CHILDHOOD OBESITY

Interrelation among Diet Quality, Lifestyle Factors, and Obesity

ROWAEDH BAWAKED

Childhood Obesity: Interrelation among Diet Quality, Lifestyle Factors, and Obesity

Rowaedh Ahmed Bawaked

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DIRECTOR

Dr. Helmut Schröder

CARDIOVASCULAR RISK AND NUTRITION RESEARCH GROUP (CARIN), EPIDEMIOLOGY AND PUBLIC HEALTH RESEARCH PROGRAM, IMIM (HOSPITAL DEL MAR MEDICAL RESEARCH INSTITUTE), BARCELONA

To my parents, my siblings,
my husband and my kids

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Rowaedh Ahmed Bawaked

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ABSTRACT

Childhood obesity remains a major public health burden. Understanding and identifying the complex relationship between diet quality and lifestyle factors is important for pediatric weight control and obesity prevention strategies. The main scope of the present thesis was to determine the complex correlation between obesogenic behaviors, diet quality and overweight and obesity in Spanish youth. This thesis is based on data from three studies: i) Enkid, a representative national study of the Spanish population aged 2 to 24 years, n=3534; ii) POIBC, a community based childhood obesity program, including children aged 8 to 10 years, n = 2250. The study was carried out during two school years, 2012 to 2014, with an average follow-up of 15 months; iii) INMA, population-based birth cohort, including children aged 4 years with an average follow-up of 3 years, n= 1480. We found that total flavonoids intake **(paper I),** meal frequency and physical activity were positively associated with adherence to the Mediterranean diet **(paper III),** while screen time and external eating were associated with poor adherence **(paper III)**. A high maternal level of education increased the odds of a child adhering to the Mediterranean diet **(paper III)**.We used the diet inflammatory index to explore the association between the inflammatory potential of diet and diet quality **(paper II).** We concluded that a healthy diet, characterized by high adherence to the Mediterranean diet, high total dietary antioxidant capacity, or low energy density, was linked to greater anti-inflammatory potential of the diet. Finally, in two studies we evaluated the impact of lifestyle obesogenic behaviors on childhood obesity and abdominal obesity. In the first study **(paper IV),** we defined four

obesogenic behaviors as: <1 hour physical activity/day; ≥2 hour/day of screen time; skipping breakfast; and having fewer than 3 meals/day. We found that the concurrence of obesogenic behaviors (high screen time, skipping breakfast, and low physical activity and meal frequency) increased risk of higher Body mass index (BMI) z-scores, higher waist-to-height ratio (WHtR) and higher odds of overweight and abdominal obesity. In addition, high maternal and parental education was associated with decreasing presence of obesogenic behaviors. In the second study **(paper V),** we constructed a child healthy lifestyle score (CHLS) comprising five target lifestyle behaviors that were either favorable (extracurricular physical activity, sleep time, plant-based food consumption) or unfavorable (television time and consumption of ultra-processed foods).We found that CHLS at age 4 years was negatively associated with BMI, waist circumference (WC) z-scores and higher odds of overweight and obesity at age 7 years. This PhD research shows an increase in BMI among Spanish children with low physical activity, meal frequency, and sleep time, and high TV time and ultra-processed food intake. The findings also highlight an inverse relationship between waist circumference and physical activity, sleep time, whereas skipping breakfast, and TV time were positively associated with WC z-score and increased the odds of abdominal obesity. Maternal educational level determines children's diet quality, and the presence of obesity lifestyle factors. Our finding highlights several key modifiable behaviors that can be targeted by policies and interventions to improve diet quality and to tackle the childhood obesity problem in Spain.

RESUMEN

Introducción

La obesidad infantil sigue siendo una importante carga para la salud pública. Comprender e identificar la compleja relación entre la calidad de la dieta y los factores del estilo de vida es importante para el control de peso en los niños y las estrategias de prevención de la obesidad infantil. Esta tesis se basa en datos de tres estudios: i) Enkid, un estudio nacional representativo de la población española de 2 a 24 años, n = 3534; ii) POIBC, un programa de obesidad infantil basado en la comunidad, que incluye niños de 8 a 10 años, n = 2250. El estudio se llevó a cabo durante dos años escolares, desde 2012 a 2014, con un seguimiento promedio de 15 meses; iii) INMA, cohorte de nacimiento de base poblacional con niños de 4 años i un seguimiento promedio de 3 años, n = 1.480. Encontramos que la ingesta total de flavonoides, la frecuencia de las comidas y la actividad física se asociaron positivamente con la adherencia a la dieta mediterránea, mientras que el tiempo de pantalla y la alimentación externa se asociaron con una mala adherencia. Un alto nivel de educación materna fue asociado a una más alta adherencia a la dieta mediterránea en los niños. Usamos el índice inflamatorio de la dieta para explorar la asociación entre el potencial inflamatorio de la dieta y su calidad. Concluimos que una dieta saludable, caracterizada por una alta adherencia a la dieta mediterránea, una alta capacidad antioxidante, o una baja densidad energética, estaba relacionada con un mayor potencial antiinflamatorio de la dieta. Finalmente, en dos estudios, evaluamos el impacto de los comportamientos obesogénicos en el estilo de vida sobre la obesidad infantil y la obesidad abdominal. En el primer estudio

(artículo IV), definimos cuatro comportamientos obesogénicos como: <1 hora de actividad física/día; ≥2 horas/día de tiempo de pantalla; saltarse el desayuno; y tener menos de 3 comidas/día. Encontramos que la concurrencia de conductas obesogénicas (tiempo de pantalla alto, saltarse el desayuno, o baja actividad física y frecuencia de comidas) aumentaba el riesgo de tener un z-score de IMC más alto, un mayor relación cintura-altura y mayores probabilidades de sobrepeso y obesidad abdominal. Además, un alto nivel de educación materna y parental se asoció con la disminución de la presencia de comportamientos obesogénicos. En el segundo estudio (artículo V), construimos un score de estilo de vida saludable infantil (CHLS, por sus siglas en inglés) que comprendía cinco comportamientos de estilo de vida de interés que eran favorables (actividad física extracurricular, tiempo de sueño, consumo de alimentos basados en plantas) o desfavorables (tiempo de televisión y consumo de alimentos ultraprocesados). Encontramos que el CHLS a los 4 años de edad se asoció negativamente con el IMC, z-score de cintura, y mayores probabilidades de sobrepeso y obesidad a los 7 años. In Conclusión, Esta investigación de doctorado demuestra un aumento en el IMC entre los niños españoles con baja actividad física, frecuencia de comidas y tiempo de sueño, y un alto tiempo de TV y consumo de alimentos ultraprocesados. Los hallazgos también resaltan una relación inversa entre la circunferencia de la cintura y la actividad física i el tiempo de sueño. En contraste con esto, observamos lo opuesto a saltarse el desayuno y el tiempo de televisión. El nivel educativo materno está asociado con la calidad de la dieta de los niños y la presencia de factores

de estilo de vida obesos. Nuestros resultados destaca varios comportamientos modificables clave que pueden ser objeto de políticas e

intervenciones para mejorar la calidad de la dieta, con el objetivo de abordar el problema de la obesidad infantil en España.

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Chapter 1

GENERAL INTRODUCTION

وَكُلُوا وَاشْرَبُوا وَلَا تُسْرِفُوا

سورة الأعراف – الآية 31

“It is easier to build strong children than to repair broken men.”

Frederick Douglass, abolitionist and statesman

(1889 –1891)

1.3 Statement of the Problem

Obesity has been recognized as a major public health problem worldwide. The prevalence of obesity has increased significantly during the last three decades in all age groups, especially in children and adolescents, in both developed and developing countries[1,2]. In some developing countries obesity even coexist with under-nutrition [3].

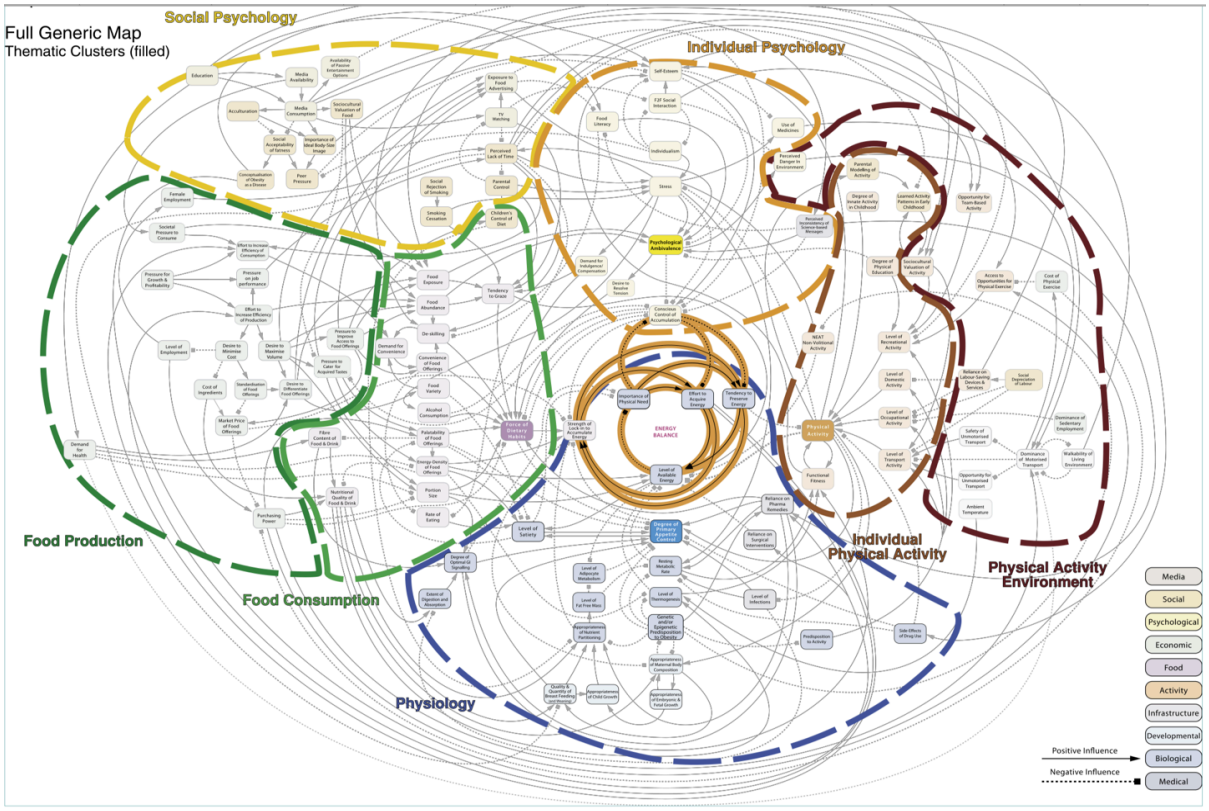
Childhood obesity is a growing problem, and obese and overweight children and adolescents are more likely to be obese in adulthood[4]. Obese children are more susceptible to cardiovascular and metabolic diseases later in life[5,6]. This poses a significant threat to public health, as obesity is associated with a number of short- and long-term health consequences, such as hypertension, diabetes mellitus, hyperlipidemia, atherosclerosis and cardiovascular diseases (CVD), which have wider social and economic costs[7].

Obesity is caused by a persistent positive energy balance where energy intake is greater than energy output [6]. However, obesity is a complex problem. Multiple etiological factors are responsible for the increased susceptibility to obesity [7]. Childhood obesity can occur as a result of children's **internal biological factors,** such as metabolism or genetics, **specific external environment** factors including, diet quality and quantity, physical activity, and lifestyle behaviors, and **general external environmental factors,** including the home, parental education level, maternal BMI, socioeconomic status, and urban environment (Figure 1.1)[8-12].

Healthy eating and lifestyle behaviors are essential for the health and well-being of children. A poor quality diet is related to cardiovascular risk factors in children, such as obesity [8] and high blood lipids [9]. It is a result of high intake of energy-dense foods and low intake of fruits and vegetables. Plant-based foods are a key element of high diet quality and a source of polyphenols such as flavonoids [10]. High intake of fruits and vegetables decrease pro-inflammatory biomarkers and is related to low oxidative stress and inflammation [11].

A vital approach to tackling obesity among children is to improve modifiable behaviors that create a lasting healthy lifestyle into adulthood. As risk factors for childhood obesity can interact, lifestyle choices and behaviors can be influenced by the obesogenic environment, which encourages excessive energy intake and low levels of physical activity [13]. Despite increasing emphasis on childhood obesity as a major public health issue, there are limited data on diet quality among children, their intake of flavonoids and ultra-processed food, and the inflammatory potential of their diet, especially in Spain. Other factors that contribute to obesity include sleep quality and duration[12,13]. The impact of obesogenic behaviors on childhood overweight and obesity has traditionally been measured individually. As a result, little is known about the cumulative effect of these behaviors on risk of overweight and obesity during childhood.

Figure 1.1 The full obesity system map with thematic clusters



Variables are represented by boxes; positive causal relationships are represented by solid arrows and negative relationships by dotted lines. The central engine is highlighted in orange at the center of the map.Source: Obesity system map, UK Government office of science Fore*sight* Tackling Obesities: Future Choices – Project report. http://systemsthinkersanonymous.com.gridhosted.co.uk/wp-content/uploads/2016/10/tackling-obesities-future-choices-report.pdf

Chapter 2

OBJECTIVES

2.1 Aim: To determine the complex correlation between obesogenic behaviors, diet quality and overweight and obesity in Spanish youth.

2.2 Objectives

1. To estimate the intake of total flavonoids and flavonoids subclasses, and describe major sources of flavonoids among Spanish children, adolescents and young adults.

2. To examine the association between flavonoid intake and diet quality (measured in terms of adherence to the Mediterranean diet) among Spanish children, adolescents and young adults.

3. To evaluate the inflammatory potential of the diet, measured by the Dietary inflammatory index (DII), and to explore its association with diet quality indicators in a representative sample of Spanish youth.

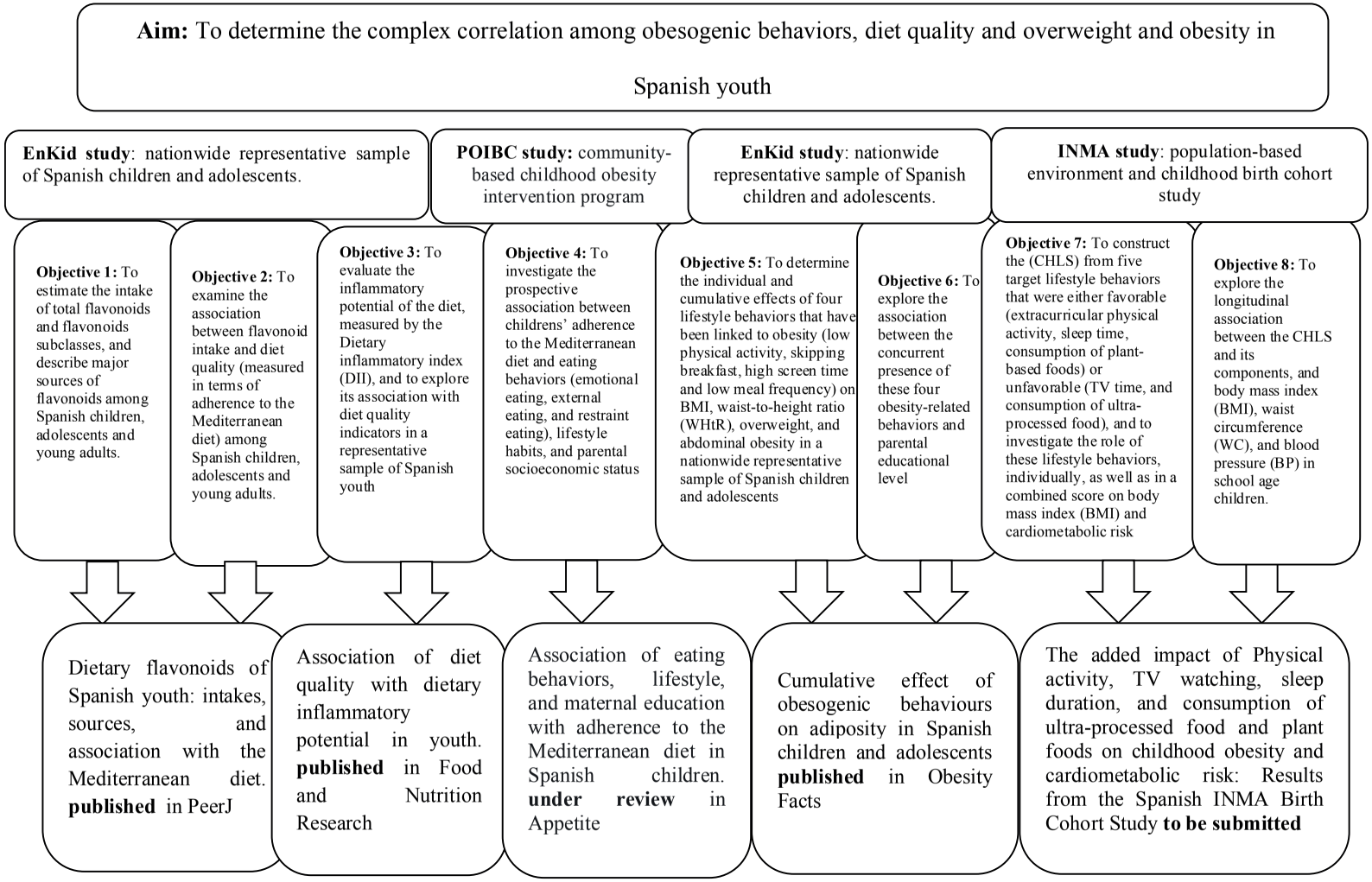
4. To investigate the prospective association between children's adherence to the Mediterranean diet and eating behaviors (**emotional eating, external eating, and restraint eating)**, lifestyle habits, and parental socioeconomic status.

5. To determine the individual and cumulative effects of four lifestyle behaviors that have been linked to obesity (low physical activity, skipping breakfast, high screen time and low meal frequency) on BMI, waist-to-height ratio (WHtR), overweight, and abdominal obesity in a nationwide representative sample of Spanish children and adolescents.

6. To explore the association between the concurrent presence of these four obesity-related behaviors and parental educational level.

7. To construct the Child Healthy Life Style Score (CHLS) from five target lifestyle behaviors that were either favorable (extracurricular physical activity, sleep time, consumption of plant-based foods) or unfavorable (TV time, and consumption of ultra-processed food) in preventing obesity, and to investigate the role of these lifestyle behaviors, individually, as well as in a combined score on body mass index (BMI) and cardiometabolic risk factors in preschool age children (4 years old).

8. To explore the longitudinal association between the CHLS and its components, and body mass index (BMI), waist circumference (WC), and blood pressure (BP) in school age children.


Aim: To determine the complex correlation among obesogenic behaviors, diet quality and overweight and obesity in Spanish youth
EnKid study: nationwide representative sample of Spanish children and adolescents.
POIBC study: community-based childhood obesity intervention program
EnKid study: nationwide representative sample of Spanish children and adolescents.
INMA study: population-based environment and childhood birth cohort study
Objective 1: To estimate the intake of total flavonoids and flavonoids subclasses, and describe major sources of flavonoids among Spanish children, adolescents and young adults.
Objective 2: To examine the association between flavonoid intake and diet quality (measured in terms of adherence to the Mediterranean diet) among Spanish children, adolescents and young adults.
Objective 3: To evaluate the inflammatory potential of the diet, measured by the Dietary inflammatory index (DII), and to explore its association with diet quality indicators in a representative sample of Spanish youth
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Objective 6: To explore the association between the concurrent presence of these four obesity-related behaviors and parental educational level
Objective 7: To construct the (CHLS) from five target lifestyle behaviors that were either favorable (extracurricular physical activity, sleep time, consumption of plant-based foods) or unfavorable (TV time, and consumption of ultra-processed food), and to investigate the role of these lifestyle behaviors, individually, as well as in a combined score on body mass index (BMI) and cardiometabolic risk
Objective 8: To explore the longitudinal association between the CHLS and its components, and body mass index (BMI), waist circumference (WC), and blood pressure (BP) in school age children.
Dietary flavonoids of Spanish youth: intakes, sources, and association with the Mediterranean diet. published in PeerJ
Association of diet quality with dietary inflammatory potential in youth. published in Food and Nutrition Research
Association of eating behaviors, lifestyle, and maternal education with adherence to the Mediterranean diet in Spanish children. under review in Appetite
Cumulative effect of obesogenic behaviours on adiposity in Spanish children and adolescents published in Obesity Facts
The added impact of Physical activity, TV watching, sleep duration, and consumption of ultra-processed food and plant foods on childhood obesity and cardiometabolic risk: Results from the Spanish INMA Birth Cohort Study to be submitted

CHAPTER 3

BACKGROUND

3.1 Definition of childhood obesity

Obesity is defined as the anomalous accumulation of excess fat characterized by different health risks[14]. Childhood obesity poses a major health issue in modern society. Its prevalence is rapidly increasing and has led to the emergence of other obesity-related comorbidities that put a strain on the healthcare system and the health status of affected individuals[6]. Studies have shown a relationship between childhood obesity and its appearance in adulthood, especially for severe cases and those with a strong family history[15]. Half of obese children become obese adults[15].

Childhood obesity is a serious global health issue in modern society that greatly affects low and middle income countries, especially in the urban environment[14]. In 2016, the percentage of obese children under the age of 5 was estimated to be over 41 million globally. A huge number of overweight children develop non-communicable illnesses at a very young age, including hypertension, cardiovascular illnesses, and diabetes, so prevention of childhood obesity is an important public health priority[16].

3.1.1 Measuring and assessing overweight and obesity

It is difficult to measure and assess overweight and childhood obesity because of the complex nature of developing a single index measurement for children. The reason for this is that their bodies go through different physiological changes of growth deviations [17]. We can measure childhood adiposity using a number of methods. Highly accurate methods to estimate adiposity include underwater weighing,

total body water, energy X-ray absorptiometry and total body electrical conductivity. However, these methods are not generally feasible in an epidemiological or public health research setting due to their high cost and complexity[18,19]. In the research setting, Body Mass Index (BMI), waist circumference, skinfold thickness and bioelectrical impedance measurements are more frequently used indicators of child weight status.

BMI is calculated simply from the child's weight and height, and is therefore the most commonly used measure for both children and adults. Obesity is diagnosed and body fat is measured differently in children versus adults because fat changes with age and it is complex to interpret BMI during phases of rapid growth. A BMI measurement affirming that a child is obese at a specific age may be different or normal at another age. Consequently, this makes it necessary to compare BMI levels among children at the same age and sex, and to determine the differences.

3.2.1 Body Mass Index

Body Mass Index (BMI) is defined as the measure of a person's weight in kilograms divided by the square of their height in meters. A child's normal BMI differs depending on their sex and age, and is commonly referred to as BMI-for-age[20]. The most significant and accurate method for measuring obesity in children is to use BMI-for-age percentiles, since the weight of a child cannot be measured exclusively using BMI. The measurement process involves calculating BMI and plotting it on the BMI-for-age percentile graph to identify the weight status of the child[21]. If the BMI level of a child is higher than the 85%

of values for other children of the same sex and age, then the child is described as overweight. If their BMI level is higher than 95% of values for other children of the same age and sex, then they are regarded as obese.

Various national and international percentile reference data sets are available for calculating childhood overweight and obesity. However, it is important to note that different reference values produce different estimates [22]. An example of a national reference data set is the US Centre for Disease Control and Prevention (CDC) national reference charts and the UK national reference charts for BMI. The International Obesity Task Force (IOTF) chart is based on data from six nationally representative populations for children aged 2 to 18 years. The IOTF BMI cut-offs are used by researchers and policy makers for international comparisons[23].

The WHO child growth reference data are widely used internationally and is based on cross-sectional data collected from six countries - Ghana, India, Norway, Brazil, Oman, and North America [24]. For this thesis, we computed the BMI z-score using age- and sex-specific reference values from the World Health Organization (WHO) [17]. Overweight and obesity were defined as BMI > 1 SD < 2 SD and BMI >2 SD, respectively, from the mean of the WHO reference population.

Table 3.1 Children weight status according to body mass index (BMI)

WHO international classification	Percentiles BMI for age and sex
Under weight	Less than the 5th percentile
Normal	5th percentile to less than the 85th percentile
Overweight	85th to less than the 95th percentile
Obese	95th percentile or greater

3.2 Epidemiology of childhood obesity

3.2.1 Prevalence and trends in Europe

The global prevalence of childhood obesity in society is increasing at a very alarming rate. Childhood obesity is a well-known health concern in Europe, and has been estimated the by the World Health Organization (WHO) to be about 20% [25]. There are notable differences in this estimate according to country and socio-economic status. One of the chief contributors to our knowledge of the epidemiology of childhood obesity is the regular implementation of research to establish its incidence, and to evaluate the success of policies implemented to address this problem. The statistics represent the cultural, socio-economic, and demographic composition of the population. The patterns of childhood obesity in Europe vary between geographical regions, time, sex, and age. One of the biggest challenges

its uneven distributed, with Southern European countries showing the highest prevalence. The prevalence also varies within countries. In Spain, 38.6% of children and adolescents are overweight or obese [26], while 16.5% have abdominal obesity[27].

The WHO European Childhood Obesity Surveillance Initiative (COSI) was introduced as a uniform methodology to measure trends in obesity and overweight among children in Europe. COSI has provided national representative data from different regions for over 10 years. According to COSI, the prevalence of obesity among children aged 7-8 years ranges from 15% in Norway to 36% in Italy. There has been a continued increase in the prevalence of the disease in all countries evaluated, which shows that all children are at risk regardless of their geographical location[28]. Socio-economic factors are chief determinants of the quality of diet and nutrition available for specific.

The collaboration between WHO and COSI provides critical data that informs the creation and implementation of policies that respond to this health challenge. The 2018 COSI report showed that, despite high rates of childhood obesity in southern Europe, the prevalence has leveled off, or even slightly decreased in many of these countries since the previous report [29].

3.2.2 Prevalence and trends in the United States of America

The National Survey of Children's Health (NSCH) in the US has been used to estimate childhood obesity rates in different states, and the geographical variations linked to behavioral and social factors. 17% of children and teenagers in the US are considered obese and the

prevalence has continued to increase across different socioeconomic, age, sex, and ethnic groups[30].

It is essential to note that incidence also varies in states with the highest rates, such as the Southeastern states. Mississippi has the highest prevalence, while the Western states have the lowest. The incidence of childhood obesity increases significantly with decreasing levels of income, reduced access to parks or sidewalks, increasing time spent on computers and social networks, and increasing time watching television. Hispanic and Black children have a higher prevalence of obesity that White children (21.9% and 19.5%, respectively). Historically, the incidence of childhood obesity among children aged 6 to 10 years in the US has tripled over time. Nonetheless, few studies report a decrease in obesity among preschool children in the US[31], and a recent study by AC Skinner et al. found an increase in overweight and obesity for all childrens' ages, and a sharp increase among preschool age children compared to previous prevalence cycle[32]. Variations in the incidence of childhood obesity in the US are recorded based on race, gender, age, and geographical regions[33]. These cases are also associated with obesity in adulthood and different chronic illnesses that are characterized by increased costs.

In a recent simulation study, US obesity trends will continue and more than 57% of today's youth will be obese by age 35 years [34]. Of those predicted to have obesity as adults, half will develop it as children[34].

3.2.3 Worldwide prevalence and trends

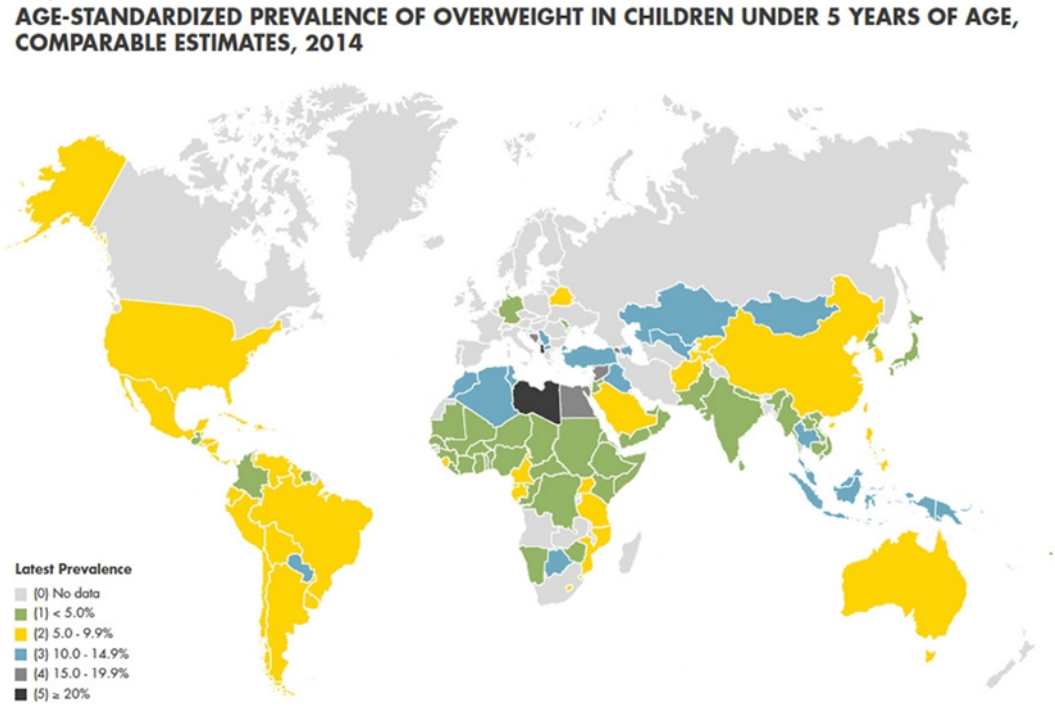
The global prevalence of childhood obesity has reached pandemic levels in various nations. A recent report by the commission to end childhood obesity, estimated that over 41 million children under 5 years of age are overweight or obese[35]. Almost half of all overweight children under five live in Asia and one quarter live in Africa. Overall, in 2016 over 340 million children and adolescents were overweight or obese[35]. Figure 2.1 shows the global prevalence of overweight among children under 5 years of age. Figure 2.2 shows the prevalence of overweight for each WHO region and World Bank income group.

On average, 20% of children in the US are overweight, 10% are obese, and 70% of these children will grow up to become obese adults, especially those who are obese during their teenage years[36]. In Europe, the prevalence is higher in Mediterranean countries than in Scandinavia, although it has been increasing in both regions. The highest incidence of childhood obesity are observed in developed nations, although developing nations such as the Middle East also have high rates[37]. Girls are more likely than boys to become overweight, in both developing and developed countries.

A WHO study, *Global prevalence and trends in overweight and obesity among preschool children,* included 450 cross-sectional national surveys from 144 countries. The WHO standard median was used to define the proportions, and a linear mixed-effects model was used to estimate the rates of the affected children. The results show that, in 2010, an estimated 40 million children were overweight or obese, and 91 million were at risk of being overweight. The worldwide incidence increased from 4% in 1990 to 7% in 2010. The prevalence was lower in Asia than

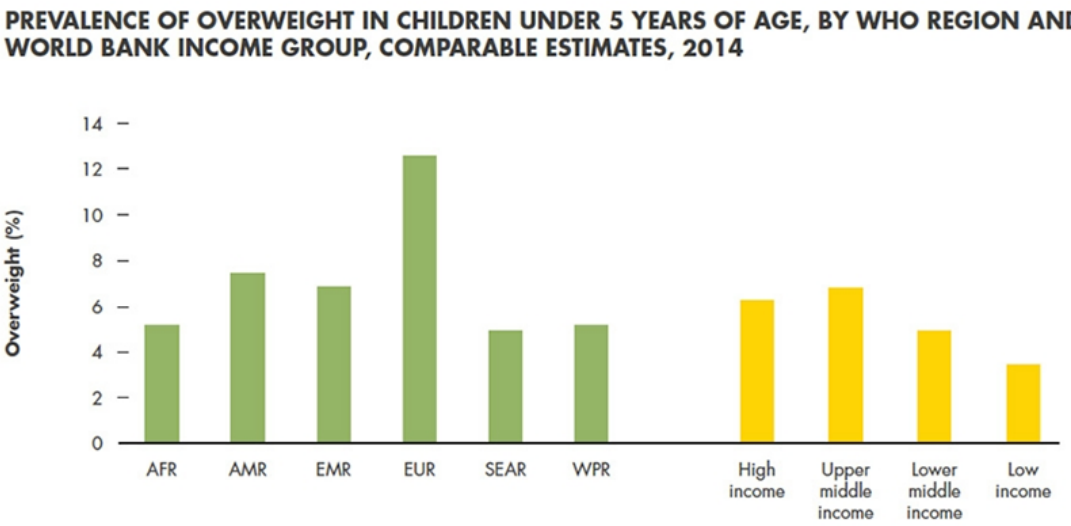
in Africa, although the number of affected children was higher in Asia [37]. A high percentage of overweight or obese children live in developing nations and there has been an increase of more than 30% in the rate of childhood obesity in these countries compared to developed nations. Studies show that if these trends continue, there will be an estimated 70 million obsese children by 2025[38].

Figure 3.1



Source: Tracking tool http://www.who.int/nutrition/trackingtool

Figure 3.2



AFR=African Region, AMR=Region of Americas, SEAR=South-East Asia Region, EUR=European Region, EMR=Eastern Mediterranean Region, WPR=Western Paci c Region. Source: UNICEF, WHO, The World Bank. Joint Child Malnutrition Estimates. (UNICEF, New York; WHO, Geneva; The World Bank, Washington, DC; 2015).

3.3 **Etiology and contributors to childhood obesity**

There are several common and widely acknowledged determinants of childhood obesity, include genetics, birth weight, environmental factors, and lifestyle factors such as dietary patterns, sedentary behavior, physical activity, and sleep duration [39,40]. A family history of obesity and genetics factors are predictors of childhood obesity. Family influence is a vital factor in children's susceptibility to weight gain. Parental obesity has been shown by several studies to be a main risk factor for childhood obesity[41–43]. Moreover, children from some ethnic origins are more likely to be affected by obesity than their peers

[44]. However, in this thesis, we will focus on modifiable lifestyle factors that contribute to childhood obesity.

Behavioral characteristics such as a sedentary lifestyle, low physical activity, low sleeping time, high intake of ultra-processed foods and low intake of vegetables and fruits are known contributors to obesity among children[45–48]. In modern society childhood obesity can be linked to the change in activity behaviors over time from outside play to enclosed sources of leisure, such as the internet, computer games, and watching television[49]. Research confirms that a decrease in sedentary time is directly linked to reduced health risks among children and teens aged 5 to 17 years [50]. Watching television for an extended period of time leads to increased BMI. Skipping breakfast, which is considered to be the most essential meal of the day, leads to increased food intake during lunch, and studies show that individuals who tend to skip breakfast have a higher chance of developing obesity[51]. Moreover, lower eating frequency is associated with higher body weight in children and adolescents, mainly in boys [52]. All of these behaviors are prevalent in young populations [53–56], and all have been linked to an increased risk of childhood obesity. Therefore, they are defined as obesogenic behaviors [53–56].

The recent report of the Commission on Ending Childhood Obesity (ECHO) proposed six key areas that target the risk factors contributing to childhood obesity (figure 3.2)

Figure 3.2 Six-key areas of action

3.3.1 Dietary intake and food patterns

Diet has been studied extensively because of its contribution to rising rates of obesity. Several studies have been carried out to assess the relationship between dietary components and obesity. Westernized dietary patterns (increased consumption of high-density food coupled with consumption of nutrient-poor food) contributes to the development of obesity in children. The consumption of sweets, desserts, processed

meats, fries, and sugar-sweetened beverages is a chief factor in the high incidence of obesity among children. They have low nutritional value and low fiber intake, and provide higher total energy, saturated fat , and total fat intakes.[57]. Studies among Brazilian adolescents have demonstrated an association between consumption of these foods and risk of metabolic syndrome [58] and obesity [59]. Ultra-processed food is also linked to the high intake of refine carbohydrates, free sugars, total and saturated fats, and energy density [60].

In contrast, high intake of plant-based foods such as fruits and vegetables is an essential characteristic of high diet quality and is linked to favorable health outcomes [61,62]. Plant-based diets are low in energy density and high in fiber and water, which may increase satiety and resting energy expenditure. A recent study examined the association between intake of fruit, vegetables, legumes and nuts and BMI in 201,871 adolescents (13–14 years) and 77,243 children (6–7 years) from various countries. Adolescents who consumed fruit, vegetables, legumes and nuts ≥3 times per week had a lower BMI than those who never or only occasionally consumed these foods; eating nuts ≥3 times a week was associated with a BMI of 0.274 kg/m^2 lower than the never/occasionally group ($p < 0.001$)[63].

Food patterns have significantly changed in recent decades and food has become more affordable to the larger population. This is mainly due to the substantial decrease in prices. However, ease of access has affected the concept of *food* from being a nourishing product to a source of satisfaction and an indicator of a certain lifestyle[64]. A good example is the fact that in modern society, an increase in physical activity is

unlikely to compensate for poor nutrition because it would require 1 to 2 hours of intense activity for a single large-sized fast food meal. The nutritional change, commonly referred to as the western diet, contains refined grains, fast foods, and increased quantities of meats and snacks, and explains the continued increase in childhood obesity[65]. The dramatic changes that have been recorded in children's meal patterns is related to their weight status.

3.3.2 Eating behaviors

Eating behavior is acquired during early childhood and represents traits that can change over time based on personal preferences. Various social factors have a profound influence on dietary intake and family influences play a huge role in eating behavior, food consumption patterns, and childhood obesity. Eating behaviors are strongly linked to childhood obesity, and are dependent on appetite and satiety[66]. Satiety and appetite are determined by factors such as reinforcement of food, eating rate, energy compensation, food preferences, and response to food.

Energy compensation is the response to reduced energy consumption during a meal due to previous consumption of a high-calorie food. This concept is assessed by the rate of compensation, which is evident among children who consume high-energy snacks. Studies show that children suffering from obesity are vulnerable to overeating behavior and consume more energy compared to normal weight children[66].

Another factor that influences energy compensation in children is watching television. Eating while watching TV increases energy intake,

which affects energy compensation. Thus, children who have more screen time tend to eat more. Eating rate, which is the speed of eating, is a determinant of obesity and a sign of decreased response to satiety. Increased eating rate indicates high motivation for greater food consumption compared to a slower rate. Obese individuals are characterized by increased eating rate, which means that they end up consuming more food than a normal weight individuals[66].

Various studies suggest that obese children consume twice the energy when they are not hungry as that consumed by normal-weight children, and most of this energy is associated with weight gain[67]. Reinforcement of appetizing foods means that they are consumed even after energy intake is achieved. The pleasure of food consumption is a motivating factor for poor eating habits[64]. One of the major differences between obese and non-obese children is food preference. Children often prefer foods with higher in energy densities, since they provide them with pleasure. Food preference is also linked to the acceptability and familiarity of the type of food. Social facilitation influences food preference, and is defined as the process of watching another person eat a certain food. Thus, in children it is mainly the parents who influence and regulate eating behavior. Eating behaviors also have an impact on children's diet quality, such as eating fewer than three meals per day [68], eating more meals away from home [69], and eating in response to negative emotions.

3.3.3 Physical activity

The decline in physical activity in different age groups has had a significant effect on rates of obesity[70]. Physical activity has a major

influence on weight gain, and most studies show that sedentary behavior such as playing computer games and watching television is linked to the increased prevalence of obesity among children[71]. Recent data from various studies show that most parents prefer to have their children indoors instead of having them playing outside unattended. There has also been a rise in the percentage of children who are driven to school as opposed to walking, low participation in sports such as football and physical education[72,73]. This is particularly common among adolescent girls. The fact that most of these decisions and behaviors stem from parents highlights the important influence of the parental relationship on obesity. A child's cultural environment can influence them and promote a more physically active lifestyle that has increases health benefits and reduced risks. It is important to encourage children to increase the time they spend on sports and physical activity to at least 60 minutes per day. Physical activity is key for preventing obesity, although it is a poor predictor of the increase of excess fat in the body[74]. Various studies have shown a reverse relationship, where obesity leads to reduced physical activity. Changes in the balance between energy intake and expenditure over time results in a relationship between body weight and energy flux.

The energy imbalance experienced in the body is what leads to obesity, whereby large numbers of calories are consumed, while few are burned. Being active helps children to lose the excess weight and maintain a healthy weight. The more active an individual is the higher the chances they will maintain a healthy weight; conversely, the more inactive an individual is the greater the chance of increased weight gain and obesity. Physical activity increases the total energy expenditure, reduces fat

around the waistline, strengthens muscles and increases energy. It also reduces anxiety and depression, which are contributors to obesity[71].

3.3.4 Sedentary behaviors

Sedentary behavior is that which requires little energy use, such as watching television, sitting, lying down, and playing video games, using a computer, driving, and reading. Sedentary behavior is different from physical inactivity[74]. Physical inactivity refers to not doing substantial activity, while sedentary behavior refers to lying down or sitting for prolonged time periods. This means that an individual can be physically active but still lead a sedentary lifestyle at home, school, or work. Sedentary behavior in modern society affects many children who spend most of their time indoors, as opposed to playing with their peers outside. They prefer to watch television, play video games, and use their computers and mobile phones. Sedentary behavior is a significant risk factor for childhood obesity. Each additional hour of television per day increased the prevalence of obesity by 2%[75]. This association may be explained by several mechanisms, including displacement of physical activity and adverse effects on the quality and quantity of the foods consumed[76]. In modern society, children's brains are more active than other parts of their body, which makes them more sedentary. Civilization is characterized by less physical activity and advancements in technology, which has changed the lifestyle of children. A sedentary lifestyle does not expose them to physical activities but rather to more screen time. Moreover, the invention of home-based equipment has reduced traditional household chores.

3.3.5 Socio-demographic factors

Overweight and obesity in children is affected by rapid changes in the social, physical, and economic factors. These factors have contributed to an energy imbalance because of new dietary patterns and reduced physical activity[77]. Family and parental influences have an impact on childhood obesity not only through the genetic makeup but through their shared environment, which determines a child's level of physical activity, lifestyle, social interactions, and nutrition. Socio-economic factors also play a huge role in health, and have long-term consequences of future generations. The urban lifestyle contributes to the increased incidence of childhood obesity, due to food choices that chiefly consists of processed foods and sweetened beverages[78]. Parental risk factors such as education, BMI, occupation, age, and demographic factors, including the place of residence and family size, are associated with increased rates of childhood obesity[79]. Different factors affect the prevalence of childhood obesity, including food prices, the external environment, decreased opportunities for physical activities such as recreational parks and sidewalks, advertising of fast foods and sweetened beverages, and school nutrition policies.

3.4 Diet quality indices and their association with health-related outcomes in children

3.4.1 *A posteriori* methods to assess dietary patterns

A posteriori measurement of dietary pattern points out the similarities of dietary intakes that are based on data-driven analysis from actual population food intake [80]. The variables, which in this case are dietary intakes, are classified into different clusters and subsets, where each set shares a common trait. The clusters are predefined and the numbers of

each cluster step are determined during the final analysis. Principle component analysis (PCA) is a posterior analysis method that uses nutritional information to identify different components that can be used for dimensionality reduction in a data set.

Several studies in children and adolescents in several countries have analyzed the association between dietary patterns and cardiovascular risk factors. The main dietary patterns evaluated in these studies are Western or Unhealthy patterns, characterized by high intake of processed food such as cold cuts of meat, sweets, pastries, fast food, sweetened beverages, fried foods and snacks; and Healthy or Traditional patterns, characterized by higher intake of plant-based foods and fish.

Many studies have analyzed the association between dietary patterns and adiposity, and have confirmed a positive association between the Western dietary pattern and general and abdominal adiposity. In contrast, Healthy dietary patterns have an inverse association with childhood obesity[81–84].

3.4.2 A priori method to assess dietary patterns

Diet quality indices are tools that provide general measures of a person's dietary intake on a statistical scale, with reference to their suggested nutrition plan. The use of diet quality indices in children is under-studied, compared to that among adults. Notably, the development and application of these tools has a range of benefits in addressing eating patterns and behavior among obese children. Many indices have been created for the incidence of overweight and obesity to capture food habits and dietary intakes that are important contributors to this

epidemic. The elements of these indices are adjusted for energy balance, and target the prevention and treatment of obesity[85]. Nevertheless, the measurements for these diets are quite expensive, and require skilled personnel and effective time management. This limitation partly explains why they are not common for childhood obesity.

Diet quality indices form a vital element of diet assessment. An *a priori* approach to assessing diet quality can based either on dietary guidelines or on the principals of traditional diets, and these approaches evaluate the level of adherence to that diet [80]. A number of pediatric diet quality indices have emerged, such as the North American Youth Healthy Eating Index (YHEI)[86], the Revised Children's Diet Quality Index (RC-DQI)[87], and the Australian Child and Adolescent Recommended Foods Score (ACARFS) [88]. The other category of *a priori* dietary indices include those that measure adherence to a specific diet such as the Mediterranean diet, Nordic diet, or vegetarian diet. In a recent review, Marshall *et al.* identified 80 different diet quality indices used in 119 studies involving children. In the 56 studies that investigated health-related outcomes, weight status was the most researched.

Nutritional epidemiology consists of using different approaches to assess diet quality including the use various dietary indices. For this thesis, I highlight the following dietary indices and measurements.

a. KIDMED index

The Mediterranean diet is defined by relatively high consumption of cereals, vegetables, fruits, olive oil, nuts, legumes, dairy products, and fish, and realtively low consumption of red and processed

meat, sweets, and saturated fat. This dietary pattern is mainly encountered in areas near the Mediterranean sea, and various research studies show that it has a range of health benefits including reduced childhood obesity[89].

The KIDMED index, derived from a 16-item questionnaire administered separately from 24-hour recalls as part of the enKid survey [90](Serra-Majem et al., 2004). The KIDMED index was created specifically to estimate adherence to the Mediterranean diet among children and young adults, based on the principles that sustain the Mediterranean dietary pattern and those that undermine it. Four items denoting lower adherence were assigned a value of -1 (Goes to a fast-food restaurant more than once a week; skips breakfast; has commercially baked goods or pastries for breakfast; takes sweets and candy several times every day), and 12 items denoting higher adherence were scored +1 (consumes fruit or fruit juice every day; has a second fruit every day; eats fresh or cooked vegetables once a day; has fresh or cooked vegetables more than once a day; consumes fish regularly; likes pulses and eats them more than once a week; consumes pasta or rice almost every day (five or more times per week); has cereals or grains (bread, etc.) for breakfast; consumes nuts regularly (at least 2 to3 times per week); uses olive oil at home; has a dairy product for breakfast (yoghurt, milk, etc.); eats two yoghurts and/or some cheese (40 g) daily). Scores range from -4 to 12, with higher scores indicating greater adherence to the Mediterranean diet. Low, intermediate, and high adherence to the Mediterranean diet are defined as scoring <4, 4 to 7, and >7 points for the KIDMED index, respectively.

b. Dietary inflammatory index

Diet plays a crucial role in regulating chronic inflammation[91,92] (1,2) as many foods and nutrients alter the inflammatory process. In 2014, Shivappa et al. [93] developed a new dietary inflammatory index (DII) as an improved measure over previous versions .

The DII is based on the evidence of the effect of diet on inflammation, as supported by a review of 1943 articles. These articles studied the association between intake of 45 food/nutrients and six inflammatory biomarkers (CRP, IL-1β, IL-4, IL-6, IL-10, and TNF-α) derived from cell culture and animal experiments, and from cross-sectional, longitudinal, and intervention trials in humans from 11 populations. The articles were weighted based on study characteristics, and the weighted values were used to obtain food parameter-specific pro-inflammatory and anti-inflammatory scores. Each food parameter in each article was scored by assigning (+1) for pro-inflammatory effect, (−1) for anti-inflammatory effect, or (0) for no effect, and weighted according to the study design[93]. The overall inflammatory score for each food parameter was calculated by subtracting anti-inflammatory scores from pro-inflammatory scores for each food parameter, multiplying by the number of articles, and adjusting for the total number of articles assessing the individual food parameter. A world database for the food parameters was created using data from several countries to calculate a world mean and standard deviation for each parameter. Next, individual the dietary consumption for each study subject's was used to calculate a z-score and centered percentile for each parameter. The centered percentiles were then multiplied by the overall inflammatory score to

find the DII score specific to a certain food parameter in one subject, and all food parameter-specific scores were added to find an overall DII score for a specific study subject[93]. Higher DII scores indicate a more pro-inflammatory diet, while lower DII scores indicate a more anti-inflammatory diet. The DII has been studied extensively in relation to a range of outcomes including obesity, overweight, diet quality, and cardiometabolic risk. However, these studies were mainly conducted among adult populations. Therefore, in the context of this thesis we measured the DII in the Enkid population, aged 6–24 years, to determine the association between the diet inflammatory potential and with diet quality indicators. In a recent study on adolescents, the DII was positively associated with IL-6 and the overall inflammatory biomarker score [94]. A study carried out to determine the inflammatory potential for fast foods, the Mediterranean diet, and the macrobiotic plans showed a high pro-inflammatory potential for fast foods, and the opposite for the Mediterranean and macrobiotic diets. Adopting a vegan diet has also been associated with high anti-inflammatory index[95].

c. Dietary energy density

The energy density of a diet is a measure of the amount of calories per gram of food [kcal/g (kJ/g)]. The energy density of a single food is the ratio of energy [kcal (kJ)] to weight (g). Low energy foods contain fewer calories per gram of food, which means that one can have enough quantities of such foods at a relatively low calorie intake. Low energy density foods include those with high water content; such as vegetables, and fruits. High energy density foods have low water content and are high in fats. High energy density foods include butter, oils,

industrialized snacks and treats, and dried fruit. In the results section of this thesis, we present data based on dietary density calculations that included food only and all foods together with all caloric beverages. Children with a low energy density diet make healthier food choices than those with a high density diet[96]. Children suffering from obesity are prone to consuming high energy density foods to satisfy their pleasure as opposed for nutritional value[97]. The high energy diets in children in modern society often result in overeating and being overweight into adulthood.

d. Total dietary antioxidants capacity

Dietary antioxidant intake protects against oxidative damage as well as other clinical complications. There is a link between food intake and oxidative stress modulation based on energy restriction and the limited level of oxidative stress capacity[98]. Oxidative stress has previously been connected to the development of childhood obesity in various studies. Obese children have been found to have greater oxidative burden than those with normal weigh[99]. Total dietary antioxidant capacity is a useful measure for evaluating the potential health effects of dietary antioxidants found in mixed diets[100]. The relationship between oxidative stress and obesity is reduced by low-calorie diets, weight loss, and antioxidant-rich diets. Notably, reduced energy intake is also related to decreased oxidative stress that reduces risk of obesity[98]. Moreover, total dietary antioxidant capacity is an indicator of diet quality and is a reliable model for assessing antioxidant intake

3.5 Impact of diet on cardiometabolic health in children and adolescents

Funtikova AN, Navarro E, Bawaked RA, Fíto M, Schröder H. Impact of diet on cardiometabolic health in children and adolescents. Nutr J. 2015 Dec 14;14(1):118. DOI: 10.1186/s12937-015-0107-z

Chapter 4

METHODS

This chapter provides a general overview of the methods applied to evaluate the research hypotheses linked with the present thesis. A more specific and detailed description of the methods followed is enclosed in the papers that are presented in the section of results. The scientific production generated in this thesis has been based on the following three studies:

4.1 The enKid study

4.1 The POBIC study

4.1 The INMA Birth Cohort Studies

Summary of the participants, outcome, exposure and other variables for each article are shown in table 4.1

4.1 The enKid study

The enKid study is a population-based cross-sectional study carried out by Serra-Majem et al [1] on a random sample of the Spanish population aged 2–24 y (n=3534; 1629 boys and 1905 girls)[1]. It was conducted between 1998 and 2000. Participants were selected by multistage random sampling procedures based on a population register. The final sample size of the EnKid study was 3,534 individuals.

Forty-three dietitians and nutritionists who had undergone a rigorous selection and training process to standardize the data collection conducted home interviews. Information on child feeding practices, diet and physical activity has been collected through questionnaires

administered to the parents of children aged 8 years and under. Questions covered dietary habits, consumption of supplements, physical activity on weekdays as well as leisure time, tobacco and alcohol use and information about food and nutrition. The anthropometric variables were collected for each participant. Body weight, height, and waist circumferences were measured on the day of the interview. The interviewers also gathered data about family socioeconomic status, including maternal and paternal education level and occupation

Parental written consent was obtained on behalf of each participant younger than 18 years. The ethics committee of the Spanish Society of Community Nutrition approved the study protocol.Based on this study, I have produced three papers:

Paper 1: Dietary flavonoids of Spanish youth: intakes, sources, and association with the Mediterranean diet.

Paper 2: Association of diet quality with dietary inflammatory potential in youth.

Paper 4: Cumulative effect of obesogenic behaviours on adiposity in Spanish children and adolescents.

4.2 The POBIC study

The POIBC study (Prevención de la Obesidad Infantil Basada en la Comunidad) was funded through a grant from the Health Research Fund (FIS) of the Carlos III Health Institute. It was carried out between 2012 and 2014. The general aim of the intervention is to evaluate the effect of the Thao-Child Health Program (TCHP), a community-based, multi

setting, multilevel intervention program for healthy weight development and lifestyle choices.

We recruited 2250 children aged 0 to 10 years from four Catalan cities. We randomly selected two cities to go under the TCHP interventions and the other two cities followed usual health care policy. The number of the school were included in the intervention was 41 elementary school. We measured Weight, height, and waist circumference at baseline and after 15 month of follow-up. Trained field researchers collected data on children's physical activity and adherence to the Mediterranean diet by validated questionnaires, at baseline and follow up. In addition, Parental education level was collected and categorized into 5 levels: i) no schooling, ii) primary school, iii) secondary school, iv) technical or other university degree, and v) higher (graduate-level) university degree.

For the scope of this thesis, we carried out a prospective cohort analysis within the framework of the POIBC study. We measured eating behaviors (External Eating, Emotional Eating, and Restrained Eating) by the validated Dutch Eating Behavior Questionnaire for Children (DEBQ-C). The following revised manuscript with findings from this study is under review:

Association of eating behaviors, lifestyle, and maternal education with adherence to the Mediterranean diet in Spanish children (paper 3).

4.3 The INMA Birth Cohort Studies

The INMA-“INfancia y Medio Ambiente” (Environment and Childhood) project is a network of seven prospective population- based birth cohort studies in different Spanish regions that have followed a total of more than 3000 mother-child pairs from early pregnancy throughout childhood and adolescence [101] . The scope of the study for this thesis is to investigate the role of life style behaviors at preschool aged children on child cardiometabolic health. The range of exposures that are evaluated includes extracurricular physical activity, sedentary behaviors, TV watching time, sleep time, plant based food consumption and consumption of ultra-processed food. The studied health outcomes include BMI, WC, lipids (HDL, LDL, triglycerides, lipid score), systolic and diastolic blood pressure, and cardiometabolic risk score.

The INMA birth cohorts contain three old and four relatively new cohorts. The three older cohorts conducted in the Spanish regions of Ribera d´Ebre, Menorca and Granada. Recruitment period was between 1997 and 2002) . The four new cohorts were from the regions Asturias, Gipuzkoa, Sabadell and Valencia. Mothers were recruited between 2003 and 2008 (Figure 4.1). The inclusion criteria for the mothers were age equal or above the 16 years, intention to give birth in the reference hospital, no communication problems, singleton pregnancy and not to have followed any program of assisted reproduction. For the purpose of this thesis we used from the INMA-new cohorts in the regions of Gipuzkoa, Sabadell and Valencia In the INMA-new birth cohorts, mother-child pairs were recruited in the first prenatal visit at 10-13 weeks of gestation in the main public hospital or health center of each study region. The recruitment periods were from April 2006 to January

2008 in Gipuzkoa (N=638), from July 2004 to July 2006 in Sabadell (N=657) and from November 2003 to June 2005 in Valencia (N=855). Mother-child pairs have been afterwards followed in the third trimester of pregnancy, at birth and at child ages of 6 months and 1, 4 and 7 years using the same study protocol in all cohorts. Interviewed- based questionnaires collected information about parental and child characteristics including information on environmental exposures and sociodemographic, lifestyle and behavioral factors. Repeated weight and height measurements of the child in the first year of life were extracted from the medical records. Special trained personnel of the research team at postnatal follow-ups measured Child weight, height, waist circumference and blood pressure. The following manuscript with findings from this study is to be submitted: The added impact of lifestyle behaviors in early childhood on obesity and cardiometabolic risk in Children: Results from the Spanish INMA Birth Cohort Study (paper 5)

Figure 4.3 Geographical locations of the seven INMA Birth Cohort Studies in Spain

Table 4.1 Summary of the outcome, exposures, and other variables assessed in children across the five articles

	Paper I	Paper II	Paper III	Paper IV	Paper V
Study	**EnKid study**	**EnKid study**	**POIBC study**	**EnKid study**	**INMA study**
Participants	3,534 children and young adults, aged 2–24 years	2889 children and young adults aged 6–24 years.	1639 children aged 8 – 10 years	1614 children aged 5–18 years	1480 children aged 4 years
Outcome variables	Adherence to the Mediterranean diet (KIDMED index)	Energy density, total dietary antioxidant capacity, adherence to the Mediterranean diet (KIDMED index)	Adherence to the Mediterranean diet (KIDMED index) at follow- up	BMI z-score, waist-to-height ratio (WHtR), overweight and abdominal obesity	Obesity and cardio-metabolic risk (BMI, WC, SBP, DBP, HDL, TG) z-scores
Exposure variables	Flavonoid intake	Dietary inflammatory potential, measured by the dietary inflammatory index	Eating behaviors (External Eating, Emotional Eating, and Restrained Eating), physical activity, level, screen time, meal frequency and parental socioeconomic status	Obesogenic Behavior Score, Physical activity (PA), screen time, breakfast consumption and meal frequency	Extracurricular physical activity, sleep time, plant based food consumption, TV time and consumption of ultra-processed food
Other variables	Region, community size, maternal education level energy intake.	Physical activity, maternal education level, energy intake, energy underreporting, energy over reporting, community size, region	Maternal education	Maternal education level, energy intake, energy underreporting, energy over reporting and community size	Parental educational level, social class, maternal BMI, energy intake, and region

Chapter 5

RESULTS

5.1 Dietary flavonoids of Spanish youth: intakes, sources, and association with the Mediterranean diet.

Bawaked RA, Schröder H, Ribas-Barba L, Cárdenas G, Peña-Quintana L, Pérez-Rodrigo C, et al. Dietary flavonoids of Spanish youth: intakes, sources, and association with the Mediterranean diet. PeerJ. 2017 May 17;5:e3304. DOI: 10.7717/peerj.3304

5.2 Association of diet quality with dietary inflammatory potential in youth.

Bawaked RA, Schröder H, Ribas-Barba L, Izquierdo-Pulido M, Pérez-Rodrigo C, Fíto M, et al. Association of diet quality with dietary inflammatory potential in youth. Food Nutr Res. 2017 Jan 7;61(1):1328961. DOI: 10.1080/16546628.2017.1328961

5.3 Association of eating behaviors, lifestyle, and maternal education with adherence to the Mediterranean diet in Spanish children.

Bawaked RA, Gomez SF, Homs C, Casas Esteve R, Cardenas G, Fíto M, et al. Association of eating behaviors, lifestyle, and maternal education with adherence to the Mediterranean diet in Spanish children. Appetite. 2018 Nov 1;130:279–85. DOI: 10.1016/j.appet.2018.08.024

5.4 Cumulative Effect of Obesogenic Behaviours on Adiposity in Spanish Children and Adolescents

Schröder H, Bawaked RA, Ribas-Barba L, Izquierdo-Pulido M, Roman-Viñas B, Fíto M, et al. Cumulative Effect of Obesogenic Behaviours on Adiposity in Spanish Children and Adolescents. Obes Facts. 2017;10(6):584–96. DOI: 10.1159/000480403

5.4 The added impact of lifestyle behaviors in early childhood on obesity and cardiometabolic risk in Children: Results from the Spanish INMA Birth Cohort Study

Bawaked RA, Fernández-Barrés S, Navarrete‐Muñoz EM, González‐Palacios S, Guxens M, Irizar A, et al. Impact of lifestyle behaviors in early childhood on obesity and cardiometabolic risk in children: Results from the Spanish INMA birth cohort study. Pediatr Obes. 2020 Mar 2;15(3). DOI: 10.1111/ijpo.12590

Chapter 6

DISCUSSION

6.1 Main Findings

The first part of this thesis focuses on the associations between children's dietary intake and diet quality. For this purpose, we conducted two analyses using data from the EnKid study, a national representative sample of Spanish youth. In the first analysis we included 3,534 children and young people, aged 2–24 year, and estimated their average daily intake and sources of flavonoids (Paper I). In the second analysis, we estimated the dietary inflammatory potential using the DII, and estimated its association with diet quality, which was measured by three conceptually different measures: the Mediterranean Diet Quality Index for children and adolescents (KIDMED), energy density, and total dietary antioxidant capacity. In this analysis, we included 2889 children aged 6 – 24 years (Paper II). The mean intake of total flavonoids was 70.7 mg/d, mainly of the flavan-3-ols subclass, and the main dietary source was fruits and fruit juice. High flavonoid intake was associated with increased adherence to the Mediterranean diet. Diets with anti-inflammatory potential tended to have higher diet quality.

The second part of this thesis focuses on evaluating the association between adherence to the Mediterranean diet and eating behaviors, lifestyle habits, and parental socioeconomic status. For this analysis, we used data for 1639 children aged 8 to 10 years, with follow-up during two school years (Paper III). Physical activity, low meal frequency, low screen time, and tendency to eat in response to external cues were

prospectively associated with higher adherence to the Mediterranean diet.

The third part of this thesis focuses on assessing the association between lifestyle behaviors and childhood obesity, abdominal obesity and cardiometabolic risk using data from the EnKid study (Paper IV, n=1614) and INMA cohorts study (Paper V, n=1480). It is widely acknowledged that multiple obesity risk behaviors cluster in children and adolescents[179]. For the purpose of this thesis we determined, first in the ENKID population, the individual and cumulative effect of obesogenic behaviors (low physical activity, skipping breakfast, high screen time and low meal frequency) on BMI, waist-to-height ratio (WHtR), overweight, and abdominal obesity. In addition, we evaluated the association between the concurrent presence of these obesity-related behaviors and parental educational level. We observed that BMI z-score and WHtR were positively associated with increasing numbers of concurrent obesogenic behaviors. Children and adolescents with more obesogenic behaviors had greater risk of overweight and abdominal obesity. In addition, children with three or more obesogenic behaviors had higher odds of low maternal or paternal education, compared to children with no obesogenic behaviors.

Second, in the INMA population of children aged 4 years, we evaluated the association between five lifestyle behaviors, individually and combined using a predefined score, on obesity and cardio-metabolic risk at age 4 years, and on obesity and blood pressure at age 7 years. Since ultra-processed food has recently been suggest to be associated with obesity in adults [140] and adolescents [141], we included the intake of ultra-processed food in the lifestyle behavior assessment, in order to

study its relation to obesity in children. The five lifestyle behaviors included are extracurricular physical activity, TV time, sleep time, intake of plant-based foods and ultra-processed foods. We constructed the child healthy lifestyle score (CHLS), which is comprised of these five target lifestyle behaviors at age 4 years. The CHLS ranges from 1 to 11 points, with higher scores representing healthier lifestyles. Our results showed that CHLS at age 4 years was negatively associated with BMI and WC z-scores, but not with blood pressure at age 7 years. In the following section, I provide an update on current research related to our findings.

6.2 Update on recent research

Dietary patterns and diet quality

A vast amount of literature supports the beneficial role of fruit and vegetables in diet quality and disease prevention. Fruit and vegetables are rich in polyphenol flavonoids, which may partly explain the protective effect of fruit and vegetable intake on major chronic diseases. High flavonoid intake was found to be inversely associated with obesity[180], cardiovascular diseases[181,182], breast[183] and prostate cancer[184], diabetes [185], and C-reactive protein levels in women [180]. However, in European children, especially in southern Europe, fruit and vegetable intake is far below current dietary guidelines[77]. Because of the lack of data on flavonoid intake in Spanish children, we decided to estimate the intake of flavonoids, and to describe its major sources. Our findings verify the low intake of fruit and vegetables in Spanish children [186]. Compared to the results of older studies among

US [187]and Australian children[188], the mean flavonoids intake was lower in our study. Note that after excluding tea flavonoids, flavonoid intake in Australian youth decreased significantly. Comparing flavonoid intakes between different populations and time periods has some limitations, depending on the dietary assessment method and time, the flavonoid data base used, and the study sample. In general, our study used the KIDMED index as a measure of diet quality to test our hypothesis that flavonoid intake is related to higher diet quality in young people. All classes of flavonoids except flavones were positively associated with the KIDMED index. This result is consistent with previous studies where higher flavonoid intake was positively associated with consuming the recommended number of servings of fruit and vegetables [189], and diet quality, measured using the healthy-eating index (HEI)[10].

Diet is known to play a vital role in the process of inflammation. Only a few studies have investigated the notion that an anti-inflammatory diet is associated with better diet quality, and all of them were conducted in the adult population [190,191]. The Macrobiotic diet, Mediterranean diet, and vegan, vegetarian, or pescovegetarian diet have all been linked to higher dietary anti-inflammatory potential [191,192]. In our study we employed different measures to measure diet quality, namely the KIDMED index, energy density, and total dietary antioxidant capacity. These three diet quality indicators capture different dietary dimensions. Our results show that higher diet quality is associated with increased dietary anti-inflammatory potential according to all three indices. A similar pattern of results was obtained in a study that examined the

association between three diet quality measures (Healthy Eating Index 2010, the Alternative Healthy Eating Index, and the Dietary Approaches to Stop Hypertension Index) and dietary inflammatory potential as measured by the DII [193]. It is interesting to note that these indices showed poor agreement between each other, depending on the food consumed according to the measure had been used.

Eating behavior, physical activity and diet quality

The Mediterranean diet emphasizes high intake of fruits, vegetables, whole grains, legumes, fish and nuts, and the liberal use of olive oil in food preparation[194]. While the Mediterranean is considered to be one of the healthiest diets, with a protective role against cardiovascular diseases, we are currently witnessing the loss of the Mediterranean diet in its countries of origin towards a more Western-type diet[195,196]

Lifestyle habits and eating behaviors are important factors for optimizing children's ability to follow a Mediterranean diet. We used the KIDMED index to evaluate adherence to the Mediterranean diet. Because the KIDMED is a simple and easy tool, in a recent systemic review, 38 out of 58 studies used the KIDMED score to evaluate adherence to the Mediterranean diet. [197]. In line with our results, several cross-sectional studies found a relationship between physical activity level, sedentary behavior and adherence to the Mediterranean diet [197]. Results in this thesis showed that higher meal frequency and lower external eating predict better adherence to the Mediterranean diet after 15 month of follow-up. As far as we know, our work is the first prospective study to examine associations between eating behaviors and diet quality in Spanish children. It is well known that indicators of better

socioeconomic status are associated with higher intake of healthy food and diet quality in children[198]. In this study, maternal education is demonstrated as a socioeconomic indicator. Children whose mothers had a university degree were more likely to adhere to the Mediterranean diet at follow-up. Socioeconomic status could influence children's dietary behaviors through their parent's level of nutritional knowledge, food affordability at home and school, and access to food stores [184-187]. Several studies have suggested that children from families with a lower socioeconomic status have lower diet quality than those with higher socioeconomic status[198].

Lifestyle behaviors and childhood obesity

Obesity in children remains an important public health problem in Spain, and worldwide. Several health-related lifestyle behaviors are important determinants of overweight and obesity in children [199,200]. Physical activity, less sedentary behaviors such as screen time[160,166], regularly eating breakfast[54], daily consumption of fruit and vegetables, and lower intake of ultra-processed food such as soft drinks, sweets, processed meat, and fast food reduce risk of overweight and obesity [59,201]. Several of these detrimental lifestyle behaviors are common in young people [179,202], particularly those with lower socioeconomic status [132,203]. However, less is known about the cumulative effect of unhealthy lifestyle behaviors on risk of obesity [104]. Few studies have comprehensively analyzed the association between a range of lifestyle factors and adiposity measures [104]. In the fourth paper of this thesis, we evaluated whether adding a second, third

or fourth unhealthy lifestyle behavior significantly increased the effect size of the association with weight gain or obesity. We found that, children with zero obesogenic behaviors in compare with children with concurrent of 4 obesogenic behaviors (Physical activity, screen time, breakfast consumption and meal frequency) had increased the risk of obesity and abdominal obesity by 168% and 112%, respectively. However, when we analyzed each obesogenic behavior individually, only low physical activity was associated with significantly higher odds of overweight and abdominal obesity, while skipping breakfast increased the odds of abdominal obesity. In the fifth paper of this thesis, we constructed a child healthy lifestyle score (CHLS) including five target lifestyle behaviors (extracurricular physical activity, sleep time, consumption of plant-based foods, TV time, and consumption of ultra-processed food), and assessed its association with obesity and blood pressure after three years of follow-up. The five lifestyle factors combined were associated with obesity and abdominal obesity. Our results from both papers are in line those of previous studies on the impact of combined lifestyle factors and risk of childhood obesity [137,149,150,158]. In the enKid population, high screen time was the most prominent obesity-related behavior, and in the INMA population, TV time was a strong predictor for obesity and abdominal obesity. Screen time exposes children to advertisements about “unhealthy” food [164], interrupts their sleep time[165], reduce the time they spend being physically active, and promotes the consumption of high quantities of lower quality food while watching TV [76,204]. All of these mechanisms could explain why high screen time is highly related to overweight and obesity.

In contrast, regular physical activity, such as unstructured playtime, walking and cycling to and from school, and participation in sports, is associated with lower levels of overweight in children [205,206].According to the COSI 2018 report, 47% of Spanish children go to and from school by vehicles and motorized vehicles.

One of the key determinants of obesity is diet. While caloric intake mainly impacts weight gain and loss, food quality is an equally important determent for weight control[138]. Ultra-processed foods are high in calories and nutritionally imbalanced[139]. In our study we defined UPF according to the NOVA classification. We observed an association between higher intake of UPF at age 4, and higher BMI z-score at age 7. There have been no previous studies on the association between UPF and BMI in children, although this association was found in adults [140]. In Spain, ultra-processed foods accounts for 61% of energy intake [175], and across 19 European countries UPF counts for a quarter of all the food available in the household [207]. Remarkably, the obesity prevalence in each country was associated with household availability of UPF [207].

6.3 Strengths and limitations

The main strength of this thesis research is that it is based on three study samples, the Enkid, POIBC, and INMA studies, which cover diverse child populations and different age groups in Spain. enKid is a nationwide population-based sample, in which all anthropometric variables were measured objectively, and the completion of validated questionnaires was guided by an interviewer. However, enKid has several limitations. The cross-sectional study design prevents us from

drawing causal inferences. Exposure variables such as physical activity, screen time, and meal frequency, were self- reported, and are therefore prone to recall bias. Because of daily variations in food intake, 4-hour recall—and particularly a single day's recall— have inherent limitations in the individual assessment of dietary intake. The enKid data are now 17 years old, which raises questions about their current relevance for young people. Obesogenic behaviors remain highly prevalent in Spanish children and adolescents, who are increasingly sedentary. For example, according to enKid data, average screen time has increased from the 1.6 h/day in 2000 to 2.5 h/day in 2013 [208]. Spain's 2016 report card on physical activity among children and young people showed that recommended physical activity levels are not being met [209]. In this context, our findings based on the EnKid data are timely, although the true current effect size of the associations may be even larger than our estimations.

POIBC included a large number of participants aged 8 years of age and older. This could be a limitation because children take more than 30 minutes to answer all the questionnaires, and at that age children have a shorter attention span. Data for dietary behaviors, lifestyle, and diet patterns were self-reported, and therefore prone to recall bias.

The main strength of the INMA study, compared to previous literature on the cumulative impact of lifestyle behaviors on childhood obesity, is its prospective design. The study sample is from a population-based birth cohort study from several regions in Spain. All anthropometrics, lipids, and blood pressure measures were measured objectively. However, our study also has important limitations. We used subjective selfreporting of lifestyle variables to determine adequate or inadequate

physical activity, television time, and sleep time. The question of extracurricular physical activity was different in the Valencia subcohort compared to to the other two subcohorts. In the Valencia subcohort the question asked about one activity a day, while in the other two subcohorts the question was about three physical activities a day. This could lead to misclassification in the Valencia cohort. Dietary data was collected using the FFQ, which can cause recall bias, even though it has previously been validated [153]. We used a predefined score based on lifestyle factors, categoriing the lifestyle variable and the score into cohort-specific tertiles. Using categorical instead of continues variables could be less precise. Although, we adjusted for a range of confounding factors, we cannot exclude the hypothesis of potential residual confounding. Lipids only were only measured in a subset of children at 4 years, and WC at 4 years was only measured in the Valencia and Sabadell subcohorts. In addition, in the Valencia subcohort, lipids were measured from fasting blood samples. In the other two subcohorts, blood samples were non-fasting, which could impact lipid levels

6.4 Contribution to the Current State of Evidence

This PhD thesis addresses a relevant research question in Spain, In light of the very recent WHO Childhood Obesity Surveillance Initiative (COSI) report, which shows that southern European countries have the highest rate of child obesity. Children in Spain appear to have lost Mediterranean diet patterns. Our findings contribute to: 1) determining the predictors of adherence to the Mediterranean diet and high diet quality; 2) providing primary baseline data about flavonoid intake and

main food sources in Spanish children. This data provide a foundation for future studies on the association between flavonoid intake and children's health; 3) understanding the impact of healthy lifestyle factors on obesity and cardiometabolic risk factors (waist circumference, lipids and blood pressure), 4) shedding light on the role of parental educational level and socioeconomic status on children's lifestyle behaviors and diet quality.

6.5 Implications for Public Health

In terms of diet quality in Spanish children and their level of adherence to the Mediterranean diet, it is important to address the factors associated with los of Mediterranean diet in the younger generation[210]. The main consequence of declining adherence to the Mediterranean diet in Mediterranean countries is the increase in childhood obesity[29]. Overweight and obesity are caused by high intake of energy-dense, nutrient-poor foods and beverages, such as chips, salted snacks, candies, and sugary drinks, low intake of nutrient-rich food such as fruits and vegetables, and sedentary behaviors. In addition, our data suggest that less external eating behavior predicts better adherence to the Mediterranean in children. Our studies suggest that policies to improve children's lifestyle factors by increasing the time children stay physically active, and encourage the availability of healthy food in public dining places may improve diet quality, especially among disadvantaged children and families.

Tackling childhood obesity is about more than just diet and exercise

Excess fat accumulated through high energy intake and low energy expenditure[211]; however the etiology of obesity is very complex. Obesity intervention and prevention programs should focus on broad modification of individual behaviors, and on providing environments that promote healthy living. To achieve effective obesity policies and interventions, we need to consider complex lifestyle factors.

Our data suggest that parents play an important role in managing child weight development. Therefore the home environment is critical for designing interventions and strategies to tackle obesity.

In our studies we observed considerably high consumption of ultra-processed foods, such as soft drinks and energy-dense foods, with a mean of nine servings per day. Strategies for promoting healthy food choices could include: labeling, not only in grocery shops and supermarkets, but also in fast food restaurants; and taxes on sugary and soft drinks. Exposure to TV in early childhood is a stronger predictor of obesity and abdominal obesity in school-age children in our population. Several reports about children's exposure to marketing found that most food advertisements targeting children and adolescents are about foods that are high-calorie, nutrient-poor, and have high sugar, salt and fat content [212,213]. In contrast, there is little advertising for fruit and vegetables.

The likelihood of being overweight and having abdominal obesity was significantly higher in children who spent less than <1 h/day doing physical activity, compared to those who were more active. Therefore, it is important to promote physical activity in children's daily routine and in the school curriculum.

6.6 Future perspectives

Childhood obesity is still one of the most serious global public health challenges. Although the numbers of obese children have started to level off in some countries, the prevalence remains alarmingly high. In our research group, we started with the MELI-POP intervention study (pilot version). MELI-POP is a multicenter, parallel, randomized controlled clinical trial of a cohort of children initially aged 3 to 6 years who are at risk of obesity. The trial will be conducted in Health Centers of 7 cities: Barcelona, Cordoba, Pamplona, Reus, Santiago de Compostela, Valencia and Zaragoza.

The control group will receive usual care by primary care professionals. The intervention group will receive intensive education on Mediterranean lifestyle (Mediterranean diet and promotion of physical activity). We will provide the intervention families with extra virgin olive oil and fish, which should be consumed at least 3 times a week.
We will offer free activities so that children have access to 3 weekly 60 minutes sessions of moderate or intense physical activity. Adherence to the intervention will be monitored regularly. The main objective is to measure differences in the incidence of obesity between the intervention group and the control group. As secondary objectives, we will measure differences between groups in changes in body composition, physical condition and cardiometabolic risk factors. The objective is to maintain the intervention and follow-up of the cohort for 10 years.

Chapter 7

CONCLUSION

5.1 Conclusions

1. Our studies provide the first basic data for estimated flavonoid intake and their sources among Spanish youth. Fruit was the main dietary source of flavonoids. Flavan-3-ol was the major contributor for total flavonoid intake.
2. In children, adolescents, and young adults, flavonoid intake was positively associated with good diet quality, indicated by higher adherence to the Mediterranean diet.
3. In children, adolescents and young adults, high diet quality, as indicated by higher KIDMED index scores, higher total dietary antioxidant capacity, and lower energy density, are positively associated with the anti-inflammatory potential of the diet, as measured using the DII in Spanish youth.
4. Less screen time, higher levels of physical activity, higher meal frequency, and a less external eating were prospectively associated with high adherence to the Mediterranean diet independently of baseline diet quality in children.
    - Maternal education level was a predictor of high diet quality in children
5. The cumulative effect of children's and adolescents' low physical activity, high screen time, skipping breakfast and low meal frequency increased their risk of higher BMI z-scores, higher WHtR and greater risk of overweight and abdominal obesity. Surrogate markers of adiposity increased with the number of concurrent obesogenic behaviors.

- In contrast, parental and maternal education level were strongly associated with the concurrent presence of these obesogenic behaviors.

6. Greater adherence at preschool age to the Child Healthy Lifestyle Score (comprised of five lifestyle behaviors: high TV time; consumption of ultra-processed food; low sleep time; physical activity; and consumption of plant-based foods) increased the risk of higher BMI, WC z-scores, overweight, obesity, and abdominal obesity in school aged children.
7. This thesis demonstrates that diet quality and childhood obesity are driven by a complex set of risk factors. To successfully tackle childhood obesity, we require strategies, policies and interventions that address multilevel behavior modifications. Moreover, the home food environment and parental influence on children diet quality and lifestyle behaviors are significant determinants of childhood obesity.

Appendix I

Supplementary information for papers

Supporting Material for Paper I

DIETARY FLAVONOIDS OF SPANISH YOUTH: INTAKES, SOURCES, AND ASSOCIATION WITH THE MEDITERRANEAN DIET

Rowaedh Ahmed Bawaked[1,2], Helmut Schröder[1,3], Lourdes Ribas-Barba[4,5], Gabriela Cárdenas[1,2], Luis Peña-Quintana[5,6], Carmen Pérez-Rodrigo[7], Montserrat Fito[1,5] and Lluis Serra-Majem[5,6,8]

Institut Hospital del Mar d'Investigacions Mèdiques

BACKGROUND

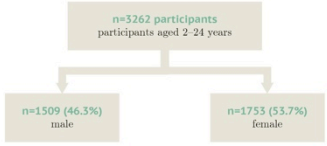
Plant-based diets have been linked to high diet quality and reduced risk of cardiovascular diseases. The health impact of plant-based diets might be partially explained by the concomitant intake of flavonoids. Estimation of flavonoids intake in children and adolescents is limited.

OBJECTIVES

- Estimate the intake of flavonoids.
- Describe major sources of flavonoids.
- Evaluate the association between flavonoids intake and diet quality among Spanish children, adolescence and young adults.

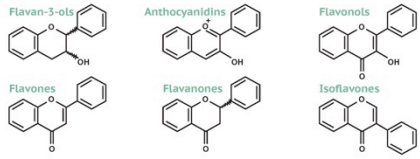
METHODS

Study design:

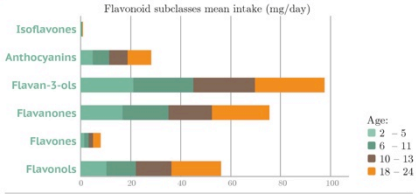


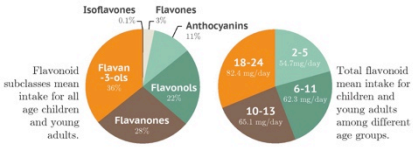
KIDMED index:
Adherence to the Mediterranean diet was estimated by the KIDMED index, derived from a 16-item questionnaire administered separately from the 24-hour recalls as part of the enKid survey.

Flavonoid food composition:
(1) The Phenol-Explorer database was used in estimating dietary flavonoid intake.
(2) US Department of Agriculture (USDA) databases were used to determine the flavonoids content of foods not available from Phenol-Explorer data.
(3) We measured total flavonoid intake from 6 subclasses.



RESULTS





Flavonoid subclasses mean intake for all age children and young adults.

Total flavonoid mean intake for children and young adults among different age groups.

Association between flavonoid intake and adherence to the Mediterranean diet measured by the KIDMED index.

KIDMED score	Poor < 3		Medium 4–7		High < 10		P
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Total flavonoids	50.76	35.9–65.54	63.6	59.9–67.39	80.8	76.2–85.4	<0.001
Flavonols	12.24	6.88–17.6	13.6	12.3–15.0	18.1	16.3–19.8	<0.001
Flavones	1.64	0.10–3.19	2.07	1.62–2.53	2.43	1.99–2.86	0.3
Flavanones	8.3	3.50–13.1	17.6	16.0–19.3	23.1	21.3–24.9	<0.001
Flavan-3-ols	21.5	13.8–29.2	23.8	21.6–5.32	27.5	24.9–29.9	0.05
Anthocyanins	7.02	2.42–11.6	6.36	5.32–7.41	9.54	7.90–11.1	0.01
Isoflavones	0.03	0.00–0.05	0.04	0.01–0.07	0.15	0.05–0.25	0.08

CONCLUSION

The results of this study provide primary information about flavonoids intake and main food sources in Spanish children, adolescents and young adults. Participants with high daily mean intake of flavonoids have higher adherence to the Mediterranean diet.

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CONTACT US: **Rowaedh Bawaked**, rowaedh.bawaked01@estudiant.upf.edu

1 Cardiovascular Risk and Nutrition Research Group (CARIN), Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain
2 Department of Experimental and Health Sciences, University of Pompeu Fabra, Barcelona, Spain
3 CIBER Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain
4 Fundación para la Investigación Nutricional (Nutrition Research Foundation), Barcelona, Spain
5 CIBER Physiopathology of Obesity and Nutrition (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain
6 Research Institute of Biomedical and Health Sciences, University of Las Palmas de Gran Canaria, Gran Canaria, Spain
7 FIDEC Foundation, University of the Basque Country (UPV/EHU) Bilbao, Bilbao, Spain
8 Department of Nutrition, Food Sciences and Gastronomy, University of Barcelona, Barcelona, Spain
* 18-24 years old. For 2-17 years old mean intake is 0.66 mg/day.

Supporting material for paper II

Bawaked RA, Schröder H, Ribas-Barba L, Izquierdo-Pulido M, Pérez-Rodrigo C, Fíto M, et al. Association of diet quality with dietary inflammatory potential in youth. Food Nutr Res. 2017 Jan 7;61(1):1328961. DOI: 10.1080/16546628.2017.1328961

Supporting Material for paper V

Bawaked RA, Fernández-Barrés S, Navarrete‐Muñoz EM, González‐Palacios S, Guxens M, Irizar A, et al. Impact of lifestyle behaviors in early childhood on obesity and cardiometabolic risk in children: Results from the Spanish INMA birth cohort study. Pediatr Obes. 2020 Mar 2;15(3). DOI: 10.1111/ijpo.12590

Appendix II

About the author

About the Author

Rowaedh Baswaked received her Bachelor degree in Medical laboratory sciences at King Abdulaziz University, Saudi Arabia in 2007. She obtained a scholarship from her previous employer (KSAU university in Saudi Arabia) to continue her master studies. She received her Master of Medical science-Microbiology at the University of Rhode Island, USA in 2012. She joined Hospital del Mar Medical Research Institute (IMIM) in 2015 where the present thesis has been executed. As part of her PhD training, she did a 4-month stay as a research scholar at the ISGlobal research center (September 2017-February 2018). A summary of the research activity of the author during the thesis is provided below.

Publications related to the thesis

- Gomez, Santiago Casas, Esteve, Rafael, Subirana, Isaac, Serra Majem, Lluis, Ahmed Bawaked, Rowaedh, Fíto, Montserrat, Schröder H. **Effect of a community-based childhood obesity intervention program on changes in anthropometric variables, incidence of obesity, and lifestyle choices in Spanish children aged 8 to 10 years.** Submitted to European Journal of Pediatrics
- Cárdenas Fuentes G, Bawaked RA, Martínez González MÁ, Corella D, Subirana Cachinero I, SalasSalvadó J, Estruch R, Serra-Majem L, Ros E, Lapetra Peralta J, Fiol M, Rekondo J, Gómez-Gracia E, Tur Marí JA, Pinto Sala X, Babio N, Ortega C, Martínez JA, Schröder H. **Association of physical activity with**

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