacco and the air that passes though the coal into the shisha head); (iv) the shisha user inhales the air in the shisha bowl through the hose; (v) the available air (above

the water surface) in the bowl is removed creating a negative pressure in the bowl; (vi) as a result of the negative pressure created in the shisha bowl, new air passes through the burning charcoals/coals, heats up, passes through the shisha head, and heats up the tobacco; (vii) the heated tobacco releases vapours that mix with the new air to generate the shisha smoke; (viii) the shisha smoke enters and passes through the body (vertical stem) of the shisha and come out from the lower open tip of the stem which lies about 2–3 cm below the water surface of the water in the shisha bowl; (ix) as the shisha smoke exits the lower open tip of the submerged part of the stem, it moves into the water, cools down, and emerge from the water surface; (x) as it emerges, it passes the space in the bowl to enter the shisha hose; (xi) the smoke passes through the shisha hose to the mouthpiece where it is received by the mouth of the user [5].

Shisha Smoke: Biochemical Analysis and Safety Profile

Shisha smoke contain several chemical substances and nanoparticles which have the capacity to cause dysfunctions in the human body; these dysfunctions could range from inhibition of platelet aggregation to carcinogenesis [2, 6–29] (Table 10.1).

Chronic exposure to tobacco smokes, including shisha smokes, is very lethal to an individual irrespective of his/her biological stage of life, be it foetal life or late stage of life. For example, among the (born and/or unborn) children population, clinical

Table 10.1 Chemical substances in shisha smoke and their dysfunctional effects on the human body

Chemical substance	Dysfunctional effects on the human body
Nitric oxide (NO)	Inhibition of platelet aggregation, blockage of pain transmission [10–12]
Carbon monoxide (CO)	Hypoxic injuries to body tissues [13]
Polycyclic aromatic hydrocarbons (PAHs)	Eye irritation, nausea, vomiting, diarrhoea, confusion, carcinogenesis, cataract formation, renal and hepatic injuries, impairment of foetal development [14, 15]
Volatile aldehydes	Carcinogenesis, breathlessness [16–20]
Nicotine	Irritation of the upper aero-digestive tract, dependence, carcinogenesis, elevated blood sugar, immunosuppression, cataract formation, myocardial ischaemia, emphysema, chronic kidney disease (CKD), erectile dysfunction, anovulation, alteration of menstrual cycle, impaired foetal growth, still birth, miscarriage, mental retardation [21–28]
Furans	Carcinogenesis [29]
Nanoparticles	Carcinogenesis [9]

research had shown that chronic tobacco smoke exposure can cause/increase the risk of sudden infant death syndrome [30], asthma [31], bronchiolitis [32], orofacial cleft [33], dental caries [34], middle ear diseases [35], invasive meningococcal infections [36], neural tube defects [37], etc. among them. Also, among adults, chronic exposure to tobacco smoke can cause gastro-oesophageal reflux disorder (GERD) [26], peptic ulcer disease (PUD) [26], coronary artery disease [38], chronic obstructive pulmonary disease [39], diabetes [40], cancer [41], and many more.

Based on the above, it can be concluded that shisha smoking, be it active or passive, is very unsafe health-wise, irrespective of the stage of life – intrauterine (foetal life) or extra-uterine (neonatal life to late stage of life).

Shisha Smoking History and Epidemiology: An Overview

Shisha smoking practice has been in existence for several hundreds of years [20]. Although the specific origin of the practice is not clear cut; however, many people are of the belief that shisha smoking started from India [20]. From India, the practice was said to spread to Asia, Africa, and other continents of the world [20].

Globally, about 100 million people actively smoke shisha on daily basis [42] and every year, there is 0.3–1.0% increase in the population of active shisha smokers, generally [43]. Shisha smoking practice is most prevalent in the European and Eastern Mediterranean regions. Also, the global prevalence of shisha smoking is higher among the youth than the adults [43] and these prevalence rates are highest amongst the youth living in the European and Eastern Mediterranean regions [43].

Still, there is no particular scientific study that has given the global prevalence of passive shisha smokers and active shisha smokers combined. However, through logical reasoning, it can be concluded that the combined global prevalence of passive and active shisha smokers should be almost or at least double the total number of active shisha smokers, since shisha smoking is a common gregarious behaviour, often done in the groups of family and friends [3, 44]. Also, studies had shown that the majority of the population of active shisha smokers are young males [42, 43]; hence, it can also be inferred that all other population groups (including pregnant and non-pregnant women, children, and the elderly) will/might constitute the majority of the population of passive shisha smokers in the world.

Shisha Smoking in Extreme Ages

As earlier discussed, shisha smoking is a behaviour that affects all age groups, directly or indirectly [30–37]. For instance, an active shisha smoking mother can expose her child/children, advertently or inadvertently, to shisha smokes. Likewise, household shisha smoking among breadwinners can expose their dependents (including children, and elderly) to shisha smokes. Such exposures can cause short-term and/or

long-term damages to the health of their dependents, depending on the level of chronicity of such exposures [30–41].

However, available epidemiological studies on shisha smoking/exposure have largely been focused on youth and young adults [3, 42, 43], with little to no particular study specifically exploring the prevalence of shisha smoking/exposure among those in the extreme ages (i.e. young children and elderly). This shows that a dearth of scientific literature exists in this area on shisha use. However, in the real sense, it is unimaginable to rule out the fact that some people, who are in the extremity of ages, are not exposed to shisha smokes; this is because, more often than not, we have seen both children and elderly being exposed to such smokes in our microscopic societies. Worrisomely, those in the extreme ages are more susceptible than those in-between ages.

The above discussion—shisha smoke exposure among people in extreme ages—reveals an issue of social and public health importance. The observed gaps, over the years, on the studied population groups on issues pertaining to shisha smoking need to be bridged. The global scientific community need to seriously look into this neglected area of research interest. Also, by looking into this area, the healthcare needs of this population group with respect to safety from shisha smoke can be taken care of through evidence-based research that informs policy making and implementation.

Social Issues on Shisha

There is a growing popularity on shisha in many, if not all, parts of the world [3, 45]; more and more people are becoming active and/or passive shisha smokers on annual basis [3, 45]. Shisha, in its social context, is called many names, depending on the geographical location [3, 46]; however, the commonest of these names are shisha, hookah, narghile, argileh, goza, and water-pipe [46].

The reasons why people actively smoke shisha are many, ranging from safety issues to sexual issues [47–59] (Table 10.2). For example, some people smoke shisha because they want to boost their energy in order to perform "well" during sex [53] while some, especially the women, smoke it because they feel socially protected when they join others to smoke shisha [58]. Worrisomely, the majority of people that actively/passively smoke shisha lacked adequate knowledge about the health hazards associated with shisha smoke inhalation [47–52, 56, 59]; this is a very unfortunate situation. To make it worse, shisha smoking is a widely accepted social behaviour in many societies [3, 53]; this wide social acceptance has silently encouraged people to actively/passively smoke shisha in social gatherings [3, 53].

The social media plays a very strong role of influence on shisha smoking. On various social media networks, people advertise shisha and even teach others on how to make a shisha apparatus and smoke it [60]. Through social media, many people have got initiated into shisha smoking practice. Unfortunately, shisha smoke contains nicotine—a substance that can cause addiction [2, 22–24]. Hence, shisha smoking is an addictive behaviour which may be difficult to quit once it is started [2, 53, 59];

Table 10.2 Reasons why people smoke shisha

Reasons why people smoke shisha
Perceived "safety" profile of shisha—no/less harm [47–52, 56, 59]
To boost sexual energy [53]
For socializing [53, 56, 58]
Flavour of shisha tobacco [54]
High socio-economic class [55]
Boredom/need for amusement [56–58]
Easy accessibility [59]
Curiosity [58, 59]
Peer pressure [53, 58]
Fashion [58]
Social acceptance of shisha smoking [3, 53]
Having social and/or family problems [57]
For social protection [58]
Desire for non-feminine activities (among women) [58]

however, the initiation of such habit should be prevented among people through the use of primary prevention approach.

As discussed above, many people are ignorant of the health hazards posed by exposure to shisha smokes; hence, significant works need to be done to salvage the public from this public health threat. In order to achieve this, scientists had recommended public health education and social orientation programmes as a major means to sensitize the public about the safety profile of shisha and as well discourage them about shisha use [44, 60, 61]. If these recommendations are followed by the public health systems of our societies, more and more people will be sensitized and encouraged to avoid themselves from dangerous exposures to shisha smokes.

Shisha and Its Legal Issues

Whilst the tobacco product regulatory laws/policies of many nations of the world were focused on cigarette production, marketing, and consumption, only few nations have active laws/policies regulating shisha [3, 62, 63]. In the developed countries, for instance, there is selective bias in the control laws/policies formulated and implemented towards shisha, compared to other tobacco products, as shisha products and its smoking venues are exempted from these laws/policies [3]. On the other hand, in the developing countries, there is weak enforcement of laws/policies regulating the production, marketing, and consumption of tobacco products [62, 63].

As stated above, there is a need to review the existing laws/policies regulating tobacco control in many nations of the world. This situation should be declared as

Table 10.3 Recommendations on tobacco law/policy review

Summary of recommendations made by WHO's TobReg [3]
All concerned nations should review their tobacco regulatory policies/laws, with the policies/laws having a full coverage on all tobacco products and not just only cigarettes
All tobacco production, and marketing companies must give transparent account of their activities in all concerned nations where they are doing tobacco business
Indoor shisha smoking should be banned by the government of all concerned nations, as second-hand tobacco smoke exposure endangers human health
All concerned nations should make policies/laws that will ensure that all shisha tobacco products are regularly tested and regulated, as per their contents and safety profile
All concerned nations should make policies/laws that will ensure that the promotional activities (including advertisement, marketing) of shisha are strictly regulated
All concerned nations should make policies/laws that will ensure that all information accompanying all shisha parts and accessories must be accurate and not misleading
All concerned nations should make policies/laws that will ensure that health warnings in relation to shisha use must be clearly and boldly indicated on shisha packaging and labelling
All concerned nations should make policies/laws that will ensure that comprehensive public health education and awareness campaigns are successfully done
All concerned nations should make policies/laws that will ensure that shisha smokers benefit from clinical tobacco cessation programmes

a state of emergency, as so many people, in large numbers, are dying of tobacco smoke exposures, on yearly basis [64]. As a matter of fact, the the World Health Organization (WHO) Study Group on Tobacco Product Regulation (TobReg) [3], in 2015, recommended that the United Nations member states should review their tobacco regulatory policies/laws due to some observed pitfalls regarding shisha regulatory policies/laws in the global community. Table 10.3 shows the summary of the recommendations made by TobReg.

Chronic Shisha Smoking, Longevity, and Quality of Life

Both active and passive smokers, irrespective of the age, are at health risks due to exposure to burnt tobacco smoke [46, 65, 66]. The existing body of scientific literature on shisha had clearly shown that the constituents of shisha smoke have the inherent capacity to cause myriads of biological dysfunctions in the human body [2, 6–29]. It had been well-established that chronic exposure to shisha smoke can cause seriously debilitating and life-threatening medical conditions both in the foetus and the elderly [3, 30–41]. Although, the clinical associations between chronic shisha smoke exposure and diseases had been well studied [2], yet little or no extensive scientific study had ever been done, over the life course, in exploring the associations between chronic shisha smoking (passive or active), longevity and quality of life. The aspect of longevity and shisha smoking in the extreme ages is a highly understudied

area of scientific significance; this calls for the urgent need for conducting large multidisciplinary longitudinal studies on this area, over the life course.

Tackling the Burden of Shisha Use in the 21st Century: Recommended Strategies

There is still a great deal of work that needs to be done in tackling the global burden of shisha use in the 21st Century. With the growing popularity on shisha in so many parts of the world, it remains very clear that the issue of shisha use is both a health and a social problem of huge global concern. In order to tackle this global problem, we recommend a four-faceted approach which involves proper policy reformation and implementation, public health intervention, clinical intervention, and scientific research.

Proper policy reformation and implementation: This is a very crucial aspect that is very important in eradicating the rising burden of shisha use in the global community; in fact, it forms the basic foundation upon which other strategies are built upon. A strong policy is a powerful fuel for a successful intervention, both at the public health level and as well the clinical level [67]. Since the existing policies on shisha tobacco regulation are weak [3], we strongly recommend that a radical approach should be taken by all relevant stakeholders involved in the in-depth reformation and implementation of these policies. Furthermore, these policies should be in complete accordance with the TobReg recommendations [3].

Public health intervention: Through proper public health intervention (i.e. disease prevention and health promotion) strategies, the public can be properly educated about the dangers of shisha smoking. Specifically, in the areas of public health intervention on shisha smoking, the relevant stakeholders should try and ensure that such interventions are focused on: positive transformation of public's perception of shisha; convincing people to see shisha smoking as a socially unacceptable behaviour; training people, more especially the youth, on how to resist peer influence/pressure to smoke shisha; and adequately educating people on the socioeconomic and health implications of shisha smoking [61].

***Clinical intervention*:** Shisha tobacco smoking eradication strategies are incomplete without proper clinical intervention [68, 69]. As more and more people are smoking shisha, on yearly basis [43], more and more shisha smokers are willing to quit shisha smoking habits [3, 53, 70]. Unfortunately, many countries, especially the developing African countries, are yet to have well-structured and optimally functional national tobacco cessation programmes [71]. Clinical intervention programmes have been found to be very effective in supporting tobacco smokers in achieving a quit [72, 73]. Through the establishment of a well-structured and a highly functional national tobacco cessation programmes in every country, the burden of shisha smoking can be brought to the barest minimum.

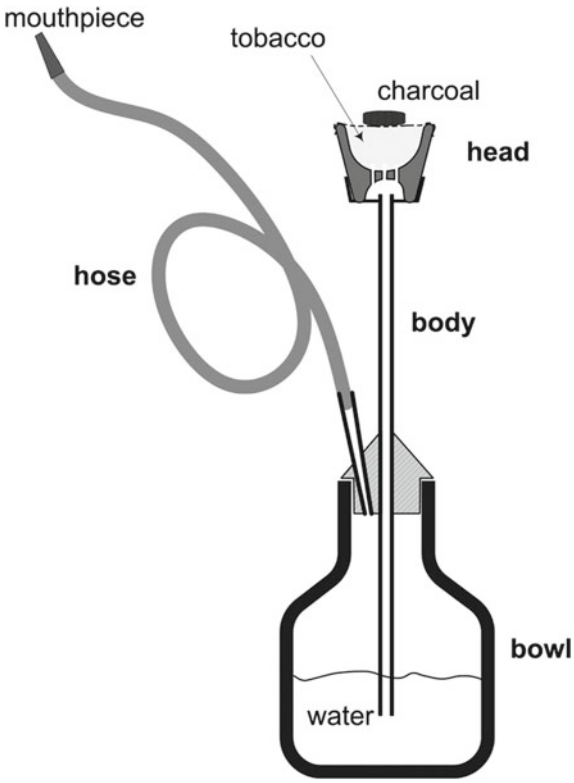

Fig. 10.1 A labelled diagram of shisha. *Source* Kadhum et al. [2]

***Scientific research*:** In addition to the above, the health, legal and social aspects of shisha smoking is yet to be fully explored generally, as many research questions on how to eradicate shisha smoking practices are yet to have clear answers to them [3, 74]. Some of the reasons for this can be attributed to limited funding, and complexity of the social context of shisha smoking (including, cultural diversity, genetic differences, and evolution of shisha) [3, 74]. If the government and other relevant stakeholders can painstakingly put in more efforts into shisha-related research, this will provide vital opportunities for a better understanding on how to appropriately and effectively prevent and control public shisha use. Through this, the burden of disease caused by chronic exposure to shisha smoke and other smoked tobacco products will be brought down to the barest minimum (Fig. 10.1).

Conclusion

Shisha smoking—a popular behaviour—is a social and health issue of global concern. It is a behaviour that affects all ages, directly or indirectly, due to the hazardous

social and health effects associated with the practice. More and more people are becoming shisha smokers on yearly basis; unfortunately, the public health, legal, and social interventions targeted at reducing the rising burden of the practice is not commensurate with the rise. We recommend that multi-faceted and well-planned efforts should be adopted in stemming the rising scourge of shisha smoking in our societies.

> The more you smoke, the more you should fear the pains of death
>
> —Kehinde Kazeem Kanmodi, 2021.

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Definition of Key Terms

Longevity: living for a long time [75].

Passive shisha smoker: a person, be it a child or an adult, which involuntarily inhale a mixture of the smoke given off directly by the burning of tobacco and the smoke exhaled by smokers. A passive shisha smoker is also referred to as a second-hand smoker or an involuntary smoker [65].

Quality of life: an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns [76].

Shisha: a water-pipe, popular in many Arab countries, in which fruit-scented tobacco is burnt using coal, passed through an ornate water vessel and inhaled through a hose [4].

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Chapter 11
Risk Factors and Lifestyle Habits Leading to Alcohol Consumption from Youth

Deep Shikha, Richa Sinha, and Vidisha Vallabh

"We found that the risk of all-cause mortality, and of cancers specifically, rises with increasing levels of consumption (of alcohol), and the level of consumption (of alcohol) that minimises health loss is zero."
—GBD 2016 Alcohol Collaborators

Abstract This chapter aims to bring out the problem of alcohol use, its risk factors and lifestyle habits which leads to its initiation from early phases of life. This chapter also focuses on important consequences, preventive measures, corrective intervention and effective treatment of the problem. Alcohol use from early phases of life remains a major public health concern in various nations. It creates serious consequences among alcohol users affecting whole nation individually, socially, economically not even sparing their families and communities in which they reside. Adolescents and youth represents an important segment of society constituting majority of the population. Alcohol is the most commonly abused psychoactive drug accounting for greater morbidity and mortality among youth. It is a 'gateway drug' for consumers because its use often precedes the use of other illicit substances causing serious and potential life threatening problems. Prevention strategies are an integral part of reducing alcohol use at young ages.

Keywords Youth risk behavior · Substance use · Alcohol misuse · Preventive strategies · Models for alcohol prevention · Protective factors · Risky drinking

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Background

Adolescents and youth represent an important segment of society constituting majority of the population. They form the bulk in terms of proportions, and also act as the repertoire for future leaders, and are the promise of a better life for the community[1].

Adolescent are usually between 10 and 19 years, the phase which includes rapid changes in body size, physiology and psychological and social functioning, 'Youth' are from 15 to 24 years and 'Young People' are from 10 to 24 years [2]. This phase of life is full of opportunities and healthy adolescents and youths, are a great asset for contributing to national development. Youth are particularly vulnerable to alcohol use and its consequences at this time for varied reasons, depending on individual, biological and behavioral factors. Their developing brain at this young age is particularly susceptible to long- term negative effects of alcohol use [3].

Substance abuse is a major public health problem globally and has increased in alarming proportions in both developed and developing countries not because of the novely or magnitude of the problem itself but because of the changing trends of substance use [4].

Cannabis remains the world's most widely used drug, however alcohol is the most commonly used psychoactive drug and accounts for the greater morbidity and mortality [5]. Being the most abused drug among youth it acts as a 'gateway drug' as it opens the doors to other prohibited and addictive substances leading to serious and potential life threatening problems.

Alcohol is responsible for four percent of the global burden of disease and has emerged as one of the major international threats to public health [6, 7]. In addition to chronic diseases with high mortality and poor prognosis like liver cirrhosis, cancer and cardiovascular diseases, alcohol abuse acts as a causative agentfor more than two hundred different health conditions [8, 9].

Alcohol consumption finds its mention as early as 7000 BC and records can be seen in Egypt, China and India. Thus this intoxicant has grown and is deeply embedded in the history and culture of humankind. Alcohol consumption has the ability to enhance positive moods and has effects on stress-relieving and thus making alcohol drinking a social activity, embedded present day in conventional and socio cultural contexts [10].

Problem Statement

Contributing to four percent of the global burden of disease, alcohol directly attributes to approximately 2.5 million deaths each year, out of which 9% of deaths occurs in 15–29 year age group. Alcohol is the world's 3rd largest risk factor for diseases [11, 12].

National Youth Risk Behavior Survey conducted in United States (2019), revealed current alcohol use among 29.2% of the youth, while 13.7% were current binge drinking and 15.0% had consumed alcohol for the first time before 13 years of age (see Box 1) [13].

Box 1 Problem statement and disease burden for alcohol use worldwide

- Global Status report (2018) suggested that a total of 5.3% of the all deaths, i.e approximately 3 million death is resulted by harmful use of alcohol.
- An astounding 5.1% of global burden of disease and injury, reported in disability-adjusted-life-years (DALYs), is attributed to alcohol only.
- Alcohol consumption attributes to 13.5% of total death in the age group of 20–39 years resulting in death and disability in early life.
- Global burden of disease is very high among men and women (7.1% & 2.2% respectively), if there is harmful level of alcohol consumption [9].

In various international studies, prevalence of alcohol consumption varied from around four percent in 12–13 years aged to 51.6% in 18–20 years [14]. In Ethiopia (2010), prevalence of alcohol consumption was 22.2% among students [15]. Earlier surveys often reported steep rates of daily alcohol use and binge drinking amongst men as compared to women, but never studies have shown a narrowing of this gap [16]. Data from national epidemiological survey U.S. showed that prevalence of DSM IV alcohol dependence was highest among 18–20 years old (Fig. 11.1), and another survey from European school project on alcohol and drugs described that

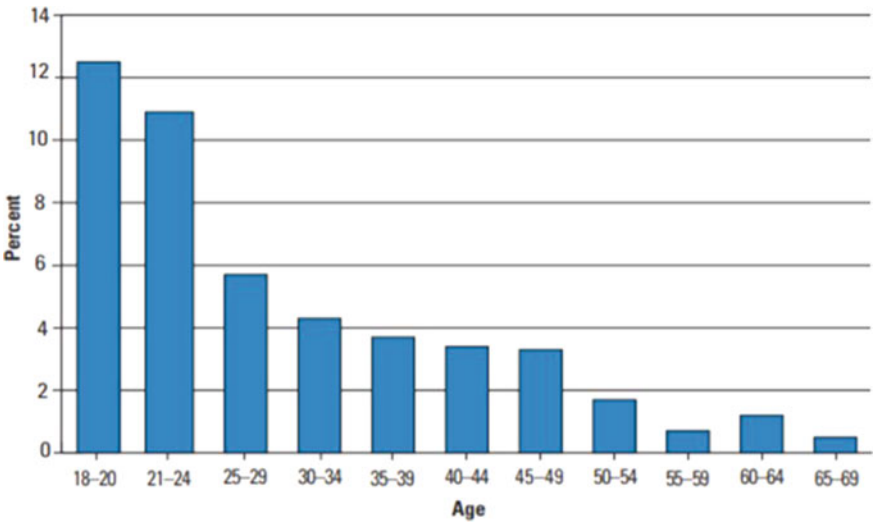

Fig. 11.1 Prevalence of DSM-IV alcohol dependance-U.S

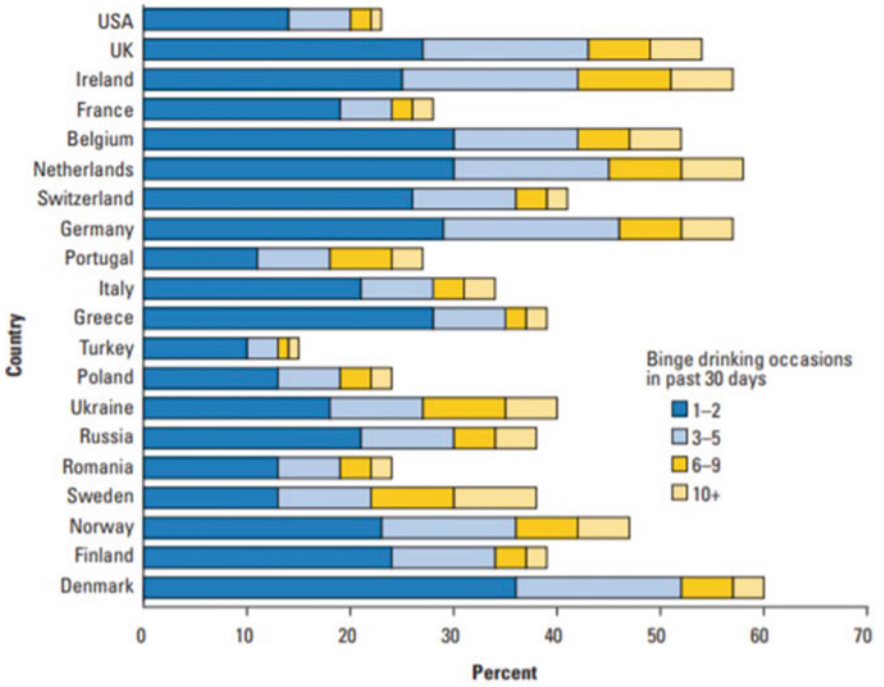

Fig. 11.2 Percentage of adolescents 15–16 years of age engaged in Binge drinking

many students from 15 to 16 years in European countries were involved in binge drinking in the past 30 days (Fig. 11.2) [3].

Risk Factors for Alcohol Use in Early Ages

Alcoholism affects people of any age, race, sex, and socioeconomic background without discrimination. It is multifactorial in origin, as a lot of factors can influence the risk of developing an alcoholic use disorders among users. The more susceptibilities a person has, the more likely he develops alcohol-related problems as a result of alcohol consumption [17]. The effect of these factors is singular for consumers, and thus even in the presence of these factors, addiction to alcohol is unpredictable (Table 11.1).

Table 11.1 Risk factors of alcohol use

Belonging To A Vulnerable Group	Social And Cultural Factors	Interpersonal And Individual Risk Factors
• Drug misuse by parents • Abuse within the family • Homeless • Young offenders • School non- attenders • Young sex workers • Mental health problems	• High level of neighbourhood poverty, decay and crime • Free access to drugs • Social acceptance of alcohol and drug use • Extensive use of alcohol and drugs socially • Lack of knowledge about risk involved in drug use. • Poor perception of drug-related risks.	• Physiological and psychological factors • Conflict & instability among family members • Behavioural difficulties • Academic problems • Alcohol and drugs consumption among peers. • Addiction of tobacco smoking, alcohol and drug in early age.

Other Factors Influencing Early Alcohol Consumption

Environmental Factors

Familial Factors

Parents are the single most important factor who have influence on their children's decision to become involved in substance use or not. The theory of 'social learning' dictates that human behavior is a result of observation and learning. As youngsters are inducted into the society and culture, their first lessons are from their family members, in which their parents play the most profound role. Substance use and abuse lies in the same domain of 'watch and learn' with parents being the main 'influencers' when it comes to drinking habits in formative years [18]. These young adults with early exposure to heavy alcohol consumption are more likely to develop an alchol use disorder than their counterparts. Similarily, adolescents are also negatively influenced by their elder sibling in alcohol use [19].

Thus it can be argued that children with alcoholic parents are more susceptible to develop alcoholism (the percentage as high as 30%) as opposed to their sober contemporaries [20–22]. Infact, maternal alcoholism especially during pregnancy strongly influences alcohol abuse in the resulting offsprings [23].

Other alcohol-abuse influencers among family-related factors that predict drinking behaviors in adolescents include inter-familial warmth and relationship, and parental monitoring [24–28]. Parents with a tolerant view on early-age drinking have an unfavourable impact on their children when it comes to alcohol use [29].

Loss of a parent, separation and divorce, prolonged family disorganization and conflicts, communication-gap amongst family members fosters poor lifestyle choices like alcoholism in adolescents [30]. Children from broken homes or homeless youth are more likely to develop alcoholism [31]. Familial discord is a strong predictor of

alcoholism as children with single parent or with multigamist parents are three times more likely to binge on alcohol [19].

Hence strong family values, careful parental monitoring with strict disapproval of underage drinking and close bonds between family members has a protective role against adolescent alcohol use [32, 33].

Peer Influence

Peer influence occurs from childhood to adolescent and youth started spending more time with their peers in comparison to parents, so if peer groups are consuming more of alcohol then there will be higher chances of alcohol consumption by youths [34].

Adolescence and youth is redolent with risk-taking behavior, with peers often encouraging undertaking of perilous adventures and habits among their companions. Hence adolescents with alcohol-using peers are more likely to take on the drink [35]. Young people are also influenced by how much their friends are drinking. Having older friends and spending more time with drinking friends are likely to promote excessive drinking habits [36].

Genetic Factors

Individuals who have a biological parent with an "alcohol use disorder" (AUD) are far more likely to develop an AUD themselves.Genetic factors influence an individual's vulnerability to alcoholism [37, 38]**.**

Alcohol dependence in monozygotic twins is more than twice as in dizygotic. Genetic studies found that from 40 to 60% of biological parents influence children alcoholism [39]. Adolescent children of alcoholics have been shown to have an abnormal P300 response and abnormalities in brain structure and function [40].

Social Factors

Social factors can also play a significant role in a person's likelihood of abusing or becoming addicted to alcohol. Social factors have consistently been implicated as a cause of vulnerability to alcohol use and abuse.

Alcohol commercials particularly affects younger minds propensity to consume alcohol. A longitudinal study from the West of Scotland (N = 2586 pupils) explored the causal effects of alcohol (mis)use and antisocial behaviour in pupils followed up between the ages of 11 and 15 years and the findings suggested that antisocial behaviour was the main predictor of alcohol misuse and alcohol-related trouble in this under-age cohort [41].

Cultural Factors

Alcohol is a psychoactive substance with dependence-producing properties that has been widely used in many cultures for centuries. Cultural norms and beliefs are strong predictors of both current drinking and frequent heavy drinking [42].

Across race and ethnicity, African Americans and Latins report more conservative attitudes toward drinking compared with Whites [43, 44]. Asians are integrated with their ethnic cultures and are generally thought to have higher abstention rates when compared with other racial and ethnic groups [45].

Advertising Influence

Mass media has received great attention as a socializing agent as it is the most dominant form and has considerable & unquestionable influence on consumer [46].

Socialization of alcohol on media has greater impact on adolescent minds because of its association with many seemingly successful models (who exhibit sexual prowess and allure, desire by opposite sex, unbelievable feats, elegance, popularity—a much coveted ' James Dean' like 'cool' or 'it' factor) admired by them, thus market increases the positive expactancies and reduce the negative expectancies of alcohol consumption [47].

In recent years youths are exposed passively and actively to alcohol marketing and display of pro- alcohol messages on various social medial web sites, such as YouTube, Twitter, Instagram, and Facebook [48, 49]. Access to these social networking sites is a common pastime by youth and it is not easy to obtaincorrect demographic data. Over the past several years brand marketing of alcohol has increased using highly effective platform settings [50].

Although restrictions are enforced to protect young population from exposure to alcohol advertisements on traditional media channels however these modern sites falls outside the purview of regulatory authorities. Advertisement of alcohol products on these platform reaches out to adolescent and certainly influence the initiation or the first drink and consumption pattern. Infact, alcohol-based merchandise including brand water or soda, shirts, bottle openers are deeply linked to early alcohol usage among adolescents [51].

Easy Availability

Alcohol industry has introduced many different and newer formulations of alcohol-containing products to appeal youths which can be easily ordered online. These products include but are not limited to alcoholic jell-os, alcoholic soda pops, fruit-flavored beers, caffeinated cocktails, vaping alcohol (vaportini), powdered alcohol (palcohol), light beers like breezers and chocolate and candy liqueur that effectively masquerade the bitterness or make alcohol look trendy, thus making more palatable for the consumer market. Devices that allow for the vaping of alcohol can be ordered

online, and do-it-yourself online video, allowing youth to experiment alcohol use [52].

When these newer products are posed and popularized amongst youth as 'happening', the consumption of alcohol by the underage rises rapidly. Consumption of this masqueraded and stylized alcohol in the form of fruity or caffeinated alcoholic increases the instances of more drink per sitting, more sittings per month and more binges of greater quantity of alcohol in adolescents attributing to higher instances of alcohol intoxication and alcohol attributable harms [53, 54].

Psychological Factors

Many individuals with psychological illnesses or social anxiety, consider alcohol as coping mechanism for their illness and are often more likely to abuse, become addicted to it or other substances.

Externalizing issues in early childhood, specifically in conduct disorder, have been shown to foresee alcohol and substance use issues in later period of life [41, 55–57]. Adolescents with ADHD (attention deficit hyperactivity disorder) have higher risk of drug use disorders yet the evidence for causal relationship with AUDs is ambivalent [58, 59].

Furthermore, according to several researches underage drinking often translates to AUD in adults. Population-level alcohol policies (raised taxes, dry days, strict ID'ing at bars and shops) are instrumental in decreasing alcohol consumption at individual, community and national levels [59].

Other Factors

Apart from the above factors, some special focus groups for increased risk of alcohol misuse are: LGBTQIA+ adolescents, as they are vulnerable to greater risk of depression and suicide [60, 61].

The Risks for Consumers: How Alcohol Degrades Your Health?

Alcohol is a psychoactive agent with known immunosuppressant, carcinogenic and toxic properties [62, 63]. More diseases and injuries are now found to be associated with harmful use of alcohol. It has caused nearly three million deaths per year which contribute to 5.3% of all deaths, which is much more than disease-specific mortality due to diabetes, tuberculosis and AIDS. Alcohol consumption is often associated

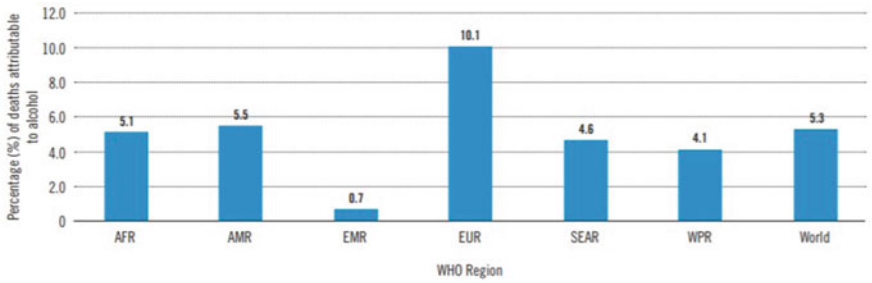

Fig. 11.3 WHO regionwise percentage of deaths due to alcohol consumption, 2016 [8]

with relatively early death and disability in life. Nearly 13.5% of the total deaths among 20–39 years of age group, are attributed to alcohol use. Overall, alcohol has contributed 132.6 million DALYs which amounted to 5.1% of total DALYs [8, 17] (Fig. 11.3).

The role of harmful use of alcohol has been well established in the causation of a host of diseases and injuries including communicable diseases like HIV/AIDS and tuberculosis; mental and behavioural disorders including alcohol abuse, delirium tremens, Wernicke-Korsakoff Syndrome; and non-communicable diseases [17, 64, 65].

Non-communicable diseases are the fastest emerging diseases group causing heavy morbidity and mortality worldwide; to which alcohol has contributed 1.7 million casualties (2016). Of these, nearly 1.2 million deaths were from digestive and cardiovascular diseases and 0.4 million deaths from cancers [9, 63].

Risk taking behavior is inherent to harmful use of alcohol and globally an estimated 0.9 million injury deaths were attributable to alcohol, including deaths due to road injuries, self-harm and interpersonal violence [9] (Table 11.2).

Apart from devastaing health consequences, severe economic losses and widespread societal disruption are also a result of alcohol abuse [17, 64, 65].

Risks for the Society: How Alcohol Degrades Your Social Life?

> Alcohol robbed me of the ability to see others—and understand what they might be feeling or going through. Drinking to escape was profoundly selfish, and all those unresolved resentments and worries metastasized while I drank to ignore them.
>
> —Elizabeth Vargas, Between Breaths: A Memoir of Panic and Addiction.

Alcohol and risk taking are intimately related [66]. Alcohol stimulates the release of endorphins which promote a sense of well being, encouraging to drink more and thus initiating a vicious cycle. Plied with alcohol, the user loses self control

Table 11.2 Alcohol related diseases and injuries [9]

Detrimental	Noncommunicable diseases	Developmental	Injuries
•Communicable, maternal, perinatal and nutritional conditions •Tuberculosis, HIV/AIDS, lower respiratory infections	•Lip and oral cavity, •pharyngeal cancers, •oesophagus, colon and rectum cancers, • liver cancer, •breast cancer, •larynx cancer, •alcohol use disorders, •hypertension •heart disease, • haemorrhagic stroke, •alcoholic cardiomyopathy, •atrial fibrillation • cirrhosis of the liver, •pancreatitis, •alcohol-attributable unipolar depressive disorders, sleeping disorders	•Fetal alcohol syndrome	•Unintentional injuries (Road injury, poisonings, falls, fire, heat and hot substances, drowning, exposure to mechanical forces, other unintentional injuries) •Intentional injuries (self-harm, interpersonal violence)

and becomes euphoric, disinhibited, uncoordinated, loquacious and even argumentative and confrontational [67]. Often this leads to aggression, violence including sexual aggression, risky sexual behavior, accident-related injuries and fatalities; and dangerous/risky driving patterns [68].

According to the Global status report on alcohol and health, 7.2% of global premature mortality is a result of alcohol use, of which younger people were inordinately affected as compared to the older population, which can be attributed to risky behavior [9]. Heavy drinkers are twice likely to die at any age, in younger the reason being drunk-driving and in older, suicide [69, 70].

Alcohol and Violence

Mock courage gained by alcohol is often a major perpetrator of violence and is often consumed before confrontations. Harmful use of alcohol makes the user emotionally labile and thus vulnerable to aggression and due to reduced coordination and poor decision making, a target for perpetrators as well. Alcohol is one of the major causes of intimate partner violence too. Alcohol has often been used as a means of coping with violence or as cure-all both by the perpetrator and the victim. Sometimes this delinquent behavior of the perpetrator can be a result of prenatal alcohol exposure (resulting in fetal alcohol syndrome or fetal alcohol effects) which is often associated with behavioral problems [69].

Drink Driving

Users dependent on alcohol dependence have diminished spatio-visual and motor speed responses as well as poor decision making [71–73]. Adolescents and young people are more likely to consume alcohol in risky situations thereby becoming more vulnerable to drunk driving and crashing, injuries due to assault and violence. Infact, alcohol has been the main perpetrator of early death and morbidity in adolescents due to homicides, suicides and violent accidents, accounting for nearly 80% of such accidental events [67].

Alcohol and Unsafe Sex

Higher alcohol consumption is associated with a significantly higher prevalence of sexual risk behaviours. Inebrietion is often associated with sexual encounters at an early age in young drinkers (as compared to people practicing alcohol abstinence), unprotected sex especially during the first encounter, adolescent pregnancy, and the likelihood of contracting sexually transmitted diseases including HIV/AIDS. Partners of alcohol dependents are more likely to suffer from intimate partner violence and sexual violence which can result in accidental deaths.

Alcohol Can Impair Brain Development

Potentially adverse consequences for children and young people who misuse alcohol are much graver. Adolescents and children have a lower tolerance to alcohol, with side effects including but not limited to appetite changes, weight loss and early onset of lifestyle diseases. Since the brain undergoes cardinal structural and functional development in childhood and adolescence, it is more likely to be damaged by alcohol use than a developed adult brain [67, 71–74]. Alcohol also interferes with the neurological development leading to subtle brain damage and long-lasting cognitive deficits affecting academic performance. Alcohol may change brain structure and thus trigger a behavioural response [71]. Poor mental health as a consequence of the harmful use of alcohol is associated with depression, and sleep disturbances [75, 76].

Mixing Alcohol with Other Drugs

Risky behaviors have a tendency to flock together; be it unsafe sex, alcohol use or other substance abuse [70]. Alcohol users are more likely to consume other psychoactive substances like cannabis as compared to their peers practicing abstinence [77, 78].

Alcohol acts as a gateway to other psychoactive substances like cannabis, cocaine, LSD, Hashish etc [79–81].

Protective Factors for Alcohol Consumption

Protective factors are the tour de force in ameliorating risk factors from adolescent life. Delaying the time of the first drink can potentially reduce the harmful effects of alcohol. Deep association with religion is found to be inhibitory to harmful use of alcohol.

The location of the first drink and the company available has a profound effect on alcohol use by young adults. Revisiting the 'social learning theory'; first introduction to alcohol under a controlled home environment as opposed to introduction by peers has a protective effect against alcohol misuse. Therefore alcohol use under the supervision of an adult who is well controlled can shape the alcohol use habits of the young adult [82–84].

Late initiation to alcohol by well informed and supportive family is effectives in reducing the future misuse of alcohol by the children [75]. Parental guidance and restriction is an effective technique only when children are living with their parents. With growing age, freedom and autonomy, indirect control like education has been the only effective strategy [71] (Table 11.3).

Table 11.3 Protective factors of alcohol use

Youth Alcohol Prevention Programs

> We are supposed to consume alcohol and enjoy it, but we're not supposed to become alcoholics. Imagine if this were the same with cocaine. Except, it's not...The point is not that alcohol is worse than cocaine. The point is that we have a really clear understanding that cocaine is toxic and addictive. We know there's no safe amount of it, no such thing as "moderate" cocaine use; we know it can hook us and rob us of everything we care about...We know we are better off not tangling with it at all.
>
> **—Holly Whitaker, Quit Like a Woman: The Radical Choice to Not Drink in a Culture Obsessed with Alcohol**.

Planning for a national level prevention programme must be guided by the magnitude of the problem in a country, which requires a multi-stakeholder involvement and devotion to the cause [85].

A prudent approach is to focus on strategies that combat previously mentioned risk factors of alcohol use among adolescents and identify high-risk [86, 87].

A risk-protective and a protective-protective approach is often found to be useful where the first component is used to bolster the second. The role of protective factors has often been stressed upon and poor integration of these factors in alcohol prevention programs often proves fatal for the program. Therefore, a protective factor based prevention program is invariably more effective in reducing the risk factors as well.

Social skills training programs are protective factors to improve communication and interrelationship skills among adolescents. Participants in such programs develop a healthy resistance to peer pressure and a balanced attitude towards drinking. It also motivates development of self-control and problem-solving skills and stress-management thus bringing about a positive attitude towards life-issues [62, 87–90].

An in-depth understanding of risk factors and protective mechanisms against alcohol use is imperative in formulating policies which are being brought into play by many countries worldwide [86, 91]. Alcohol consumption can be reduced by simultaneous implementation of various policies viz. raised taxes, strict age limits for buying and consuming alcoholic beverages, regulated hours and venue of sale. Of these, low availability and higher prices are often more successful in reducing onsumption frequency as compared to age limit and fixed sale point and hours [92]. Cessation of advertisements and parental control on the internet has also helped in increasing the first age of contact with alcohol [22, 93, 94].

Preventing Young People from Risky Drinking

> We love to protect alcohol and our right to consume it, and to vilify people who can't handle it. We venerate the substance; we demonize those who get sick from using it.
>
> **—Holly Whitaker, Quit Like a Woman: The Radical Choice to Not Drink in a Culture Obsessed with Alcohol**.

Long term changes and reduction in alcohol consumption patterns among adolescents is possible only with individual and family-based behavioural interventions [88]. Such preventative interventions can be developed at national level and embedded in public health policy to target early key risk factors for substance use disorders [69, 70].

Investing in health education focusing on healthy lifestyle, as primordial prevention strategies is an effective tool against dangers of under-age drinking. A healthy dialogue at home between parents and children focussing on the harmful use of alcohol can bring about the much needed primordial prevention back to life [82].

Prevention of Alcohol Use and Misuse in Early Ages

Prevention is an integral part of reducing alcohol use at young ages. There are different levels where multiple strategies can be applied for youths who have either started consuming alcohol or are in high risk of initiating it in coming years (Fig. 11.4). Various intervention levels and their strategies are as follows [22, 95–110]:

Individual Level

At individual level we can:

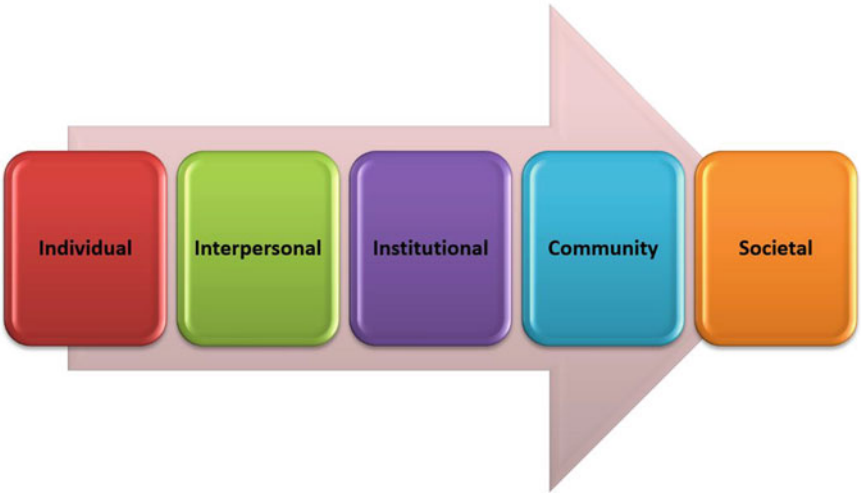

Fig. 11.4 Level of intervention for prevention of Alcohol use from early Ages

1. Educate young minds about adverse effects of alcohol and other prohibited substance usage
2. Strengthen training programs in refusal skills
3. Provide guidancein self-protective skills
4. Identify more susceptible individuals and increase their self efficacy
5. Reinforce messages regarding ill-effects of alcohol use, using various social media platforms
6. Teach them about the facts of risk involved in alcohol use
7. Modify attitude toward alcohol drinking
8. Help the growing individuals in diverting their mind and engage them in constructive and interesting activities like sports, entertainment, meditation, and other extra-curricular activities
9. They should be trained for adapting to changes and handle stress events appropriately in healthy ways
10. Effective social problem solving skills must be taught from young age.

Interpersonal/Family Level

At this level various strategies that can be applied are as follows:

1. Cultivate the communication skills among peers to change social norms about alcohol use
2. Plan peer (preferably from same group) education programs about harmful effects of alcohol and drugs
3. Locate the peer leaders, who serve as role model for them and train them for better communication among the susceptible students and probable alcohol users
4. Parents must be encouraged to inspire their offsprings and no-alcohol rules must be enforced at household level
5. Provide family education programs about alcohol harms and involvement of parents in day to day school activities
6. Exemplary adults of the family and community including the teachers, can be instrumental in motivating positive lifestyle behaviors in youngsters by constant support and encouragement of their healthful activities
7. Bond with family members will enable supportive environment for child and improve child's own coping efforts.

School/College/Institutional Level

Different strategies under this level are:

1. Involvement in extra-curricular activities and other social events
2. Alcohol awareness weeks and counselling sessions can be planned

3. Create a healthy social environment that promotes healthy lifestyle habits
4. Ban the use and sales of prohibited products in and around schools and colleges by enforcing policies, laws and regulations
5. Anti-alcohol campaign through different platforms must be promoted
6. Posters and charts can be displayed in and around school/college premises showing hazards of alcohol use and laws related to these substances
7. School magazines containing messages from peers (anonymous) about de-addiction and life free of alcohol and drugs can be circulated for more relatability
8. Senior students can be trained about harmful effects of alcohol use and may serve as role model for their juniors
9. School/college wardens and other staff should be trained to educate students about alcohol use hazards and also be able to recognize the users among them
10. Helpline numbers regarding information, counseling and help in emergency situation should be displayed at prime locations like outside mess, hostel notice boards, main entries, and corridors
11. Anonymity of the user should be maintained at all levels and this should also be ensured among the informers.

Community Level

Community level involves following strategies:

1. Behaviour change communication among community members
2. Formation of youth self-help groups
3. Encourage community participation for vigilance and alertness about any kind of unlawful practice regarding alcohol or other substance use
4. Locate irresponsible alcohol sellers and take action against them
5. Limiting the point and hours of sale of alcohol
6. Owners of shops and outlets can be approached for responsible attitude and follow rules and regulations as per government norms
7. Promote counseling activities for adolescents in the community with the help of NGOs or health centres
8. Positive use of media and promotion of social marketing involving exemplary role models and leaders of the community
9. Raising minimum age for drinking
10. No underage sale of prohibited products should be ensured by community leaders
11. A task force of community leaders, peer leaders, healthcare providers and NGOs must be assembled for prevention, control, treatment and rehabilitation of alcohol and drug use
12. Messages regarding rules and regulations of alcohol usage must be displayed in bold outside all sale outlets

13. All public areas must contain IEC material regarding harmful effects of alcohol and drug use
14. Helpline no. must be written at all probable places where adolescents and youths frequently visits.

Societal Level

Intervention at the level of society plays a very important role in prevention of alcholol use and misuse. The strategies which can be applied are:

1. National anti-alcohol policy with strict enforcement
2. Use of social media platforms and other forums for spreading messages regarding alcohol and drug use, its hazards, and fine related to unlawful activities
3. Strategies to reduce alcohol sale like hike in excise tax, strict prohibition for underage sale
4. Restrict the number of outlets, reduce the time for sale and apply some no-sale days for alcohol
5. Media promotions of alcohol use via advertisements and promotion in movies showing heroes and role models using alcohol drinks must be banned
6. Illegal sale and purchase of alcohol must face increased fine and cash penalties
7. Minimum age of purchase must be strictly followed
8. Advertising of adverse affects of alcohol to bust the glamorous image of alcohol industry
9. Budgets for anti-alcohol activities should be addressed when finance plan of country is presented
10. Anti-alcohol interventions must be focused in areas where massive numbers of youth and adolescents can be targeted
11. Common national anti-alcohol committee and helpline number must be created for handling with these issues specifically
12. Facilitate and encourage multi-level and inter-sectoral coordination for sustainable and long term success of anti-alcohol movement.

Model for Prevention of Alcohol Consumption Among Adolescents and Youth

> Be kind to drunk people, for every one of them is fighting an enormous battle.
> —Sarah Hepola, Blackout: Remembering the Things I Drank to Forget.

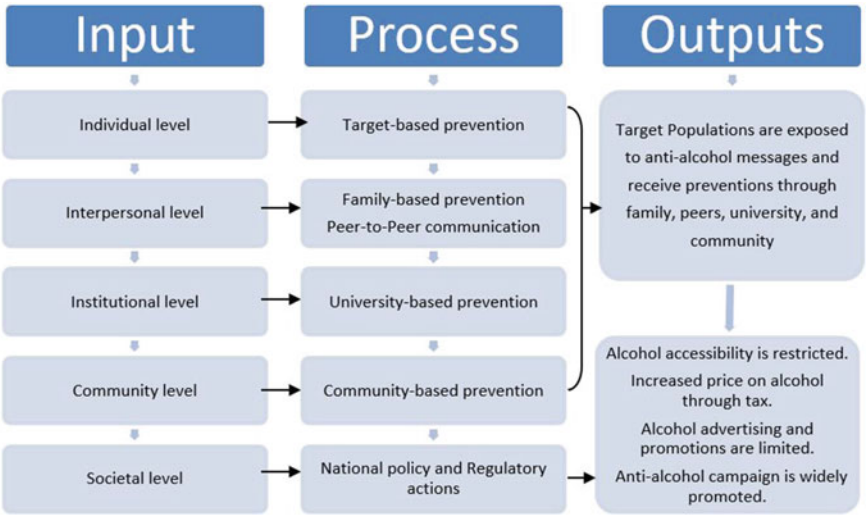

Fig. 11.5 a The logic model for preventing alcohol consumption among adolescents and youth. b. The logic model for preventing alcohol consumption among adolescents and youth

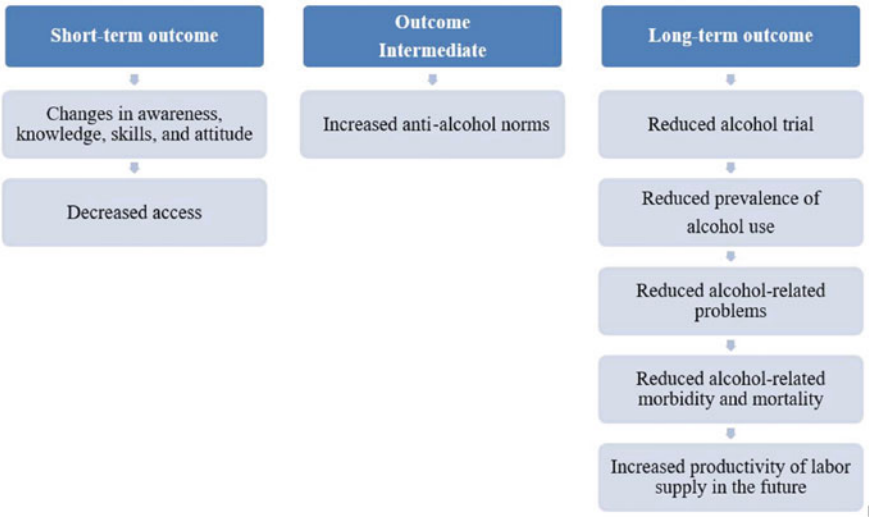

Fig. 11.5 (continued)

The logic model (Fig. 11.5a and b) proposes a simultaneous induction of all intervention at all levels, thereby promoting anti-alcohol advocacy and effective intervention among the high-risk groups at individual, family and community level [95].

Fig. 11.6 Goals for prevention of underage drinking

Goals for Prevention of Underage Drinking

Under-age drinking is a long-drawn, resistant and complicated health and social issue, requiring integrated and comprehensive solution. Evidence-based approach provides a ray of hope in providing a sustainable solution to this age-old problem. The below mentioned six goals can be applied by any nation to prevent underage drinking (Fig. 11.6).

Conclusion

Though it seems implausible, but underage drinking is a grave issue worldwide, especially when it commences at a young age. Alcohol consumption by minors mars their relationship with themselves, their families and their community, blighting their social and economic development. Thus underage drinking has serious consequences that affects the whole nation.

Drinking at a young age and in adolescence is associated with alcohol misuse and dependance in adolescence as well as adults, thus affecting the dynamic developmental processes as well. The solution must therefore be provided within a developmental framework for prevention and control of underage drinking. This framework to prevent underage drinking should be based on the human development, societal

influences during early years and the characteristics of the individual minor that influence them to drink.

A stricter policy and intervention program that focuses on alcohol taxes, restricted alcohol accessibility and zero tolerance to advertising and promotion is crucial to curb this epidemic worldwide.

Underage alcohol use is the Medusa born of human errors and can only be defeated by the evidence-based sword of Perseus.

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Chapter 12
Lifestyle Factors, Depression, Anxiety and Stress Related to the Internet Addiction Among School Children

Abdulbari Bener, Dinesh Bhugra, and Antonio Ventriglio

Abstract *Aim*: This study investigated the association between Internet Addition (IA) and fatigue, sleep disturbance, depression, and life style factors among school children. *Subjects and Methods*: A cross-sectional survey was conducted on 1366 intermediate and secondary school students in Istanbul. The study included socio-demographic, Internet Addiction (IA) test, Fatigue Scale, Epworth Sleepiness Scale [ESS], depression, anxiety and stress (DASS21), test lifestyle and dietary habits. *Results*: The overall prevalence of IA among school children was 22.8%. The IA score was significantly higher among males (53.7%) than in females (46.3%; $p = 0.028$), significantly associated with school performance ($p = 0.006$) and family income ($p = 0.024$). Also, students with IA reported significantly less hours of sleep (6.21 ± 0.87 vs. 6.51 ± 1.29; $p < 0.001$), higher internet use (hours spent: 3.82 ± 1.64 vs. 3.03 ± 1.64; $p < 0.001$), when compared to the healthy ones. The rates of internet use among students with IA were: gratifying site (17.0% vs. 12.2%; $p = 0.028$), browsed games (37.3% vs. 30.1%; $p = 0.017$), chat sites (28.6% vs. 22.7%; $p = 0.013$), emails (54.3% vs. 62.7%; $p = 0.008$), and online research (60.8% vs. 693%; $p = 0.005$). A multivariate stepwise regression has shown that a significantly larger proportion of IA students reported higher internet use than normal subjects (as expected; $p < 0.001$), more fatigue physical symptoms ($p < 0.001$), higher Epworth

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sleepiness score ($p < 0.001$), more stress ($p < 0.001$), more fatigue mental symptom ($p < 0.001$) and sleeping hours ($p = 0.008$), more depression($p = 0.009$), headache ($p = 0.018$), dizziness ($p = 0.024$), anxiety ($p = 0.047$), and game playing problems were significantly associated to their internet addiction ($p = 0.050$). *Conclusion* This study suggested the evidence that IA children are vulnerable to physical and mental issues related to their problematic internet use.

Keywords Internet addiction · Video game · Sleep · Fatigue · Depression · Stress

Introduction

Over the past two decades, Internet Addiction (IA) has become a major public health problem globally ([1–5]; Morris and Gore 2010). The phenomenon of internet addiction has been described in the 1990s by Young in the US and Griffiths in the UK ([6]; Young 1998). Many authors pointed out that the use of internet websites, especially those aimed to online socializing, may affect human behaviour and lead to pathological adjustment ([1, 3–5, 7–9]. Also, children and adolescents, in particular, show increasing rates of internet-games addiction as well as adults may report alcohol, drug addiction or gambling [3, 4, 10–12].

It is of interest that previous studies have shown that IA is often comorbid with psychiatric symptoms, including depression ([1, 8, 13, 14], sleeping disorders [2], irregular dietary habits, physical inactivity [1, 2, 15], and social anxiety ([13, 16]).

This study aimed to investigate the relationship between IA and depression, anxiety, stress, fatigue and life style factors among school children.

Subjects and Methods

This is a cross-sectional study based on a survey conducted among intermediate and secondary school students in Istanbul, aged 13–18 years old. A total of 1837 students were approached using a multistage stratified sampling and 1366 students (74.3%) joined the survey from February to June 2018. The consent for this study were obtained from all participants, as well as the parents or legal guardians of any minor included in the study. Istanbul Medipol University, International School of Medicine, Institutional Review Board (IRB) committee approved the verbal consent procedures for the research entitled: ''Lifestyle factors, depression, anxiety and stress related to the internet addiction among school children" conducted in Istanbul.

Assessment

Depression Anxiety Stress Scale (DASS-21)

The 21-item DASS has been used to assess depression, anxiety and stress [17]. Each item reports four scores ranging from 0 to 3. The total score of DASS-21 is obtained by summing each sub-scale score and multiplying the total by two. In the present study the reliability coefficients for depression, anxiety and stress were $\alpha = 0.84$, 0.82, and 0.77, respectively, and the overall Cronbach's α was 0.85. The following cut-off values, as recommended by the manual, have been considered: depression was categorized as normal (0–9), mild (10–20), and severe ($\geq$21); anxiety was categorized as normal (0–7), mild (8–14), and severe ($\geq$15), and stress was categorized as normal (0–14), mild (15–25), and severe ($\geq$26). Nonetheless, these scores are not considered to be diagnostic. In the present study the reliability coefficients of the subscales were all valid for depression ($\alpha = 0.85$), anxiety ($\alpha = 0.80$) and stress ($\alpha = 0.78$). Cronbach alpha internal consistency coefficient for the whole scale was computed as $\alpha = 0.82$.

Young's Internet Addiction Test (IAT)

Young's Internet Addiction Test (IAT, Young 1998) consisted of 20 Likert scales designed to identify students with mild, moderate or severe internet addiction. The maximum total score is 100; then, 49 is considered as normal, 50–79 problematic, and 80–100 as significantly problematic (Young 1998). In this study, students scoring $\geq$ 50 were considered as reporting an IA. The Young's Internet Addiction Test total Cronbach alpha coefficient was found to be 0.850.

Fatigue Measure and Design of Scale

Fatigue is defined as a condition characterized by a lessened capacity for work and reduced efficiency of accomplishment, usually accompanied by a feeling of weariness and tiredness. The Fatigue scale is composed by 14 statements including 1–8 items for physical fatigue and 9–14 items for mental fatigue [18]. The total Cronbach alpha coefficient was found to be 0.834.

The Epworth Sleepiness Scale

The Epworth Sleepiness Scale ([19]; ESS) is an useful tool to identify symptoms of daytime sleepiness based on a questionnaire including eight items scoring from 0 to 24 (scores $\geq$ 11 are considered as abnormal). The ESS questionnaire had a high level of internal consistency as measured by Cronbach's alpha (> or = 0.871). The test–retest intraclass correlation coefficient was r = 0.80 (95% confidence interval: 0.65–0.90).

Statistical Methods

The Chi-square and Fisher's exact tests (two-tailed) were performed to test for differences in proportions of categorical variables between two or more groups. Student-t test was used to ascertain the significance of differences between mean values of two continuous variables. A multivariate stepwise regression model was conducted to identify the best predictors for internet addiction as potential confounders. The level $p < 0.05$ was considered as the cut-off value for significance.

Results

The prevalence of IA among school children was found to be 22.8% and significant differences between IA and healthy students were found regarding the gender ($p = 0.028$), school performance ($p = 0.006$), father educational level ($p = 0.039$), mother educational level ($p = 0.011$) and family income ($p = 0.024$) (Table 12.1).

Table 12.2 shows the lifestyle, diet habits and co-morbid factors of the surveyed students. Those with IA reported significantly less hours of sleep (6.21 ± 0.87vs. 6.51 ± 1.26; $p < 0.001$), higher time spent in using internet (4.66 ± 1.64 vs. 3.99 ± 1.69; $p < 0.001$). A significantly larger proportion of IA students, if compared to healthy ones, reported headaches ($p = 0.007$), double vision ($p = 0.014$), eye hurt ($p = 0.005$), eye tired ($p = 0.002$), Epworth sleeping ($p = 0.005$), less sport activity ($p = 0.039$), less physical activity ($p = 0.033$) and poor dieting ($p = 0.041$). Also, the IA students reported a significantly high number of sumptoms related to fatigue, as well as more hours spent into internet use ($p < 0.001$) than healthy ones (Table 12.3).

Table 12.4 shows comparisons between different internet activities among internet addicted and healthy students. Students with IA most frequently accessed to gratifying site (17.0% vs. 12.2%; $p = 0.028$), browsed games (37.3% vs. 30.1%; $p = 0.017$), chat sites (28.6% vs. 22.7%; $p = 0.013$), emails (54.3% vs. 62.7%; $p = 0.008$), and online research (60.8% vs. 693%; $p = 0.005$).

Table 12.5 shows the multivariate stepwise linear regression analysis to determine the potential predictors (risk factors) of the internet addiction. The results show that the time spent into internet use ($p < 0.001$), physical fatigue ($p < 0.001$), Epworth sleepiness ($p < 0.001$), stress ($p < 0.001$), mental fatigue ($p < 0.001$), reduced sleeping hours ($p = 0.008$), depression ($p = 0.009$), headache ($p = 0.018$), dizziness ($p = 0.024$), anxiety ($p = 0.047$), and game playing problem ($p = 0.050$), all were significantly associated with the IA (internet addiction) as potential leading predictors.

Table 12.1 Socio-demographics characteristic among Internet Addict and Healthy students (N = 1366)

Variable	IA N = 311	Healthy N = 1055	*p-value
Sex			
Male	167(53.7)	492(48.6)	0.028
Female	144(46.3)	563(53.4)	
Age in years			
< 15 years	89 (28.6)	354(33.6)	0.102
> 15 years	222(71.4)	701(66.4)	
Level of education			
Intermediate	184(59.2)	630(59.7)	0.862
Secondary	127(40.8)	425(40.3)	
Rank of studentin school exam			
Very Good	87(28.0)	266(25.2)	0.006
Good	105(33.8)	436(41.3)	
Average	96(32.9)	316(30.0)	
Poor	23(7.4)	37(3.5)	
Father's education			
Primary	80(25.7)	210(19.9)	0.039
Intermediate	56(18.9)	181(17.2)	
Secondary	81(26.0)	355(33.6)	
University	94(30.2)	309(29.3)	
Father's occupation			
Not working/retired	20(6.4)	63(6.0)	0.835
Sedentary/professional	116(37.3)	408(38.7)	
Manual/clerk	81(26.0)	287(27.2.3)	
Business man	22(7.1)	91(8.6)	
Government Officer	72(23.2)	206(19.5)	
Mother's education			
Primary	70(22.5)	202(19.1)	0.011
Intermediate	55(17.7)	241(22.8)	
Secondary	112(36.0)	303(28.8)	
University	74(23.8)	309(29.3)	
Mother's occupation			
House wife	110(35.4)	368(36.6)	0.446
Sedentary/professional	68(21.9)	257(24.4)	
Manual/clerk	73(23.5)	205(19.4)	
Business woman	60(19.3)	207(19.6)	

(continued)

Table 12.1 (continued)

Variable	IA N = 311	Healthy N = 1055	*p-value
Family income			
Low	83(26.7)	369(35.0)	0.024
Medium	127(40.8)	378(35.8)	
High	101(32.5)	308(29.2)	

IA = Internet Addiction, Problematic internet use, *Normal* = None Addiction or Non-problematic internet use

Discussion

The present study has shown that IA is associated with depression, anxiety and stress symptoms, as well as sleeping disturbance, co-morbid factors and poor lifestyle habits among the surveyed students. It is of note that Turkish students reported a very high prevalence of IA (22.8%) when compared to other samples surveyed in Qatar (19.8%; [1]), Taiwan (13.8%), Australia (10.2%) and in Tunisia (18%; [20]). One similar study from Korea [13] reported that IA is associated with lack of sleep, fatigue symptoms and frequent consumption of fast food. These characteristic were also described in previous studies [1, 2]. Another large study conducted in six Asian countries using the IAT with a cutoff score of 70, reported the following prevalence rates: South Korea (14%), China (19%), Hong Kong (35%), Malaysia (37.5%), Japan (48%), and Philippines (51%) [21].

Sleep problems are usually considered negative outcomes or complications of internet addiction, which was supported by many assessment tools of internet addiction and reported studies [1, 2, 7, 22–24], Furthermore, Chen and Gau [23] reported the temporal relationship of early and middle insomnia predicting internet addiction, which subsequently predicts disturbed circadian rhythm. Meanwhile, an excessive internet use leads to irregular sleep patterns due to an irregular bedtime schedule [10]. Some features of sleep problems and IA may result in difficulties interpreting their relationships and always should be treated with caution in future studies. Since, there are a wide range of prevalence rates of internet addiction reported by previous studies.

Lam and Peng [25], in China, and Ha et al. [26], in Korea, have confirmed a significant association between the IA and depression, which is consistent with the current findings. It has been reported that the risk of depression for IA students using the Internet is two and a half times higher than in not-addicted ones. More recently, Cherif et al. reported that the prevalence of Internet Addiction in Tunisia was 18.05% and daily average time of Internet use was 4.5 h. This trend has been confirmed by the present findings as well as earlier studies ([1, 15, 27]. Further, the documented association between the time spent on the internet and the access to gratifying sites, games, chat and facebook, has been confirmed in the literature [1, 15, 27, 28]. Similar results were reported in a Taiwanese study [29] and a Dutch study among adolescents [30]. Also, the present study reported that the misuse or abuse of internet is more

Table 12.2 The characteristics of lifestyle, dietary and co-morbid factors among Internet Addict and Healthy students (N = 1366)

Variables	IA N = 311	Healthy N = 1055	*p*-value[a] significance
Age (Mean ± SD)	15.65 ± 166	15.44 ± 1.74	0.062
Number of bed rooms at your house	4.13 ± 1.44	3.59 ± 1.29	0.001
Number of people are living at Home	5.94 ± 1.98	5.78 ± 1.93	0.762
Hours internet use	4.66 ± 1.64	3.99 ± 1.67	0.001
Sleeping no of hours	6.21 ± 0.87	6.51 ± 1.26	0.001
Medical-Co-morbid Factors[b]	*n (%)*	*n (%)*	
Headaches	131(42.1)	357(33.8)	0.007
Blurred vision	63(20.3)	225(21.3	0.684
Double vision	40(12.9)	87(8.2)	0.014
Eyes hurt	71(22.8)	168(15.9	0.005
Eye tire	72(23.2)	155(15.6)	0.002
Dizziness	82(26.4)	229(21.7)	0.085
Any problem with hearing	77(24.8)	231(21.9)	0.288
The epworth sleepiness scale			
Normal	76(24.4)	303(28.7)	
Mild	66(21.2)	298(28.2)	0.005
Moderate	72(23.2)	202(19.1)	
Severe	97(31.2)	252(23.9)	
Physical activities			
Sport activities	104(33.4)	421(39.9)	0.039
Physical activity	124(39.9)	493(46.7)	0.033
Dieting information and frequency of eating fast food[a]			
Daily	37(11.9)	89(8.4)	0.041
Weekly	72(23.2)	206(19.6)	
Monthly	94(30.2)	396(37.5)	
Occasionally	108(34.7)	364(34.5)	

[a]*Two sided p values based on student t test*
[b]Not adding to 100%

frequent among school students consistently with previous evidences from Tunisia [20].

It is worth to note that the Internet addiction is becoming a serious public health problem, and the incidence has been increased significantly over period in a study conducted in Japan. By Kawabe et al. [31] which reported that in two cross-sectional studies over a 4-year period, the mean IA score was significantly higher in survey conducted at the 2018 survey-II (36.0 ± 15.2) than performed in 2014 survey-I (32.4 ± 13.6) ($P < 0.001$).

Table 12.3 Physical and mental symptoms of Fatigue among Internet Addiction and Healthy students (N = 1366)

14—Item fatigue scale	IA N = 311	Healthy StudentsN = 1055	*p* value
Physical symptoms			
1. Do you have problem with tiredness?	2.67 ± 1.22	2.20 ± 1.62	0.001
2. Do you need to rest more?	2.80 ± 1.66	2.35 ± 1.02	0.001
3. Do you feel sleepy or drowsy?	2.79 ± 1.10	2.22 ± 1.13	0.001
4 Do you have problems starting things?	2.78 ± 1.27	2.46 ± 1.23	0.001
5. Do you start things without difficulty but get weak as you go on?	2.61 ± 1.11	2.44 ± 1.18	0.022
6. Are you lacking in energy?	3.06 ± 1.07	2.64 ± 1.20	0.001
7. Do you have less strength in your muscle?	2.84 ± 1.11	2.36 ± 1.19	0.001
8. Do you feel weak?	2.87 ± 1.08	2.59 ± 1.24	0.001
Mental symptoms			
9. Do you have difficulty concentrating?	2.68 ± 1.08	2.31 ± 1.00	0.001
10. Do you have problems thinking clearly	2.88 ± 1.09	2.51 ± 1.17	0.001
11. Do you make lips of the tongue when speaking?	2.47 ± 1.18	2.40 ± 1.18	0.347
12. Do you fin it more difficult to find the correct word?	2.74 ± 1.22	2.61 ± 1.23	0.099
13. How is your memory?	2.66 ± 1.14	2.35 ± 1.15	0.001
14. Have you lot interest in the thing s you used to do	2.66 ± 1.18	2.46 ± 1.13	0.008

This study may show several limitations. First, although it examined the associations between the internet use and health issues, the study—design was cross-sectional and no conclusions can be made concerning issues of causality. In addition, the questionnaire for depression, anxiety, stress, and sleeping disturbances were self-reported, with no diagnostical purposes. Fatigue also relied on participants' subjective self-report. Third the generalization to clinical populations may be limited because there are not structured clinical interviews and the participants are not from a clinical population.

Table 12.4 Internet Addiction (IAT), depression anxiety and stress (DASS21), fatigue, sleep problems (EES) and internet activities among Internet Addict and Healthy students (N = 1366)

Variables	IA N = 311	Healthy N = 1055	[a]*p*-value significance
IAT score (mean ± SD)	74.25 ± 4.60	55.07 ± 6.83	0.001
Depression (mean ± SD)	27.25 ± 6.80	20.79 ± 6.78	0.001
Anxiety	27.25 ± 6.80	20.79 ± 6.78	0.001
Stress	27.25 ± 6.80	20.79 ± 6.78	0.001
Fatigue physical symptoms	22.42 ± 3.00	19.26 ± 3.33	0.001
Fatigue mental symptoms	16.07 ± 3.10	14.64 ± 3.20	0.001
Epworth sleepiness score	13.34 ± 4.70	12.49 ± 4.37	0.003
Internet activities[b]	n (%)	n (%)	
Gratifying site	53(17.0)	129(12.2)	0.028
Games	116(37.3)	318(30.1)	0.017
Chat	89(28.6)	240(22.7)	0.033
Face book	61(19.6)	178(16.9)	0.263
Instagram	38(12.2)	147(13.9)	0.497
email	169(54.3)	662(62.7)	0.008
Research	189(60.8)	731(69.3)	0.005
Gambling	19(6.1)	67(6.4)	0.878
eBay shopping	35(11.3)	138(13.1)	0.395

[a]Two sided p values based on Chi square for categorical and student t test for the quantitative variables

[b]Multiple option and multivariable choice, percentages do not add to 100%

Conclusion

This study suggested the evidence that IA children are vulnerable to physical and mental issues related to their problematic internet use. Fatigue as well as stress, anxiety, depression, sleeping disturbances, and lifestyle risk factors should be carefully considered among school children and properly treated alongside their pathological internet addiction.

Table 12.5 Multivariate stepwise regression analysis for predictors of Internet Addiction affect (N = 1366)

Independent variables	B	Standard error	Beta	t test value	*p*-value significance
Internet use in hours	−0.032	0.006	−0.129	−5.240	0.0001
Fatigue physical symptoms	−0.041	0.003	−0.348	−13.695	0.001
Epworth sleepiness score	−0.008	0.002	−0.086	−3.450	0.001
Stress	−0.042	0.003	−0.353	−13.674	0.001
Fatigue mental symptoms	−0.013	0.003	−0.097	−3.758	0.001
Sleeping in hours	0.024	0.009	0.068	2.656	0.008
Depression	−0.035	0.013	−0.064	−2.615	0.009
Headache	0.052	0.022	0.059	2.369	0.018
Dizziness	0.057	0.025	0.057	2.265	0.024
Anxiety	−0.017	0.008	−0.049	−1.984	0.047
Games playing	0.049	0.022	0.048	1.947	0.050

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Chapter 13
The New Life After Confinement: Why Should We Increasingly Maintain an Active and Healthy Lifestyle?

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Abstract The whole world has faced the deleterious effects of the pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus). Covid-19, a disease characterized by the presence of this coronavirus, imposed several restrictions to reduce its contagion. One of its impacts was social isolation. However, to combat the covid-19, a new problem was established: the adoption of inactive and sedentary lifestyle habits. Moreover, it should be considered that new pandemics are expected to emerge, and new periods of confinement would be needed. Therefore, as much as our routines return, our activities should be thought differently with more care and with some moments of social isolation for the "new normal" era. Therefore, the usual recommendations on the practice of physical activity, reduction of sedentary behaviors, and adequate sleep time have never been more important: in addition to facing the coronavirus and the next pathogenic microorganisms that may affect the world population. It is also essential to promote the metabolic, physical and mental health of the entire population. Thus, this chapter aims to provide the literature review on changes in the population's lifestyle due to the covid-19 pandemic, and to underscore the importance of adopting healthy lifestyle habits during and after the period of social isolation.

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Introduction

At the beginning of 2020, the World Health Organization declared a global pandemic for the new virus, called "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2). The covid-19 pandemic has promoted consequences and implications in several aspects of the general population [1]. As the main strategies to mitigate its spread, the government of several countries imposed quarantine, social/physical distance, and isolation to prevent the spread of the disease, given that the development of vaccination is still in its early stages [2].

During this covid-19 pandemic period, social activities were discouraged and exercise facilities were closed. Thus, the population's eating patterns have undergone changes resulting in decreased consumption of healthy foods [3]. In this regard, these changes in the social and food environment may have contributed to negative effects on the population's health [4]. In addition, prolonged periods of physical inactivity and sedentary behavior caused concern at the public health level, especially through the association with cardiovascular diseases [5, 6]. In this sense, it is important to consider covid-19 as a syndemic, which is characterized by a set of health problems, in which the burden of the disease in a context of social and economic disparity exacerbates the adverse effects of each disease in isolation. Syndemics contribute to the increased susceptibility of an individual to aggravate your state of health, as it presents biological and social interactions [7].

These lifestyle changes, including sleep alteration, also are related to increased anxiety, depression, and stress symptoms, therefore, it's important to encourage the population to follow healthy habits, through health promotion strategies, to keep up physically active even during the pandemic [8]. In this sense, the realization of physical activities in the house has been encouraged, using the technology [5, 6]. To minimize the effects caused by the pandemic and as changes that occurred without a daily population, the basic guideline is "healthy waiting" in lifestyle. It includes social or physical detachment, hygiene measures, physical exercise practices, stress reduction, as well as smoking and alcohol restriction [9].

Thus, this chapter aims to review the literature on changes in the population's lifestyle due to the covid-19 pandemic and the importance of healthy habits adoption during and after the period of social isolation of the confinement.

Lifestyle in the "New Normal" Era: Implications for the Population's Health

In current circumstances, when the covid-19 pandemic has caused a sudden and stressful situation that restricted outdoor activities and implied long stays at home resulted in a radical change in lifestyle behaviors, such as physical activity (PA), eating habits, mental health, sleep quality, and related aspects [10–12]. This blockage

of routine work and leisure activities can result in emotional changes, such as anxiety or boredom, which are directly associated with greater energy consumption and macronutrient quantities [13], linked not only to confinement but also to the economic decline, as well as the situation of uncertainty and the increase of physical inactivity [14].

In long term, quarantine can result in an increase in lifestyle-related diseases, especially cardiovascular diseases and obesity [15]. It is associated with unhealthy behaviors, such as physical inactivity, sedentary behavior, and inappropriate eating habits [16–18]. Also, unhealthy movement behaviors increased considerably and are associated with poorer mental health during the covid-19 pandemic [12].

A review of the evidence related to quarantine periods highlighted that it can result in negative psychological effects, including symptoms of post-traumatic stress, confusion, and anger. Therefore, the psychological impact of the quarantine is broad, substantial, and can be long-lasting [19]. In addition, symptoms of anxiety, depression, and self-reported stress are common psychological reactions to the covid-19 pandemic and may be associated with sleep disorders [20].

In this segment, social isolation can also be associated with dysfunctional psychoneuroendocrine-immune interactions, which in turn can contribute to the development or worsening of psychiatric disorders. Isolated healthy individuals, including children and adolescents, may also suffer from the effects of social isolation. Therefore, it is important to emphasize that special attention must be paid to these aspects to prevent a "new generation" of groups in which the risk of developing mental disorders, such as anxiety or depression, can be increased [21].

Furthermore, the adverse situation at work, waiting for negative economic consequences, perception of worsening health and eating habits, as well as concern about the potential for covid-19 infection were associated with depressive symptoms during confinement [22]. The most vulnerable populations are more likely to manifest covid-19 due to the context of social and economic disparity, as in underdeveloped countries. Thus, when considering covid-19 as a public health problem, the view related to educational, environmental, and social aspects is broadened [7].

In this sense, changes in the natural daily life manifest the need to reorganize the activities that make up the daily routine, proposing a lifestyle in the "new normal" and preventing bad habits acquired in this period, from becoming permanent. Therefore, it is recommended that the population maintain the habit of performing physical activity regularly, even in the home, which is a strategy for a healthy life during this period [23].

Physical Activity and Attention to Food: Key Points for Maintaining Health

The population's life has been severely affected due to social isolation, mainly eating habits and active daily behaviors. These factors were influenced by the fact of staying at home, which includes limitation of practicing physical activities outdoors or in

gyms, longer time spent in the digital environment (home office), and stock of food due to shopping restrictions and limited supply of some products. Also, the work routine during isolation or social detachment can result in boredom and anxiety contributing to a greater food intake [13].

Limited access to food purchases in commercial establishments can contribute to the low consumption of healthy foods, such as fruits and vegetables, and to the increased consumption of ultra-processed foods that have a high content of sugars, salt, and fat. In addition, the psychological and emotional consequences caused during the period of social detachment increase the chances of developing eating disorders [24, 25]. The experiences of negative emotions of self-isolation make people more likely to eat more, as they seek bonuses and rewards physiologically related to food intake, as a way to escape monotony and cancel out signs of satiety and hunger. In contrast, some negative experiences can also lead to restricted food consumption due to stress that can simulate sensations associated with satiety [26–28].

Besides, this stress would increase with the news about covid-19 released by the media, further increasing the desire for food. Foods rich in carbohydrates can reduce stress as they have a positive effect on mood by stimulating serotonin production [29]. However, this effect that causes excessive consumption of these foods increases the risk of developing cardiovascular disease and obesity, also influencing a chronic inflammation capable of increasing the risk of complications for the covid-19 disease [30, 31].

Research related to the life habits of the population, in general, has been identifying different changes in this pandemic period, and in some cases the unfavorable nutritional behaviors were to compensate for boredom or anxiety, causing weight gain. There was also an increase in alcohol intake and sedentary behaviors and decreased levels of physical activity [32]. However, other individuals seem to have healthier habits in this period, observing more favorable nutritional behaviors, such as an increase in home-cooked meals and an increase and/or maintenance of physical activity [32–34].

In this sense, the global recommendations of physical activity recommends that children and adolescents realize 60 min per day, adults and older adults practice 30 min per day in moderate-intensity [35]. In this way, to preserve physical and mental health in periods of social detachment such as this, it is suggested that the general population maintain healthy lifestyle habits such as regular physical exercise, associated with occupations such as cooking, dancing, making crafts, gardening and other leisure activities that can be adapted to these situations [32, 36].

Also, the government and/or academic agencies must promote actions that would encourage healthy diet adoption and active lifestyle presenting the importance of maintaining good habits for the health of the population during the pandemic [37]. Given the unhealthy lifestyle adopted by the population during the pandemic, it becomes essential to monitor these habits [38]. Therefore, physical education professionals have innovated using the technology to realize class through online platforms, considering a form of keeping the individual active physically during the pandemic [5, 6].

Sleep and Sedentary Behaviors: How Does It Relate to Health?

The time spent on sedentary behaviors [39, 40] and sleep disorders [41] consist of health problems associated with inadequate lifestyle and the presence of diverse diseases. Before the covid-19 pandemic, actions were already being taken to adopt active behaviors to reduce the development of related diseases [42, 43]. However, during the pandemic with restrictions imposed by social distancing, it was observed that there was an increase in the presence of these inadequate behaviors, causing major preoccupations in the level of public health [44].

In this sense, it is important to recognize the deleterious effects that the long time spent in sedentary behaviors and the inadequate duration and quality of sleep cause health of the population, including cardiometabolic disorders, such as obesity, diabetes mellitus, hypertension, and dyslipidemias [45–47], in which the high time on the front of the screen increases the chances of the individuals presented health negatives changes [40, 47]. Besides, short and long sleep duration and poor quality are risks for cardiometabolic health [41, 48]. The screen time [49] and sleep duration and quality [50] also are associated with mental diseases, like depression, stress, and anxiety [51]. Also, high time in sedentary behaviors is associated with poor sleep quality and symptoms of anxiety and insomnia [52, 53].

Thus, it is suggested that to reduce sedentary behaviors and to improve sleep duration. It is important to involve parents/guardians, policymakers, healthcare providers, educators, and community organizations in the implementation of actions that encourage the individuals to spend less time in sedentary behaviors and to improve sleep duration and quality [51]. The recommendations of sedentary behaviors and sleep duration for children and adolescents are less than 2 h per day of screen time [54], and 9–11 h for children 6–13 years and 8–10 h per day of sleep for adolescents 14–17 years [55]. For adults, it is recommended to stay less than 3 h a day in front of the screen [56, 57] and to have 7–9 h of sleep for adults, and 7–8 h for older adults [55].

Strategies for reducing sedentary behaviors to encourage adopting active behaviors, such as physical activities and best duration/quality of sleep are recommended to realized activities, such as guided gentle yoga, meditation recordings, or listening to relaxing music/sounds [51]. Also, in the current situation, strategies that can contribute to the healthy sleep of the population may be online interventions that include self-help programs for sleep, stress management, relaxation practices, stimulus control, sleep hygiene, and mindfulness training [58], as well as avoiding the exposure to electronics during the night and seeking to relax one hour before bedtime. Sun exposure is also recommended for regulating sleep–wake and circadian rhythms, wake up at the same time every day and keep regularly scheduled activities, like sleep, meals, work, and social contacts are fundamental that entrainment of one's biological clock [59].

To minimize the effects of deleteriousness of the inadequate lifestyle in mental health, it is recommended to realize a multicomponent intervention [50, 60]. Thus,

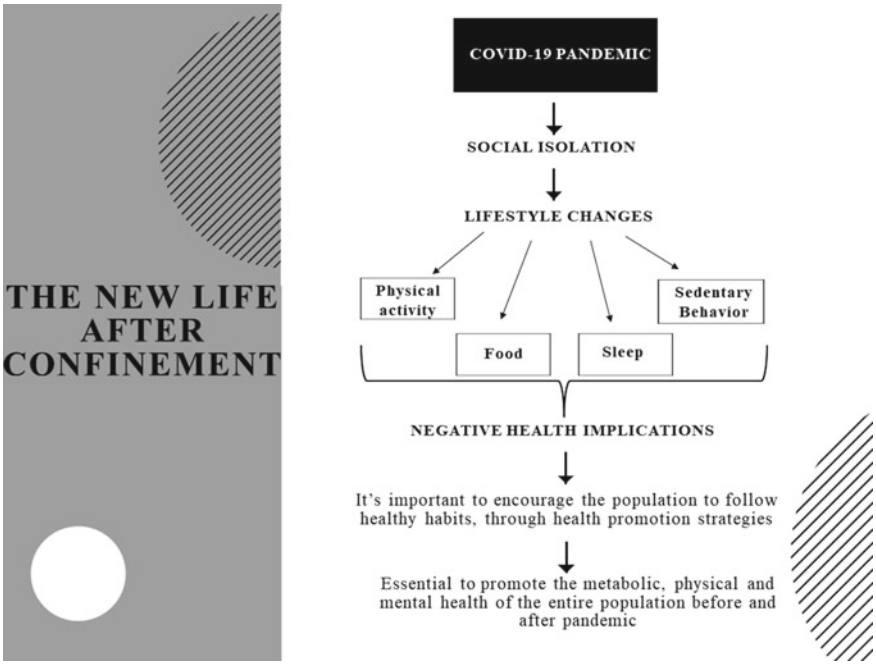

Fig. 13.1 Graphical abstract

actions that promote adopting an active lifestyle should be initiated during social distancing to avoid the development and progress of the disease during and after a pandemic [23] (Fig. 13.1).

Final Considerations

Recommendations for adopting an active and healthy lifestyle, which were already important before the covid-19 pandemic, should be reinforced during social isolation. Also, we must consider that new pandemics may affect the world population and we must be aware of the deleterious effects of a sedentary and inactive lifestyle, especially for their metabolic, physical, and mental health aspects. Therefore, in an era of uncertainty, we must foresee actions, taking the recommended precautions at times when social isolation is essential, but keeping the focus on promoting active and healthy lifestyle habits in all age groups. In addition, public policies aimed at preventing chronic non-communicable diseases are encouraged, as well as actions focused on actives lifestyles that involve all populations with greater vulnerability to covid-19 infection.

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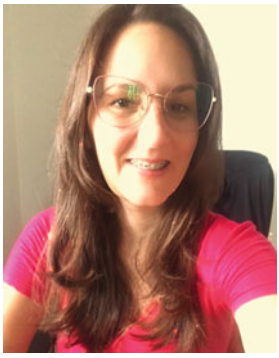

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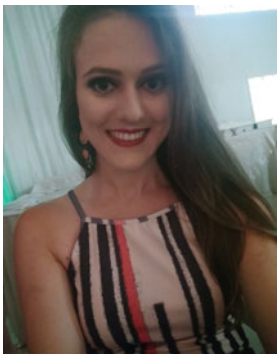

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She has been awarded several times at national and provincial levels. She has several papers and chapter related to Primordial Prevention of Non-Communicable Disease. She had more than 400 presentations in congresses, and has been the international guest speaker in some of them. She has served as WHO temporary adviser for prevention and control of childhood obesity and for primary prevention of non-communicable diseases.

Chapter 14
Exposure to Endocrine Disrupting Chemicals, Part of Lifestyle Factors Related to Growth Disorders in Childhood and Chronic Diseases in Adulthood

Zeinab Hemati, Motahar Heidari-Beni, and Roya Kelishadi

Abstract Lifestyle factors are of major determinants of environmental exposures. Endocrine signaling pathways can be disrupted by environmental chemicals. Endocrine function is established in early life and any endocrine disorders with adverse consequences can develop later in life. Evidence has shown that endocrine disrupting chemicals (EDCs) with hormone like activity have adverse health consequences in both genders. EDCs may act as obesogens and affect appetite, weight and energy balance, regulation of metabolism as well as the development of adipose tissue. In addition, EDCs may interfere in pubertal development, time of puberty and influence on pubertal height growth. It is documented that exposure to EDCs is associated with short femur length. One of the phenotypes of overweight and obesity is elevated body mass index with normal weight in presence of short stature. This type of excess weight can be considered as one of the health concern for the pediatric age group. EDCs can disturb the normal function of estrogen receptors and endogenous androgen action. They change transcription and release of growth hormone, insulin like growth factor-I (IGF-I) concentration, and in turn they would affect the normal growth of height and weight. Such growth disorders might have long-term impact on the development of chronic diseases in adulthood. Understanding the effect of EDCs on hormone functions and growth development can be important for primordial prevention of non-communicable diseases related to obesity. Following a healthy lifestyle can reduce the exposure to EDCs and their adverse effects. This chapter aims to summarize the current literature on the effect of EDCs on excess weight related to short stature and growth hormone.

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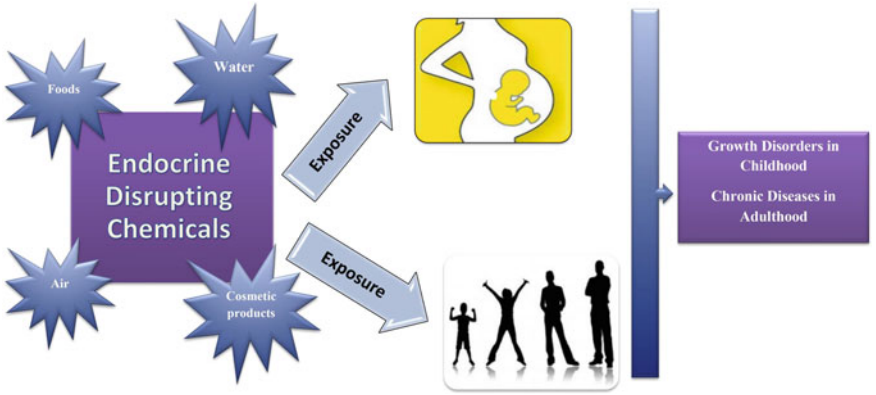
Graphical Abstract



Keywords Endocrine disruptors · Overweight · Obesity · Body height · Growth hormone · Non-communicable diseases

Introduction

Environmental pollution influences on human health. Several of these pollutants are known as endocrine disrupting chemicals (EDCs) that are the main concern of public health. Some EDCs are natural, while synthetic varieties can be found in pesticides, electronics, personal care products and cosmetics. They can also be found as additives or contaminants in food. There is an increasing concern that low-level exposure to EDCs may have adverse effects on health especially during fetal, neonatal, and childhood development. They have widespread effects on human health and lead to increase the prevalence of non-communicable diseases (NCDs) and at the final step morbidity and mortality [1–3].

Environmental pollution remains the greatest problem of the world that threatens human life and leads to morbidity and mortality. Generally, environmental pollution is higher in middle- and low-income countries than in developed countries. Being unaware about the effects of pollutants on the environment causes the production of harmful and deleterious substances. For instance, deforestation, burning of bushes, dumping of agricultural and household wastes in water bodies, use of chemicals in harvesting aquatic animals, and inappropriate disposal of electronic wastes. All of them contribute to air, land, and water pollution [1]. Increase of population growth and human activities leads to detrimental damage in the environment and the ecosystem including aquatic and terrestrial animals and microorganisms [2, 3].

Nowadays, lifestyle has changed and people prefer luxury houses and apartments. The energy that is consumed by this group of people has increased because of television, air conditioners, refrigerators at their homes. The main reason of energy deficiency in the countries is the inefficient use of energy. According to studies, income

level has a powerful impact on lifestyle changes including diet, use of private cars, and living conditions. These lifestyle changes lead to serious environmental pollution [3, 4].

Environmental pollution influences on human health. Several of these pollutants are known as endocrine disrupting chemicals (EDCs) that are the main concern of public health. They have widespread effects on human health and lead to increase the prevalence of non-communicable diseases (NCDs) and at the final step morbidity and mortality. It has been documented that EDCs are produced by plastics, plasticizers, pesticides, e-waste, food additives that are positively associated with increasing the prevalence of NCDs [5, 6].

Endocrine Disrupting Chemicals and Body Size Measurements

Obesity is one of the health challenges at global level and its prevalence has increased worldwide over the past decades. Different factors including genetic, lifestyle (physical activity and diet), behavioural and environmental factors affect excess weight [5, 6]. It is documented that endocrine disrupting chemicals (EDCs) affect the development and progression of obesity [7]. Humans can be exposed to EDCs through ingestion, inhalation, dermal contact and during intrauterine progress through placenta. EDCs as environmental obesogens enhance adipogenesis and fat accumulation by activating nuclear receptor signaling pathways and promote adipogenesis, reduced insulin sensitivity and decreased thermogenic capacity. In addition, obesogens increase the susceptibility for developing obesity later in life [8, 9]. EDCs bind to nuclear hormone receptors including estrogen receptors, thyroid hormone receptor and glucocorticoid receptor and influence on endogenous hormones metabolism or transport. Sex steroids regulate size and number of adipocyte and influence disposition and remodeling of adipose tissue [10, 11]. Estrogen receptors influence on glucose transport, glycolysis, mitochondrial activity and lipid metabolism that are correlated with metabolic disorders and obesity. EDCs are considered as metabolic disruptor and may enhance obesity [12, 13].

Experimental studies showed gestational exposure to estrogenic substances including bisphenol A (BPA) might increase body weight and adipocyte number [14, 15]. EDCs disrupt the activation of peroxisome proliferator-activated receptors (PPARα, PPARδ, and PPARγ) that are nuclear hormone receptors and regulate lipid and glucose metabolism.

Some EDCs including phthalates and perfluoroalkyl substances are PPARγ agonists and may change maternal–fetal insulin and/or glucose and increase proliferation of adipocytes and waist circumference [16–18].

EDCs influence on glucocorticoid pathway and steroid hormones production. Excess intrauterine glucocorticoid exposure disrupts satiety signal sent to

the hypothalamic pituitary-adrenal (HPA) axis. Phthalates increase glucocorticoid crossing from the mother to fetus and have obesogenic activity [19].

Children and adolescents are more sensitive to environmental contaminants than adults. They are in rapid growth and development. Thus, pediatric age groups are extensively exposed to EDCs including phthalates and the exposure levels are higher than adults [20, 21].

However, epidemiological studies that assess the relationship between postnatal phthalate exposures and obesity or body size measurements are rare.

Endocrine Disrupting Chemicals and Obesity Related to Height Growth

It is documented that one of the important biological marker for the effect of environmental contaminants in the fetal period is height growth in early life. Evidence has shown that growth restriction in early life was correlated with short stature and poor health outcomes in adulthood.

Early nutrition, socioeconomic factors and psychosocial stress determine height growth in childhood. Epidemiologic studies showed that environmental contaminants impact on birth outcomes and postnatal growth.

Some studies investigated the impact of intrauterine exposure to environmental contaminants including toxic heavy metals and reported the mechanism of placental transfer and effect on fetuses and children's health [22]. Early exposure to lead and mercury was associated with infant growth and development. Findings showed that prenatal exposure to polycyclic aromatic hydrocarbons (PAH) had negative impacts on birth outcomes and neurodevelopment [23, 24]. Several studies assessed the relationship between EDCs and pubertal age, sex steroid and gonadotropin concentrations in both genders. Study on adolescent showed a negative association between serum cadmium and testosterone and estradiol concentrations [25]. Exposure to pesticides leads to decrease serum testosterone and Luteinizing hormone (LH) values and increase serum estradiol levels. Thus, postnatal childhood exposures could interfere with normal functioning of the hypothalamic pituitary gonadal (HPG) axis.

Cohort studies showed prenatal polychlorinated biphenyls (PCB) and polychlorinated dibenzo-furans (PCDFs) exposure were associated with lower serum LH, follicle-stimulating hormone (FSH) and testosterone concentrations. These studies suggested that environmental contaminants with endocrine active properties may disrupt the HPG axis and lead to changes of serum hormone concentration and alteration in pubertal timing [26].

EDCs affect growth hormone (GH)/IGF-I axis and they have antiandrogenic properties. Prenatal exposure to phthalate (DEHP) and di-n-butylphthalate (DBP) may influence on IGF-I mRNA in reproductive tissues and decrease the levels of IGF-I [27].

It is documented that urinary concentrations of phthalate metabolites affect growth rate and anthropometric measurements including height, weight, and body surface area. Animal studies showed negative relationship between prenatal phthalate exposure and birth weight and weight gain in future. Phthalate exposure has adverse effects on thyroid hormones, growth factors and childhood growth. However, there are inconsistence findings [28]. Studies showed that urinary phthalate levels were negatively associated with body size or height gain [29]. Small children may be exposed to higher levels of phthalates associated to their body size. Food intake and body surface per kilogram of body weight are higher in small children [30].

Bisphenol A (BPA) is used in various consumer products and in the production of polycarbonate plastics and epoxy resins. It has harmful effects especially on children's health that are more vulnerable to environmental exposures. One of the important markers of the overall health status is linear growth in children.

BPA can affect several physiological receptors such as oestrogen receptor α and androgen receptor. BPA has oestrogenic and antiandrogenic effects so it can disrupt pubertal development. There are not enough findings about the effect of BPA on longitudinal bone growth in puberty [31–33].

Epidemiologic studies showed the association between BPA and obesity and related disorders among adults and children. Study on 2836 children ages 6–18 years showed significant association between increasing BPA and waist to height ratio (WHR) [34]. However, another study did not show any association and further studies are needed [35]. Significant association between BPA and WHR was found only in girl. Studies showed inverse association between prenatal BPA and childhood obesity among girls. These findings support a role for estrogen signaling pathways in the effects of BPA on obesity. There are sex differences in estrogen receptor expression and sex can change the relationship between BPA and obesity [35, 36]. Study on 2664 children and adolescents showed positive association between BPA and obesity only in boys [37]. A study among 1326 Chinese school-age children demonstrated that higher level of urinary BPA was associated with higher risk of overweight only in girls [38]. Study on Italian adults showed that urinary BPA level was significantly correlated with waist circumference but not with BMI [39]. The differences between the results are due to study designs and populations or approaches used to evaluate EDCs level.

Study among 890 Swedish people did not show any significant association between serum BPA levels and adipose tissue [40]. Study among non-Hispanic black children (6–19 years) showed that low molecular weight phthalates correlated with increasing the risk of overweight and obesity. However, these results did not find in other race and ethnic groups [41]. Cross-sectional study among Chinese children (8–15 years) reported that low and high molecular weight phthalates, and bis (2-ethylhexyl) phthalate (DEHP) were positively correlated with BMI and waist circumference [42].

These controversial findings increase interesting questions about potential differences in genders, susceptibility and life stage.

In most studies, BMI has been used rather than direct measurement of body composition. Weight disorders are defined based on age-sex-specific BMI percentiles

or z-scores in children and BMI in adults. However, BMI cannot distinguish between fat mass and lean body mass and it cannot define fat distribution. Fat distribution is a useful predictor for all-cause mortality and health outcomes. BMI may misclassify body weight status in comparison with body composition measurements [43].

There are few studies related to EDCs and height. Among the few studies that have assessed the correlation between EDCs and height, some of them showed high molecular weight phthalate and/or DEHP metabolite categories were associated with shorter stature [41, 44, 45]. One study showed negative association between MEHP and BMI/waist circumference in adolescent girls [46].

Growing up Healthy Study in East Harlem, New York showed reverse association between mono-n-butyl phthalate (MBP) and mono-3-carboxypropyl phthalate (MCPP) with height only in girls. MBP and MCPP are low and high molecular weight phthalate metabolite, respectively. Study on Danish children (ages 4–9 years) reported negative association between DEHP and height [47].

According to studies, phthalates affect some receptors including peroxisome-proliferator activated receptors that are involved in the metabolism of protein, fat and carbohydrates. Phthalates change metabolic processes and increasing adipogenesis and adipose tissue [48].

Anti-androgenic properties were reported for some phthalates. They decrease testosterone levels, insulin-like growth factor-1 (IGF-1) and thyroid function and increase estrogen/androgen ratio. These effects may explain some of the sex differences that were reported previously. Some studies reported adverse effect of phthalates on thyroid hormone, IGF-1, and height in children [41, 47].

Study on 1239 girls, aged 6–8 years demonstrated reverse association between high molecular weight phthalates and height only among normal weight girls. This study showed higher levels of IGF-1 in obese children and higher height velocity during the pre-pubertal years in comparison with normal weight children. According to these findings, adverse effect of high molecular weight phthalates on height can be blunted by increasing body weight [49].

One Study evaluated exposure to pollutants in the second trimester of pregnancy and measured heavy metals in cord blood. Findings of nine years follow-up period showed that height growth significantly correlated with prenatal airborne polycyclic aromatic hydrocarbons (PAH) levels higher than 35 ng/m^3. Other epidemiologic studies confirmed harmful effect of PAH on birth outcomes and children's height [50, 51]. Another study showed that fetal PAH exposure was significantly correlated with decreased birth length by 0.5 cm/ln-unit of PAH airborne level [52].

The exact mechanism of the effects of PAH on birth outcomes is still unclear. However, PAH may has apoptosis effects after DNA damage, anti-estrogenic effects and may bind to human aryl hydrocarbon receptor to induce P450 enzymes to receptors for placental growth factors, and at the final step decrease exchange of oxygen and nutrients [53].

Mercury, like PAH, is a global toxicant in the human environment that pass through the blood–brain barrier and placenta. Prenatal exposure to mercury influences on height gain in childhood. Mercury disrupts central nervous system and

endocrine system including hypothalamic–pituitary–gonad, thyroid, and adrenal axes and affects maturation, development and body growth [53].

Studies showed that exposure to EDCs might lead to growth disorders during childhood and increase the incidence of NCDs in adulthood. The period of rapid growth and development in childhood influences on future health and quality of life in adulthood. Optimization of growth and development in childhood is important for prevention of disease in later life. Having a life course approach to NCDs leads to prevention of disorders at early stages. The evidence points to the importance of healthy life style and avoid exposure to pollutants for decrease the prevalence of NCDs [52, 53].

EDCs could increase the risk of NCDs during developmental phases of life especially in childhood or fetal period because children are more susceptible to environmental chemical exposures. However, additional studies are needed to identify mechanisms of EDCs effects on child health and determine the association between early life EDCs exposure and childhood health outcomes. Simultaneous efforts should continue to replace these compounds with other plasticizers and to reduce the exposure to these chemicals.

In summary, specific EDCs disturb the hemostasis of thyroid and growth hormone levels and at the final step affect body size measurements particularly in pediatric age groups.

Lifestyle changes lead to inefficient use of energy and increase environmental pollution. Urbanization, high levels of vehicle emissions and westernized lifestyle are correlated to increase in environmental pollution.

Early exposure to EDCs leads to height growth slower at later age. Additional longitudinal studies with multiple repeated EDCs measurements throughout childhood and adolescence are necessary to confirm these findings.

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She has been awarded several times at national and provincial levels. She has several papers and chapter related to Primordial Prevention of Non-Communicable Disease. She had more than 400 presentations in congresses, and has been the international guest speaker in some of them. She has served as

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