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OBESITY DURING CHILDHOOD: AN ANALYSIS OF A COHORT OF NEWBORNS IN ROME

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To Me.

For being able to be true to myself.

Acronyms and Abbreviations

BMI	Body Mass Index
CDC	U.S. Centers for Disease Control and Prevention
CES-D	Center for Epidemiologic Studies-Depression
CHD	Coronary Heart Disease
COSI	(European) Childhood Obesity Surveillance Initiative
EPDS	Edinburgh postnatal depression scale
ESCAPE	European Study of Cohorts for Air Pollution Effects
GASPII	Genetica e Ambiente: Studio Prospettico sull'Infanzia in Italia
GBD	Global Burden of Disease
GEE	Generalized Estimating Equation
GIS	Geographical Information Systems
GLM	Generalized Linear Model
HDL	High-Density Lipoprotein
ICC	Intraclass Correlation Coefficient
IDEFICS	Identification and prevention of Dietary- and lifestyle – induced health Effects in Children and infantS
IOTF	International Obesity Task Force
IPW	Inverse Probability Weighting
LUR	Land Use Regression
PHQ-9	Patient Health Questionnaire-9

PAHs	Polycyclic Aromatic Carbons
OR	Odds Ratio
OSA	Obstructive Sleep Apnoea
RR	Relative Risk
SEP	Socioeconomic Position
VIF	Variance Inflation Factor
WHO	World Health Organization

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1. Introduction

Demography, as defined by its etymology (from Greek *demos*, meaning ‘people, district’, and *graphy*, meaning ‘writing, describing’), is a science carrying out research on the population and investigating its changes through time. It is a dynamic science in constant transformation, mainly studying birth, death and migration trends and their effects on the population considered. Demography is a multidisciplinary science, since it usually relies on theories from diverse fields such as sociology, statistics and economics to analyse and explain populations-related phenomena. Along demography, epidemiology (from Greek *epi*, meaning 'upon, among', *demos*, meaning 'people, district', and *logos*, meaning 'study, word, discourse') is a discipline dealing with populations’ health status, which focuses on the causes, development and consequences of health diseases among the population itself.

The link between demography and epidemiology has always been complex, since both disciplines work on populations-related phenomena and their fields of research often overlap, even if relevant studies are carried out following diverse approaches and different (but parallel) research methods. It is precisely their multidisciplinary nature and the correlated topics they investigate that support through time a process of interconnection between the two. Both demography and epidemiology study the populations’ health conditions, a topic related to a number of other issues such as the causes of death and the onset of diseases. In particular, both disciplines study mothers and children’s health status before, during and after pregnancy, investigating the causes of low birth weight, infant mortality and maternal mortality during pregnancy.

In the last decades, an increasing trend of children’s ponderal excess status in Italy and all over the world has opened the floor for new studies and related debates. In fact, it is well known that overweight/obesity since one’s childhood is a determinant of one’s health conditions, influencing their quality of life and their survival at all ages. A number of psychological, physical and social problems can be the consequences of an important ponderal excess, that call upon researchers to look for its causes not only in children’s “daily habits and lifestyles”, but also in parents’ socio-demographic factors and the environment where children grow up. As a matter of fact, this thesis explores the shared interest of

demography and epidemiology to offer a better analysis of the main causes of overweight/obesity during infancy.

1.1 Objectives of the study

The main purpose of this thesis is to study the causes of children's ponderal excess in Rome, Italy. The subjects have been followed since their birth until they are 8 years old. In fact, the ponderal excess status has become one crucial topic of research in the last ten years, since it is one main cause of people's bad health conditions and can lead to important social issues, too. In literature, there are already some studies which analyse the relations between different health conditions, one's daily habits and the onset of overweight/obesity in children.

To my knowledge, there is no study in Italy which observes the onset of children's ponderal excess in a longitudinal birth cohort. Thanks to the large amount of indications from the literature, this thesis first wants to identify the main determinants of the risk of overweight/obesity in childhood, measuring children's weight at different ages.

Secondly, apart from what is already known in literature, this thesis wants to look into other potential factors of the increase in body fat during childhood, a stage of life when measurements are particularly difficult to conduct. This is the reason why this work makes use of two specific exposures, which have been frequently debated in the last years.

The first exposure is the traffic-related air pollution, which has become one crucial environmental exposure to be studied during the last years because of its relation with a number of health outcomes. Despite the fact that there is not yet a clear connection between traffic and obesity, a few studies have already shown the existence of some relation where traffic exposure causes obesogenic effects both in children and in adults. In Italy at present there is no study aiming at verifying this association, also because data on air pollution are hardly accessible.

The second exposure related to the onset of overweight/obesity in children is the socioeconomic position (SEP) of the families where children live, even though the SEP can be actually viewed more as a condition proxy than an exposure in itself. In literature there is a large amount of studies on the topic, where the measures of the SEP are parents' educational level and occupational status, while only few studies analyse the context where children live.

The context may be a variable which not only includes children's house and parents' education/occupation, but also refers to the dwelling area (e.g., city centre, suburbs etc.), children's school, families' income and so forth. The aim here is to understand whether individual (e.g., educational level, occupational status etc.) and contextual exposures (e.g., income level, small area indicators of SEP etc.) have or not the same effects on the onset of weight excess in children.

The data used in this thesis come from a prospective birth cohort of newborns enrolled in Rome. The Italian project '*Genetica e Ambiente: Studio Prospettico sull'Infanzia in Italia'* (GASPII) is a longitudinal study, and its different research waves – here called as follow-ups or follow-up points/visits - will be later introduced. To accomplish the first goal of studying the possible determinants of the ponderal excess status, data coming from the 15-month, 4-year and 8-year follow-ups are used. To complete parts two and three of this thesis, only the 4- and 8-year follow-ups are considered.

1.2 Outline of the thesis

This thesis is structured in six parts. This outline provides a short explanation of the contents of each section in the thesis.

The second chapter introduces the background studies on the topic of this thesis, and both the global and the Italian debates on infant obesity are presented. Afterwards, the main international sources from which definitions of overweight and obesity derive are described. Furthermore, an overview of the main possible risk factors and determinants of being overweight and obese during infancy follows. In addition, this chapter also focuses on two paths that are viewed as "possible causes" of the risk of being overweight/obese: they are the effects of the environmental air pollution and families' socioeconomic condition. To conclude the chapter, the potential diseases caused by a ponderal excess during childhood are discussed.

The third chapter introduces the GASPII cohort and the methodologies used during the research. A first paragraph focuses on the importance of a cohort study, then the cohort of newborns is presented. Furthermore, data collection and questionnaires' administration are also discussed, followed by a presentation of the variables used in these analyses. Finally, the

methodological tools of this work are described, including the descriptive statistics, the Generalized Linear Model (GLM), the regression model, the Generalized Estimating Equation models (GEE) and the Inverse Probability Weighting (IPW).

The fourth chapter contains the descriptive statistics of the variables collected at the moment of birth and at each different follow-up visit. Furthermore, the results of the analyses on the possible determinants of the ponderal excess and changes on the ponderal status are presented, considering all available outcome measures collected through the different follow-ups.

The results of the analyses of environmental air pollution and the socioeconomic position as exposures are presented in Chapters five and six. The text of both chapters is taken from the manuscripts sent to two different scientific journals. The article exploring the effects of air pollution on children's ponderal excess will be published in the journal *Environmental Research*. Meanwhile, the paper on socioeconomic position has been submitted to another journal. Two brief introductions open the papers, where the exposures' assessment and the relevant methodologies are better described. Moreover, a supplementary part for the SEP article on the SEP indicator is included at the end of the article itself.

As a conclusion, a discussion on the results of each analysis is reported at the end of the thesis, including a number of final considerations to provide an overview of the entire work. Finally, five Appendixes are also included with additional tables, which are recalled within the text.

2. Background

2.1 Infant obesity worldwide and in Italy

In the last decades, the percentages of overweight and obese people have grown consistently all over the world, causing concern in the society and enhancing the interest of researchers. The World Health Organization (WHO) estimated that in 2014 around 1.9 billion individuals over 18 years were overweight, and that around 600 million people could be considered obese. It means that, in 2014, more than 39% of the adult population in the world was overweight, while 13% was obese (World Health Organization (WHO), 2014).

The prevalence of people with a ponderal excess doubled in most countries, both developed and developing ones, from 1980 to 2014. There are a lot of studies showing that the situation is getting problematic and hard to manage in different parts of the world (Diouf et al., 2010; Olsen, Baker, Holst, & Sørensen, 2006; Y. Wang, Monteiro, & Popkin, 2002). This kind of problem may generally affect people regardless of their socioeconomic status, of the context in which they live, and also irrespective of their age. Like the adult population, children can also be affected by an excess in their body weight. Infant obesity is a problem becoming everyday more alarming, more difficult to treat and eventually to prevent. The World Health Organization observed that, globally, some 42 million children aged less than 5 years old were obese in 2014 (World Health Organization (WHO), 2014).

Historically, the idea of a child's healthy status changed a lot. A long time ago, overweight/obese children were considered healthy in a world where undernutrition was a rule and the excess of body fat was then assumed to preserve them from diseases and infections. Moreover, that was a condition stressing the high socioeconomic status of the family. In modern times the perception of society dramatically changed, because the problems and the effects potentially deriving from an excess in body fat, especially during infancy, started to be evident (de Onis, Blössner, & Borghi, 2010).

Several studies showed evidence that an increasing prevalence of overweight and obese children is globally widespread, even though their distribution in the world is

asymmetrical. Obesity is one common problem, especially in most industrialized countries where there is a double prevalence of overweight and obese children, if compared to the non-industrialized ones (de Onis et al., 2010).

The distribution of the children Body Mass Index (BMI) has deeply changed in the last ten years, and the prevalence of overweight and obesity in children has rapidly increased (de Onis et al., 2010). The studies on the increasing prevalence of ponderal excess throughout the world highlighted the importance of controlling and analysing these trends in overweight and obesity in both children and toddlers. Between 2011 and 2014, in the US, the prevalence of obese children aged 2-5 years old was of 8.9%, while it was of 17.5% in obese school-aged children, from 6 to 11 years old (Ogden, Carroll, Fryar, & Flegal, 2015). In Japan, the prevalence of children at risk of obesity has shown to increase rapidly during the period of the elementary school, more for male than for female pupils (Yoshinaga et al., 2004). The same study found a similar trend without gender differentiation, showing an increasing prevalence of children becoming obese just before starting the elementary school. Furthermore, the rising risk of becoming overweight/obese during childhood has also been documented in a research by Dehghan et al. (2005), focussing on changes in overweight and obesity prevalence in several developed countries (Dehghan, Akhtar-Danesh, & Merchant, 2005).

In Europe a study called IDEFICS (namely *Identification and prevention of Dietary- and lifestyle – induced health Effects in Children and infantS*) was created with the aim of providing a common surveillance system on the spread of overweight and obesity among European children (Ahrens et al., 2006, 2011). The IDEFICS study was born to determine the origins of the ponderal excess in European children, to understand the aetiology of the disorders related to the conditions of ponderal excess and to set up a prevention programme. The population at study was composed by children below the age of 10 coming from eight countries in Europe (including Italy), and information about weight, height and anthropometric measurements was collected. In addition, information about environmental, behavioural, lifestyle, genetic and social factors was also collected, in order to explore the main determinant factors of the ponderal excess among European children. One of the last articles concerning the IDEFICS cohorts showed the distribution in Europe of the prevalence of overweight and obese children (Ahrens et al., 2014). In this study, different kinds of classification of the body mass index were used such as those developed by the IOTF, the WHO, the CDC and also the reference curves by Kromeyer-Hauschild (Zellner, 2001): this allowed a comparative analysis between different, widely-used classification methods. What

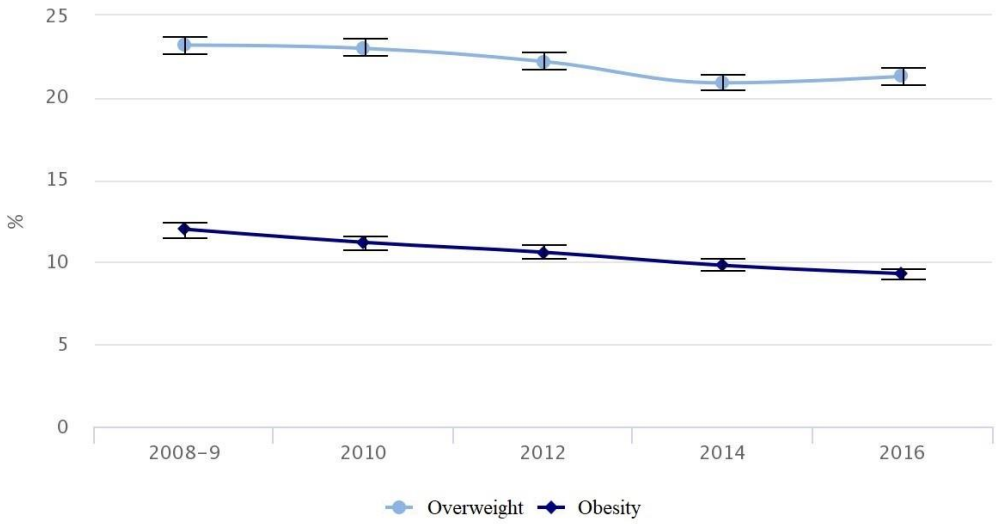
eventually emerged from this study was that the higher prevalence of obesity in Europe was condensed in its southern part, where the level of education and the socioeconomic status of the population are lower, whereas the groups from northern Europe had a lower prevalence of childhood obesity. In the study sample of the IDEFICS cohort, the overall prevalence of childhood overweight and obesity was respectively attested around 12.8% and 7%. The highest values were observed for Italy, Cyprus and Spain, while the lowest percentages were observed for Belgium and Sweden. These measurements of prevalence were all obtained considering the IOTF cut-off point (Ahrens et al., 2014).

The European Childhood Obesity Surveillance Initiative (COSI) is another European project with the aim of controlling and measuring the changes in prevalence of overweight and obesity. It is a project established by the WHO to monitor ponderal changes in primary school children, aged 6 – 9 years old (T. M. Wijnhoven et al., 2014; T. M. A. Wijnhoven et al., 2013). The project consists of different rounds (they are at the fourth now): they were only fourteen countries joining the project during the first round in 2008, while today the total number has increased to thirty-nine. Again, the results from the last round (Breda, 2017) showed a difficult situation where the prevalence of childhood overweight and obesity is increasing all over Europe, with differences between western, southern, eastern and northern countries. Despite the fact that the highest levels of childhood overweight (including obesity) have always been found in southern countries, a sharp increase of these levels has also been observed in the eastern ones.

Italy was one of the first countries to join the COSI project and it is still one of its main supporters, with data collected by the Italian Ministry of Health within the project *OKkio alla Salute*. This Italian project was inaugurated in 2008 for controlling the alarming changes in the ponderal excess of Italian children in school grade 3 (8 – 9 years old). The project assessed the prevalence of childhood overweight and obesity and examined the possible risk factors within different waves.

The results of the waves from 2008/2009, 2010, 2012, 2014 and 2016 showed a slightly decreasing trend of childhood ponderal excess (both in overweight and obesity). The prevalence of overweight decreased from 23.2% in 2008/2009 to 21.3% in 2016, while the percentages of obesity prevalence declined from 12.0% to 9.3%, as reported in Figure 1 (Nardone, 2016; Spinelli, Lamberti, Nardone, Andreozzi, & Galeone, 2010).

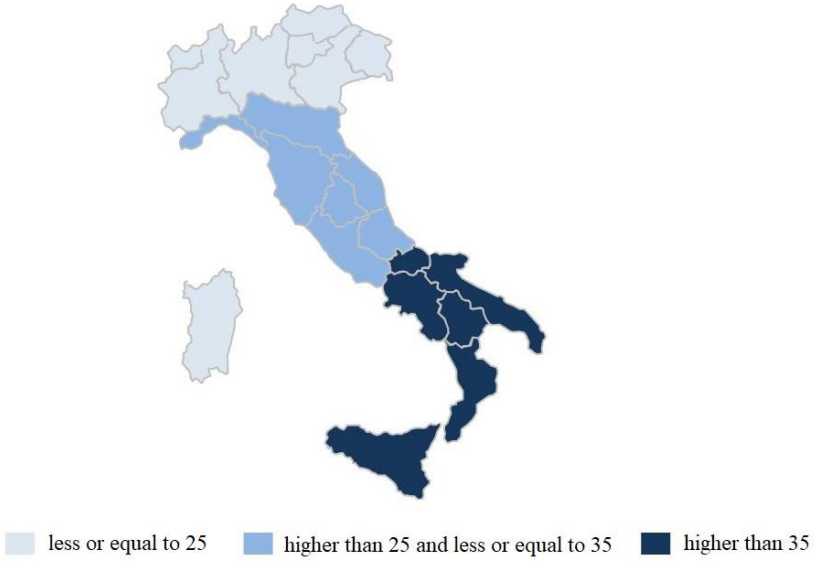
Figure 1: Trend of the overweight and obesity status of Italian children aged 8-9.



Source: OKkio alla Salute, Results 2016

Despite this phenomenon seems to be decreasing over time, the prevalence in both overweight and obesity statuses among Italian children is alarming. In 2016, three children out of ten had ponderal excess problems, and it seems that female are a bit less obese than male ones. It emerged from the last results of this survey that the prevalence in Italy is still high, and that there are yet differences between the Italian regions. Several studies showed significant differences in prevalence of obese children from northern, central and southern Italy. The regions in the South have higher values of overweight and obese children if compared with children living in the North (Bracale et al., 2013; Claudio Maffeis et al., 2006). The results of *OKkio alla Salute* showed a trend where the prevalence in the northern regions of Italy is close to the national mean (in this case, the prevalence is referred to all these overweight and obese children), as it can be seen in Figure 2.

Figure 2: Regional distribution of overweight and obese children aged 8-9, in Italy.



Source: OKkio alla Salute, Results 2016

2.2 Main international definitions of overweight and obesity (WHO, CDC, IOTF): BMI classifications

Obesity is a health condition that can come from an imbalance between assimilated energy (amount of caloric food intake) and consumed energy (amount of calories burned off with physical activities). According to the WHO, both overweight and obesity are conditions that could be defined as "*abnormal or excessive fat accumulation that presents a risk to health*". There exist different methods and indexes for measuring the body fat, in order to evaluate if a subject is or not overweight/obese. Nonetheless, the most elementary and universally-used index is the Body Mass Index (BMI).

The BMI is a raw measure of the ponderal status of an individual which allows to verify the ratio between their weight and height. The index evaluation is simple and intuitive: the weight of the individual is measured in kilos and is divided by the square of the height,

which is measured in meters (kg/m^2). The BMI is a good index of the level of body fat, it is easy in computation and therefore is the most used all over the world.

The BMI computation is used for both adults and children, with appropriate precaution. The classifications that are usually used to define the ponderal status in adults cannot be used interchangeably for assessing children's ponderal status. It actually depends on the period of life of the subject. Children are in a period of life when growth is faster (especially in the first months of life) than for adults. As a matter of fact, adults do not grow that fast and can only experience a change in their weight, more than in their height. For this reason, when children's ponderal status is taken into account, the use of different kinds of classification is strongly recommended (Dinsdale H, Ridler C, 2011). Generally speaking, all individuals above 18 years of age are considered to be part of the adult population and their BMI can be classified according to the following categories:

- obese, if the BMI has a value higher than 30 kg/m^2
- overweight, if the BMI has a value between 25 kg/m^2 and 30 kg/m^2
- normal weight, if the BMI has a value between 18.5 kg/m^2 and 25 kg/m^2
- underweight, if the BMI has a value below 18.5 kg/m2.

As mentioned before, it is not either easy or immediate to contextualize adults' standard classification when it comes to children's BMI, because when children's weight and height are discussed, their growth should also be considered. To do so, age and sex have also to be considered. This is the reason why, instead of the parameters used for adults, specific thresholds have been detected and calculated for children. These thresholds have been defined in terms of specific z-scores or percentiles to check where the children's BMI is situated, i.e. if they are over or under the threshold (BMI's z-scores and percentiles can be easily transformed from one to the other using cut-off points, which do not implicate any change). The widely used classifications are three. They are all constructed through different methodologies and with diverging objectives; therefore, they could lead to different results and interpretations, if applied on the same data (Gonzalez-Casanova et al., 2013; Monasta et al., 2010).

The main differences among the three classifications depend upon the population/s used for constructing the classifications themselves (Gonzalez-Casanova et al., 2013). The three classification systems for children's BMI, which are less than 18 years old, are presented in Table 1.

Table 1: Definition of infant obesity according to the different worldwide organization

Organization	Definition of Childhood Obesity
World Health Organization	*WHO Child Growth Standards (birth to age 5)* • **Obese:** Body mass index (BMI) > 3 standard deviations above the WHO growth standard median • **Overweight:** BMI > 2 standard deviations above the WHO growth standard median • **Underweight:** BMI < 2 standard deviations below the WHO growth standard median *WHO Reference 2007 (ages 5 to 19)* • **Obese:** Body mass index (BMI) > 2 standard deviations above the WHO growth standard median • **Overweight:** BMI > 1 standard deviation above the WHO growth standard median • **Underweight:** BMI < 2 standard deviations below the WHO growth standard median
U.S. Centers for Disease Control and Prevention	*CDC Growth Charts* In children ages 2 to 19, BMI is assessed by age- and sex-specific percentiles: • Obese: BMI > 95th percentile • Overweight: BMI > 85th and < 95th percentile • Normal weight: BMI > 5th and < 85th percentile • Underweight: BMI < 5th percentile In children from birth to age 2, the CDC uses a modified version of the WHO criteria
International Obesity Task Force	• Provides international BMI cut points by age and sex for overweight and obesity for children age 2 to 18 • The cut points correspond to an adult BMI of 25 (overweight) or 30 (obesity)

Source: Defining Childhood Obesity, Harvard School of Public Health Obesity Prevention Source Web Site

The WHO classification was developed through a sample of selected children, who were either exclusively breastfed at least for 4 months from their birth, or weaned by the age of 6 months and consequently partially breastfeed up to the first year of life. Furthermore, mothers should not have smoked during pregnancy. Children were thus selected to obtain a sample of the healthy population, which might be representative of a hypothetical and optimal growth curve during childhood.

The classification of the U.S. Centers for Disease Control and Prevention (CDC Growth Charts) was created to obtain a classification of the children population in the US. The internal population was thus used as reference population through five national surveys, which were carried out between 1963 and 1994.

The last classification is the International Obesity Task Force (IOTF), which was created to obtain an international reference population. The classification was created with data from surveys coming from six different countries in the world (i.e., Brazil, Great Britain, Hong Kong, The Netherlands, Singapore and the United States).

These three classifications were conceived to achieve different objectives and their differences actually lead to different reference thresholds. It is important to underline that the three classifications do take into consideration children's sex and age, not only because of children are different from adults, but also to take account of part of the errors which might be introduced by the classification itself. The final choice among the different classifications depends on the type of study carried out and its main goals. It is therefore recommended to consider not only their creation paths, but also their limitations. The IOTF, which was also created to obtain an international reference population, does not catch efficiently the ponderal excess, if compared to the other classifications (Gonzalez-Casanova et al., 2013). The CDC Growth Chart has been designed to have an internal reference for the United States, but now it is often used internationally. The WHO classification may lead to an overestimation of overweight and obesity, since it was created from a selected sample of healthy children. Nevertheless, the WHO Child Growth Standards will be used in this thesis, essentially because of its worldwide diffusion as a classification system for children of different ages. Furthermore, this is one of the main classifications ever created to be applicable on children from their birth until their majority age, and it is constantly updated and analysed.

2.3 Abdominal fat measurements and blood lipids levels as additional measures of ponderal excess

Another type of measure that can be used to evaluate the ponderal excess of the individual is the measurements of the abdominal fat condition, i.e. the waist circumference, the hip circumference and their ratio. These measures of central obesity have been studied as proxies of one's ponderal excess and there is scientific evidence associating it with cardiovascular diseases, hypertension, diabetes and metabolic syndrome (Bassali, Waller, Gower, Allison, & Davis, 2011; Blüher et al., 2013; C. M. Chen, 2010; Choi et al., 2017). Abdominal fat measurements are mostly used when assessing ponderal excess because they can usefully detect the visceral fat deriving from an adverse health status (in most cases, metabolic syndromes and cardiovascular diseases). This is the reason why abdominal measurements can also be a better tool to assess childhood obesity (and other kinds of pathologies, too): in fact, despite of the worldwide diffusion of the body mass index, they are used to measure the degree of the overweight/obesity status, but they do not take into account the fat distribution in the body.

These alternative measures of body fat can be screening tools in children and adolescents when used jointly with the BMI. Several studies showed the importance of measuring the waist circumference and the waist-to-hip ratio (or waist-to-height ratio), in order to evaluate the risk of overweight and obesity in children (Bassali et al., 2011; Blüher et al., 2013; C Maffeis, Grezzani, Pietrobelli, Provera, & Tatò, 2001). Despite the evidence, central overweight/obesity measurements are not yet a common practice for children, and the BMI index is the main tool to check the weight status. If there are two kinds of dimension for the ponderal excess, it would be reasonable to make use of both of them in order to have robust results or to evaluate the differences between the two measures.

Another type of measure for the body fat is the level of the blood lipids, which are known to be related to the ponderal excess. Dyslipidaemias is measured as an excess amount of different kinds of lipids in the blood (e.g. cholesterol and/or fat phospholipids, triglycerides, etc.). These health problems can derive from the genetics as well as from one's diet and lifestyle. Total and high-density lipoprotein (HDL) cholesterol are positively related to the metabolic syndrome, a metabolic disturbance which may lead to a ponderal excess. In fact, the prevalence of metabolic syndromes has been found to be high in individuals with

high levels of abdominal fat (Hospital, 1983). Moreover, high levels of blood lipids during childhood have been associated with a higher risk of cardiovascular diseases and of high lipoprotein levels during adulthood (Meral, Uslu, Ünsal, & Akçay, 2015; Sorensen, 2007; Suárez et al., 2008), despite the fact that the cut-offs needed to define the presence of dyslipidaemias are not well defined. There are studies in literature showing evidence of association between overweight and/or obesity in children and higher lipid risk profiles (Friedland, Nemet, Gorodnitsky, Wolach, & Eliakim, 2002; Meral et al., 2015; Riaño-Galán et al., 2017). Furthermore, evidence of abnormal blood lipids profiles has been found in other studies on children with ponderal excess problems, if compared with those having a normal weight (Friedemann et al., 2012; Korsten-reck, Kromeyer-hauschild, Dickhuth, & Jena, 2008). Shamai et al. (2001) showed that high levels of BMI were associated with low levels of HDL, while a study made by Friedemann et al. (2012) showed that total cholesterol levels were definitely higher in obese children, if compared to normal weight children (Friedemann et al., 2012; Shamai et al., 2011). For the reasons above, it is essential to recognize that ponderal excess is strictly related to low HDL cholesterol and to high levels of total cholesterol. This is true both in adults and in children, as Daniels assessed in his editorial (Daniels, 2011).

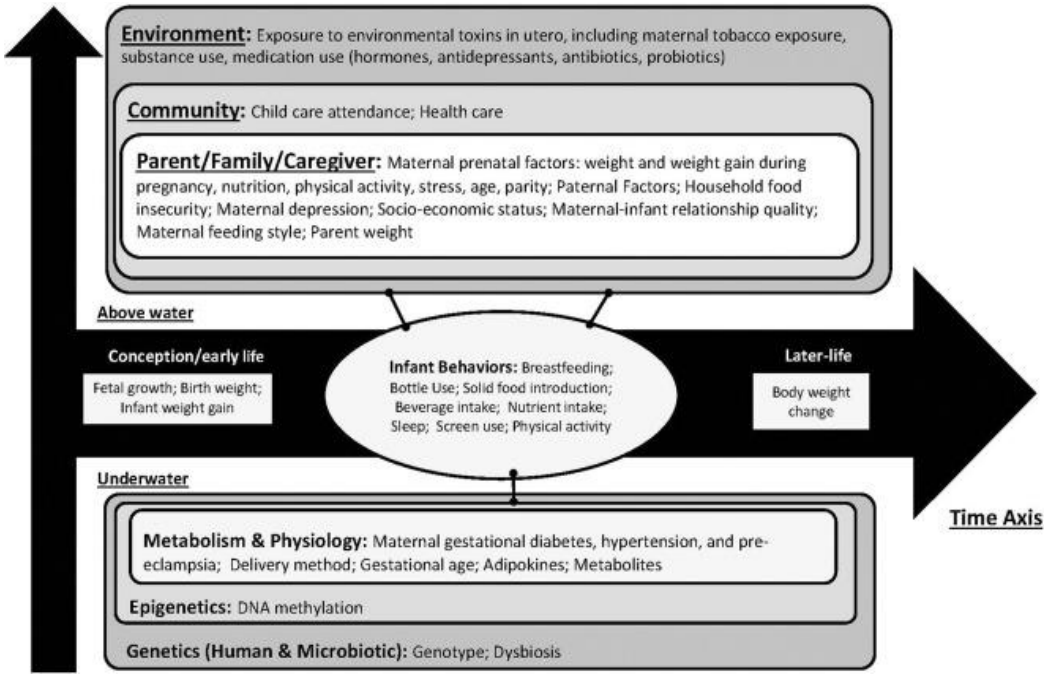
2.4 Literature review

Infant overweight/obesity is becoming a central issue all over the world. This is the reason why it is necessary to recognise all the main causes and triggers of the epidemics in children. As said before, obesity (or overweight) is a health condition with no proper balance between the calories consumed and the ones burnt. Generally speaking, more calories from an increase in food intake and a decrease in physical activity are two fundamental causes of obesity, also as consequences of modern lifestyles (e.g., less need of energy expenditure, etc.). Nevertheless, eating habits and one’s own lifestyle cannot be the only explanation to the increase in body fat, particularly when talking about childhood. Figure 3 presents the main factors related to the ponderal excess.

The community and the family (including parents and caregivers) play an important role in the health status of the children, as well as the environment where they grow up. Plausible explanations of a child's obesity/overweight may lie in the genetics and epigenetics.

Moreover, their metabolism and physiology can also depend on their parents' habits and lifestyles. There is increasing evidence of perinatal and early life factors underlying obesity in children (Ebbeling, Pawlak, & Ludwig, 2002). However, these factors can be related to mothers' status during pregnancy (including lifestyles, BMI and health conditions), to the early years of children's life (for example, their growth in weight after birth, breastfeeding and weaning, etc.) and finally to their own behaviours.

Figure 3: Conceptual framework for systematic review of childhood obesity risk factors from conception.



Source: Jennifer A. Woo Badal, Lindsey M. Locks, Erika R. Cheng, Tiffany L. Blake-Lamb, Meghan E. Perkins, Elsie M. Taveras (2016). Risk factors for childhood obesity in the first 1000 days. *American Journal of Preventive Medicine*, 50(6).

There are numerous factors related to maternal weight during pregnancy that can constitute a trigger for a child becoming obese. Many studies reportedly confirmed maternal obesity being a significant contributor to one child increase in weight (Catalano & Ehrenberg, 2006; Galtier-dereure, Boegner, & Bringer, 2000; Linabery et al., 2013). Sometimes maternal obesity is even associated with a double risk of giving birth to obese or overweight offspring (Whitaker, 2004). In addition, gain in maternal weight during pregnancy should also be closely monitored, since it is another factor increasing the risk of obese offspring (Evagelidou

et al., 2006). During pregnancy mothers should be aware of the possible onset of the gestational diabetes, that has been demonstrated to be one of the causes of weight gain in babies, also leading to other health problems such as type 2 diabetes (Evagelidou et al., 2006; Young et al., 2002).

It is well known that smoking is not a healthy behaviour in any stage of life, but smoking during childbearing can cause health problems to the child too. One of the effects of smoking during pregnancy is indeed an increasing risk of having overweight/obese children (Al Mamun et al., 2006; Whitaker, 2004). Several studies have also shown that maternal smoking during pregnancy is a reliable determinant of obesity during childhood. The BMI of children whose mothers used to smoke during pregnancy is higher than the BMI of those whose mothers did not. Furthermore, the former group of women usually have a higher weight, a lower socioeconomic status and a lower educational level, and their children have a lower weight at birth (Behl et al., 2013). Other studies instead did not find a strong association between overweight in children and smoking habits during pregnancy, since mothers that used to smoke during pregnancy can deliver low birth-weight children (Oken & Gillman, 2003) without any lasting effects on their future body size. However, it is important to consider that this group of children may have a higher likelihood of being overweight (and obese), if compared to those with higher weight at birth. Later in life, these can be assumed to be the results of neonatal exposure to nicotine, which is strongly related to the acceleration of postnatal weight gain (Al Mamun et al., 2006): nicotine can in fact alter the appetite regulation system in children's brains (Jo, Talmage, & Role, 2002). Maternal smoking habits during pregnancy can indeed affect offspring's future body size and weight, but it is important to study the likelihood of being overweight/obese taking account of different smoking habits. A differentiation is needed between those who used to smoke before and/or after being pregnant (but not when they were so), and those who used to smoke during their pregnancy, and it can be useful to fully measure the risks deriving from smoking habits in such a delicate period (Al Mamun et al., 2006).

The age of mothers at birth has been universally considered as one of the main determinants of the health status of their babies. To my knowledge, there is no study at present that analyses the direct association between mothers' age at birth and status of overweight/obesity in children. Despite that, there are a lot of studies evidencing that both too young and too aged mothers can cause negative health outcomes for their offspring (Fall et al., 2015; Myrskylä & Fenelon, 2012).

It is reasonable to say that all the factors in children's early life that may be associated with the possibility of developing obesity should be identified, in order to prevent the appearance of ponderal excess. There are a few studies investigating gestational age at delivery as a potential risk factor for an overweight status during childhood. On the one side, it is well known that prolonged gestations may lead to an alteration in body composition and to an increase in adiposity later in life. On the other side, prematurity is also correlated to ponderal excess during life. The results from studies analysing the association between gestational age and overweight/obesity during childhood are not conclusive (Blake-Lamb et al., 2016). Some studies demonstrate that preterm and small for-gestational-age children are more at risk of being overweight or obese during childhood (P. Li et al., 2012): this is due to accelerated postnatal growths, which are in turn related to pre-term births, eventually resulting in a ponderal excess status in children (Uthaya et al., 2005). Another study shows that, among pre-term infants, those with a more advanced gestational age have a higher risk of becoming overweight/obese during childhood (Vasylyeva et al., 2013). There is another study showing that post-term male babies, with a rapid gain in weight during childhood, could be exposed to a higher risk of overweight or obesity, while it is not the same for female newborns (Beltrand et al., 2012).

There are studies highlighting the possible association between maternal depressive symptoms and development of ponderal excess in infants. Maternal depression may affect the health status of children in many different ways (Zimmer & Minkovitz, 2003). The hypothesis stems from parenting practices, as mothers with depressive symptoms, for example, may breastfeed for less time or may not provide any healthy eating choice. At the same time, maternal depression may lead to a shorter duration of sleep in children, more time for them sitting in front of the television and less time spent doing physical activities. In literature, there is increasing evidence of the effects of maternal depression (not only limited to the post-partum depression) on the weight of their children. There are studies showing that chronic maternal depression during their early years increase the risk for the children of being overweight/obese later in childhood (Audelo et al., 2016; Gross, Velazco, Briggs, & Racine, 2013; L. Wang et al., 2013). The measures of maternal depression include the Edinburgh postnatal depression scale (EPDS), the Patient Health Questionnaire-9 (PHQ-9), or the Center for Epidemiologic Studies-Depression (CES-D) scale. All these scales are usually based on self-reported data; a score is calculated summing up the points obtained from each answer and a final categorization allows a classification of the depressive symptoms.

As mentioned before, post-natal factors are as important for children's health modification as maternal conditions during pregnancy. Weight at birth and consequent growth after birth are strongly related to the prevalence of overweight/obesity during childhood. Some studies report that faster growth in infants is more likely for those with a lower weight at birth or with a lower gestational age. Other studies show instead that large size at birth is associated with the risk of being overweight during childhood (Baker, Olsen, & Sørensen, 2008; Hui, Schooling, Sze, & Leung, 2008). In general, it is acknowledged that fast growth in postnatal life (i.e., during the first months of life) increases the risk of being overweight or obese, and the likelihood is even higher if weight gain in the postnatal period is taken into account (Monasta et al., 2010).

Some observational studies report that breastfeeding can be a deterrent against overweight and obesity later in life (Crume et al., 2012; Frye & Heinrich, 2003; Scott, Ng, & Cobiac, 2012; Von Kries et al., 1999). Breast milk provides the child with several benefits such as immunologic benefits or less severe diseases when they occur. The importance of breastfeeding depends on how long it is carried on: the more children are fed with maternal milk, the more they will be "protected", while on the contrary a shorter or less intensive breastfeeding reduces the degree of protection received. For an optimal diet, exclusive breastfeeding is strongly recommended during the first 6 months. The association between the risks of having overweight (or obese) children with the duration of breastfeeding was then studied: the results showed that if breastfeeding lasted one month more, there was a reduction in the odds of overweight or obesity by 4 percent. After a 9-month threshold, this effect becomes less consistent until it disappears (Harder, Bergmann, Kallischnigg, & Plagemann, 2005). In a study by Gillman et al. (2001) the duration of breastfeeding and the difference between breast milk and infant formula are taken into consideration. The results show that breastfeeding is the best choice to reduce the prevalence of obesity later in life.

The hours one sleeps at night constitute one lifestyle factor that should be considered when studying the risk of being obese. Some epidemiological studies underline the link between short sleep habits and obesity, suggesting the involvement of the metabolic hormones regulating appetite and energy expenditure. Therefore, short sleeps may cause obesity because of the metabolism. Some studies also revealed that short sleep duration produces an increase in appetite due to both a decrease in leptin (an appetite suppressing hormone) and an increase in ghrelin (an appetite stimulating hormone) (Cappuccio et al., 2008; Chaput, Brunet, & Tremblay, 2006; Must & Parisi, 2009; Taheri, Lin, Austin, Young,

& Mignot, 2004). Eventually, sleep may be an important regulator of obesity, and its effects should be considered. According to the National Sleep Foundation (https://sleepfoundation.org/), a certain minimum hours should be slept at night at each different age. In fact, the organization has tried to develop a set of age-specific recommendations, based on literature review and studies. Parents and researchers should consider these guidelines to improve the sleeping habits of children.

In addition to sleep duration, children's sedentary behaviour must be considered as one lifestyle factor associated with the risk of being obese (or overweight). The hours spent watching television or regularly practising sports activities are factors that should be taken into account, as in some studies they are associated with sleep loss. It has been demonstrated that if children are more active they can sleep more at night (Reilly et al., 2005). The amount of daily time spent watching TV or playing with the computer should also be viewed as additional factors which may cause overweight or obesity. For example, for children younger than 2 years old, the American Academy of Pediatrics has recommended not to let them watch television or play with videogames, and not to place a television in their bedrooms as to avoid an abuse of it (Education, 2001). Many studies have found out that the amount of time spent watching TV is a relevant element which contributes to overweight or obesity because less time is devoted to physical activity, also increasing the calories intake (Arpesella et al., 2008; Bracale et al., 2013). As a matter of fact, children who practise physical activity for some three or four times per week show a lower risk of becoming obese.

The family structure has always been important, since it provides social support which is fundamental for developing children's habits and behaviours. The family composition may impact on the amount of food eaten, on dietary patterns, on physical activities and so on. Research suggests that children coming from single-parent families have a higher risk of being overweight/obese and the same was true for only children (A. Y. Chen & Escarce, 2013; Gibson et al., 2007; Hunsberger et al., 2012). Grandparents play also an important role in the family structure, since they may take care of children when parents cannot be there. There is evidence suggesting that the risk for children to develop overweight or obesity is higher when grandparents take care of them (Jingxiong et al., 2007; B. Li, Adab, & Cheng, 2015; Watanabe, Lee, & Kawakubo, 2011). The influence of grandparents on their eating behaviours and/or sports habits may lead to an increasing risk of ponderal excess, as well as to wrong perceptions of children's status of health or ponderal excess.

2.5 A focus on air pollution

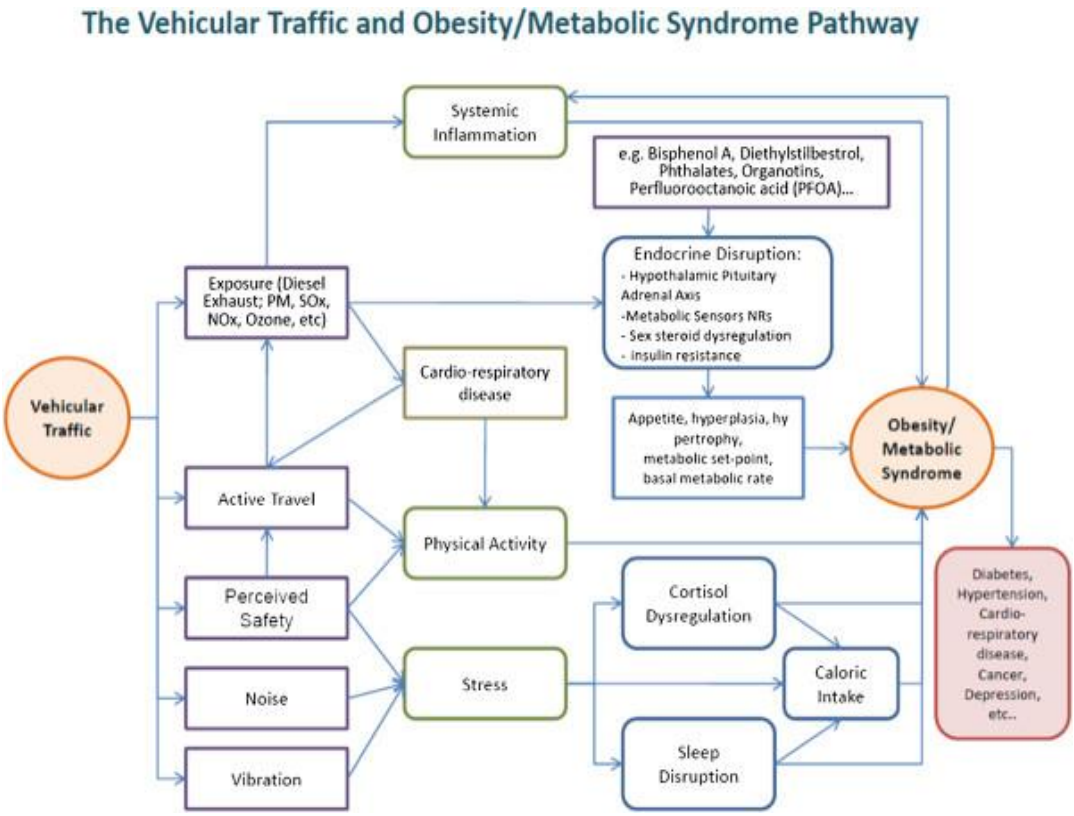
Recent studies have evidenced another possible trigger of the ponderal excess during infancy, mainly related to the pregnancy and postnatal years. In fact, the effects of air pollution have been associated with several diseases and disorders in children. For example, the exposure to traffic-related air pollution is one of the main causes of asthma exacerbation in children (Anderson, Favarato, & Atkinson, 2013). On the contrary, it is not clear yet whether there is a direct link between pollution exposure and an early asthma onset, but some studies do point to that (Gruzieva et al., 2013; Ranzi et al., 2014). Other studies instead show the existence of an association between the exposure to traffic-related air pollution and cognitive development in children of different ages (Porta et al., 2016; Sunyer et al., 2015).

Early life exposure to air pollution has also been correlated to an increase in child mortality and a reduced foetal growth. In Fleisch et al. (2015) there is evidence that being exposed to traffic-related air pollution during pregnancy may lead to a reduced foetal growth and a subsequent rapid weight gain after birth (Fleisch et al., 2015). This study uses traffic density variables as exposures, which are measured in the third trimester during pregnancy. The mechanisms behind this association may be related to maternal and placental inflammation, blood coagulation, foetal oxidative stress, related DNA damage, which can affect the nutritional transfer from mother to foetus (Kannan, Misra, Dvonch, & Krishnakumar, 2006). An experiment on mice has also demonstrated that the exposure to air pollution can cause an increase in weight gain through adipose inflammation or also through brain modifications, which alter the satiety signals (Bolton et al., 2012; Sun et al., 2009).

Being exposed to environmental pollution during pregnancy seems to affect newborns in different ways, among which there is low birth weight (Dadvand, Parker, Bell, Bonzini, & Brauer, 2013; Nieuwenhuijsen, Dadvand, Grellier, Martinez, & Vrijheid, 2013; Shah, Balkhair, & Group, 2011). As mentioned before in other parts of the chapter, children whose weight was low at birth have a higher risk of experiencing a fast growth after birth, and therefore they also have a higher risk of being overweight or obese later during childhood. In recent years the association between environmental pollution and childhood obesity has attracted the interest of researchers. In 2014 Jerrett et al. published an article where they analysed the association between traffic-related air pollution and BMI growth in children aged 5-11 years old (Jerrett et al., 2014). The authors drafted a conceptual framework to explain the

different ways in which vehicular traffic (and therefore air pollution) may affect ponderal excess and the outbreak of the metabolic syndrome (Figure 4).

Figure 4: Conceptual framework illustrating pathways from vehicle traffic to obesity and metabolic syndromes



Source: Jerrett, M., McConnell, R., Wolch, J., Chang, R., Lam, C., Dunton, G., … Berhane, K. (2014). Traffic-related air pollution and obesity formation in children: a longitudinal, multilevel analysis. *Environmental Health: A Global Access Science Source*, *13*(1), 49. doi:10.1186/1476-069X-13-4

Vehicular traffic may affect active movements and the perception of safety: this means that people will train less and that they will walk or bike less. The energy balance will change and they will be more at risk of developing overweight or obesity. On the other side, vehicular traffic producing high noise levels and vibration can cause more stress leading to cortisol dysregulation and sleep disruption. As mentioned before, sleep habits and regulation are related to caloric intake, depending on the metabolic hormones regulating appetite and the expenditure of energies. They also depend on the emissions of vehicular traffic, which may cause systemic inflammation and endocrine disruption, may lead to formation of chronic

diseases and to a future decrease of physical activities. Following this conceptualization, the authors investigate the contribution of the traffic-related air pollution over the risk of being obese in a cohort of children between five and eleven years old. The results show a positive association between the exposure to pollution and the growth of BMI, also confirming the results from a study conducted by Jerrett et al. in 2010 over a cohort of children aged 10-18 years old (Jerrett M, McConnell R, C.C. Roger Chang, Wolch J, Reynolds K, Lurmann F, Gilliland F, 2010). This paper demonstrates the association between traffic density in the neighbourhoods of children's houses and BMI levels at the end of childhood. In addition, other studies also point to the positive association between environmental pollution and ponderal excess in children.

Polycyclic aromatic carbons (PAHs) are chemicals released during combustions and they have important effects on human health. Inhaling PAHs during pregnancy apparently leads to higher levels of BMI Z-score in children aged 5-7 years old (Rundle et al., 2012). A study was conducted in China where they demonstrated the severe effects of air pollution on a group of children aged 2-14 years old, on overweight and obesity prevalence measured with the WHO standards (Dong et al., 2014). A recent article by Mao et al. (2016) explore the effects of exposure to $PM_{2.5}$ and mother's pre-pregnancy body mass index (BMI) on children's overweight and obesity, analysing the two factors both individually and jointly (Mao et al., 2016). Studying a cohort of children born in Massachusetts, they discovered that the exposure to environmental $PM_{2.5}$ during a period ranging from pregnancy until the first two years of life increases the risks of being overweight and obese during childhood. Moreover, children with mothers with ponderal excess before pregnancy and also exposed to $PM_{2.5}$ had a double or even higher risk of developing overweight or obesity.

To my knowledge, there is one Italian study analysing the effects of traffic-related air pollution on BMI levels in children (Grassi et al., 2016). The results do not show any association between traffic levels all around children's houses and schools and the prevalence of overweight and obese children. Despite this result, the authors declare that the methods for measuring traffic density were not objective: in fact, they measured vehicular traffic using parents' perceptions, that could evidently be affected by subjective bias.

2.6 A focus on socioeconomic position

It is widely known that the socioeconomic status is one of the main determinants of health during one's life (Currie & Stabile, 2003; Spencer, 2001). There are several indexes, different indicators and proxy variables which measure an individual or a family's socioeconomic position, including but not limited to the occupational status, the educational level, the income level, the poverty rate and the index of deprivation. In 2004 Galobardes et al. published a glossary with all the most important indicators of the socioeconomic status, each one with their pros and cons (Galobardes, 2006a, 2006b). The authors affirm that there is not a standard measure for the socioeconomic position, and that the choice of the final indicators depends on the aim of each single study. This is the reason why there exist different kinds of proxies as measures of the socioeconomic position.

It is well known that in Europe a low educational level (which is a measure of the socioeconomic level of the family/individual) is correlated to high mortality rates, if compared with highly educated subjects. These differences reveal some important inequalities that have to be taken into consideration (Mackenbach et al., 2003; Mackenbach J.P., Stirbu I., Roskam & Schaap, Maartje M, Menvielle G., Leinsalu M., 2008; Madsen, Andersen, Christensen, Andersen, & Osler, 2010). There is a higher prevalence of adverse health conditions for these having lower socioeconomic positions, as several studies on adult populations showed. The way the socioeconomic status (which depends on income levels) affects the mortality rate is then assessed (Lund Jensen et al., 2017; Stringhini, 2010), even if health behaviours are important determinants of the mortality rates. The effects of a low socioeconomic status are analysed in relation to outcomes such as the hospitalization rates or the mortality rates for cardiovascular surgery (N Agabiti et al., 2008; Nera Agabiti et al., 2009).

One's socioeconomic status should be assessed on the basis of their whole lifetime (Lee et al., 2017). In 2017, Lee et al. investigated the potential association between one's socioeconomic position and the risk of having a coronary heart disease (CHD), studying a cohort of people aged more than 50 years old (M. Lee, Khan, & Wright, 2017). They demonstrate here that the onset of the disease (CHD) does not only depend on the socioeconomic levels in adulthood, but also during childhood.

Therefore, health seems to be negatively affected by one's socioeconomic position both in adults and children. Nevertheless, it is true that children are the most vulnerable subjects. Several studies suggest that income and other proxies of the socioeconomic position are associated with children's adverse health conditions such as asthma, mortality and acute and chronic illnesses (G Cesaroni, Farchi, Davoli, Forastiere, & Perucci, 2003; Spencer, 2001). Furthermore, there is increasing evidence of a relation between the socioeconomic position of the family (measured in different ways) and the risk of excess weight during childhood.

Mothers' professional situation is one of the proxies measuring their socioeconomic status. During last decades, there has been a great increase in the percentage of working women in Europe. This change encouraged studies to be carried out on the effects of the female employment on child obesity. Most studies have found an association between maternal employment and the risk of overweight/obesity in children (García, Labeaga, Ortega, & Trabajo, 2006; Greve, 2008). The paternal occupational status is another proxy of the socioeconomic position, but sometimes it has not a association with the ponderal excess status (Grassi et al., 2016; Shrewsbury & Wardle, 2008). Of course, parents' educational levels are deeply related to their employment status. Parents' educational status is strongly related to the behaviours acquired by mothers (and to a lesser extent by fathers) during pregnancy (e.g., smoking habits, dietary habits, etc.). In fact, it has been demonstrated that children of mothers/fathers with a high educational status have a lower risk of developing adiposity accumulation during their first years of life (Grassi et al., 2016; Ogden, Lamb, Carroll, & Flegal, 2010; Parrino et al., 2016; Ruiz et al., 2016).

Studies where the contextual indicators (and not the individual variables) are used as proxies of the socioeconomic status of the family show similar results on ponderal excess outcomes in children. Contextual variables include different kinds of indicator based on: a) census socioeconomic information (Giulia Cesaroni, Agabiti, Rosati, Forastiere, & Perucci, 2006; Hardy et al., 2016); b) accessibility to services (Rogers et al., 2015); c) presence of a family health insurance (I. Lee, Bang, Moon, & Kim, 2016); d) poverty income indicators (Ogden et al., 2010), and so on. However, the association between contextual socioeconomic indicators and overweight/obesity in children has been clearly assessed.

The main factors leading to lower socioeconomic positions, lower educational levels or unemployed status to cause a ponderal excess in children include: a) the prices of the

obesogenic and healthier food; b) the degree of physical activity, and c) the awareness of the effects of being overweight or obese, which are often unknown. The presence of persistent socioeconomic inequalities should be avoided through programmes aimed at fighting socioeconomic disadvantages in children.

2.7 Overweight and obesity: major implications

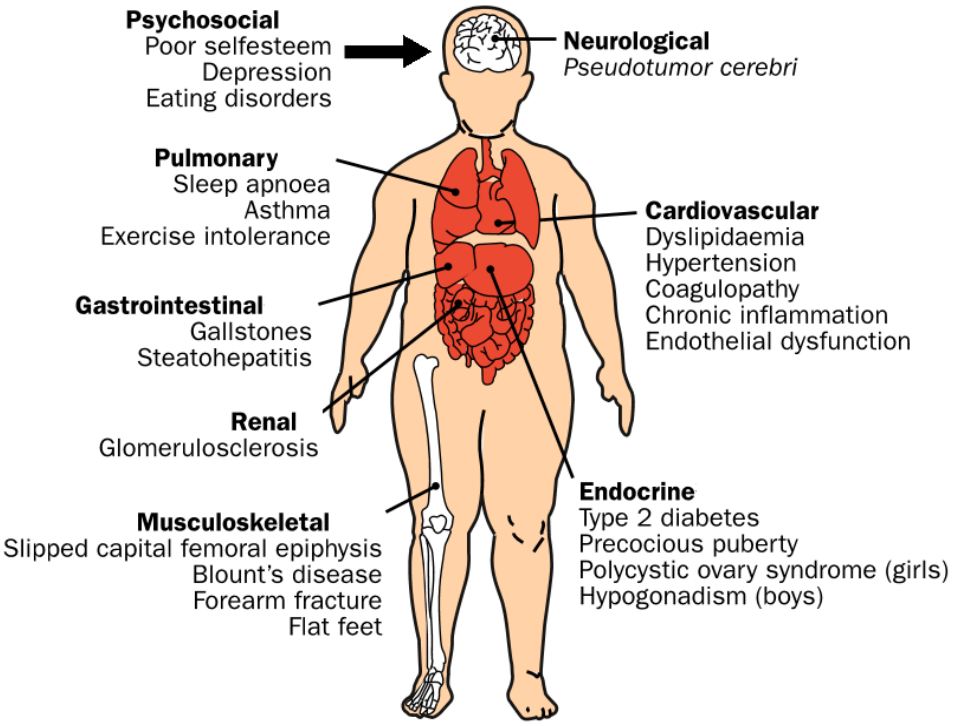
The obesity epidemics is nowadays one of the most important issues in public health because of the relevant complications and potential illnesses (also death occasionally) that could consequently arise (Ebbeling, Pawlak, & Ludwig, 2002; World Health Organization (WHO), 2000). Several studies affirm the importance of checking obesity determinants during one's whole life. Being overweight (and/or obese) during childhood increases the risk of being overweight later in life, during adolescence and adulthood. Being obese in childhood may lead to overweight or obesity in adulthood. At present, there are not yet sufficient data to assess these risks properly, but the existence of the mechanism is proved. Furthermore, even if these subjects were once obese children who were then able to lose some weight as adults, nevertheless their mortality and morbidity rates grow faster than for their "healthy" counterparts (Deckelbaum & Williams, 2001).

The excess of adiposity is the leading cause of a number of diseases both in children and adults. In Figure 5 different kinds of morbidities are reported. Other than the ponderal excess, there are just a few other problems during childhood that may have a strong influence on emotional and psychosocial status. Obese children usually have poor self-esteem, and the situation becomes even worse when they go to school and realize how their bodies are shaped (Griffiths, Parsons, & Hill, 2010; Hesketh, Wake, & Waters, 2004; Strauss, 2000). Children in ponderal excess usually have eating disorders too, that may also contribute to their alarming weight status. The development of a depressive status in children with ponderal excess is not that rare, because of the abovementioned psychosocial problems and the discrimination that they often suffer. Childhood obesity is also associated with neurological factors and diseases such as the pseudo-tumor cerebri (idiopathic intracranial hypertension) (Must & Strauss, 1999; Speiser et al., 2005; Sugerman, DeMaria, Felton, Nakatsuka, & Sismanis, 1997).

Some respiratory conditions like asthma and sleep disorders also tend to increase health problems in obese and overweight children. Obstructive sleep apnoea (OSA) is also

related to obesity status in both children and adults: in fact there is a higher prevalence in respiratory problems in subjects with ponderal excess (Must & Strauss, 1999; Speiser et al., 2005). The mechanisms for which obesity produces cardiovascular changes and alterations depend on the accumulation of visceral fat affecting cardiac output and causing an increase in blood volume. Obese children have higher risks of elevated hypertension, dyslipidaemia and chronic inflammation (Deckelbaum & Williams, 2001; Ebbeling et al., 2002), and they may also suffer from coagulopathy, endothelial dysfunction and others cardiovascular diseases (Caserta et al., 2010; McCrindle, 2015).

Figure 5: Health complications of childhood obesity



Source: Ebbeling Cara B., Pawlak Dorota B., Ludwig David S. (2002). Childhood obesity: public-health crisis, common sense cure. *Lancet* 360*: 473*–82.

In addition, obese individuals may suffer from other gastrointestinal and renal diseases, which are frequently observed in overweight/obese children too. For example, the increase in biliary excretion results in gallstones formation (Shaffer & Small, 1977). Moreover, obese children may develop steatohepatitis, a disease of the fatty liver with liver inflammation and concurrent fat accumulation (Lerret et al., 2011). At the same time, children

and adults in ponderal excess status may suffer from glomerulosclerosis, a disease of the kidneys.

In children, fat accumulation also influences the development of the musculoskeletal apparatus, causing a number of bones deformities such as slipped capital femoral epiphysis, the tibia vara (also known as Blount's disease), the forearm fracture and the flat feet (Auer, Mazzone, Robinson, Nyland, & Chan, 2016; Wabitsch et al., 2012). These complications are just some of the potential health problems of obese children, that may lead to orthopaedic issues later in life.

The association between childhood obesity and the risk of developing type 2 diabetes is becoming increasingly evident. There has been an alarming increase in prevalence of type II diabetes in children and adolescents, despite the fact that it usually occurs in adulthood (SINHA et al., 2002). While overweight and obese women may develop the "polycystic ovary syndrome", men in ponderal excess status may develop the hypogonadism disease (Corona, Vignozzi, Sforza, Mannucci, & Maggi, 2015; Magnotti & Futterweit, 2007). These endocrine diseases may show up during one's last years in childhood or being developed during adulthood: however, they constitute some of the consequences of childhood obesity. In addition to all this, some long-term effects are also produced from a condition of ponderal excess, such as an increasing risk of cancer (e.g., colon cancer, pancreas cancer, thyroid cancer, etc.).

Childhood obesity can cause a great number of severe health problems later in life. If there is no intervention at first, all adult morbidities are likely to appear earlier at younger stages of life. Despite that, some childhood-related complications may also erupt later in life and follow different developments. Nevertheless, it is not true that all overweight/obese children will suffer from the diseases as mentioned above, since they might not experience any medical complication. Childhood ponderal excess has been acknowledged as one crucial determinant of bad health conditions. The burden of diseases deriving from early obesity has become quite important: this is the reason why everyone should be aware of its consequences, even though they are not immediately evident in children.

3. Data, study design and methodology

3.1 Cohort studies: implications and utility

The data used in this thesis come from a cohort of new-borns, enrolled at the moment of birth and followed-up during time with planned questionnaires. The cohort study is the only type of observational study that has a role in the analysis of causality, and in developing analyses aiming at estimating the effects of different exposures on several kinds of outcomes.

In a cohort study, the enrolled subjects start to be part of the cohort before the occurrence of the event at study (i.e., the outcome). In this way, it is possible to identify one or more exposures that may have a role in the outcome at study. The temporal sequence of events occurring in a cohort study allow to identify the mechanisms of causality, giving a strong scientific base to endorse the results coming from the analyses. Furthermore, besides the advantages from the sequence of exposures-outcomes at study, there are other advantages that may come from a cohort study. The first is the possibility to collect simultaneously a lot of different information in a short time span; therefore, it is possible to evaluate different outcomes and consequently also different kinds of exposures. Cohort studies are often used to analyse and explore rare outcomes and diseases. Moreover, this kind of design is useful when there is the necessity to measure the same information, at different moments in time, or when it is necessary to observe the exposure's changes during time. This way, it is possible not only to calculate the prevalence of the disease, but also the incidence of the outcome at study (Jae W. Song, MD and Kevin C. Chung, MD, 2011; Levin, 2003).

Cohort studies have several advantages, but there are also some disadvantages to be considered: the first is their high costs and the long time necessary to carry on the study. When the outcome of interest is rare, it is necessary to have a large-sized sample to correctly detect the outcome. Another problem related to cohort studies is people's unwillingness to be enrolled in the studies and the drop-out rates at each single wave. The biases that may arise from these problems are related to the characteristics of the individuals that refuse to participate or to remain in the project.

Despite the difficulties that can arise with this study design, the utility behind an observational and prospective study is undeniable. Cohort studies consider a selection of individuals that belong to a population and that experience an event in a precise moment (or during an identified period): for this reason, cohorts can refer to different groups of people enrolled because of a common event they have experienced.

Cohorts of newborns are composed by children enrolled at birth, usually together with their mothers and fathers. Data coming from a cohort of newborns allow researchers to collect a lot of information related to the gestational period, the first months and years of children's life, until the adolescence or until the end of the prospective study. The relevance of collecting this type of data through children's growth years lies in the collection of information on genetics, biological and environmental factors, that may play a role in the immediate health status of children, and in their future health status during adolescence and adulthood, studying these effects from the point of view of the life cycle.

The enrolment of a cohort of newborns implies the monitoring of the subjects through time in different waves, which are used to collect information about the events occurred during the gestational, neonatal and infancy periods, that are essential to the development and the onset of diseases during one's life. In the last years, a lot of studies with this research design have been conducted, with the aim of collecting a large pool of data which are used afterwards to analyse the determinants of the health status linked to different periods of one's life.

All over the world, in the last decades the number of longitudinal birth cohort studies has deeply increased. Behind this choice, there is the awareness that a lot of pathologies occurring during one's life are strictly related to a combination of effects due to certain exposures during the intrauterine period and one's first years of life.

Nowadays, the active European birth cohort are numerous. Below follows a list of the most popular ones:

- the English cohort BiB (Wright et al., 2013)
- the Swedish cohort BAMSE (Lagrelius, Wahlgren, Matura, Kull, & Lid??n, 2015) and the one of the project CATSS (Anckarsäter et al., 2011)
- the French cohort of the project EDEN (Galéra et al., 2015; Melchior et al., 2015)
- the German cohort MAS (Grabenhenrich et al., 2014)

- the Spanish cohort INMA (Monica Guxens et al., 2012)
- the Dutch cohorts PIAMA (Wijga et al., 2014) and GENERATION – R (Jaddoe et al., 2010)
- the IDEFICS and COSI European birth cohorts (Ahrens et al., 2011; Breda, 2017).

The European cohorts are mostly based on the same design, which considers the enrolment of a group of children at birth, coming from different birth centres designated to recruit parents (the recruitment can be done during the last trimester of pregnancy, throughout the pre-natal courses, or immediately before/after the delivery), to collect parental consensus to the enrolment (it happens sometimes that only mothers apply because of fathers' absence) and to collect several waves of data after children's birth and during their first years of life. The information from parents' questionnaires focuses on children's health issues, parents and children's health status, their medical history, demographic characteristics, the household environment where children grow up and families' habits and lifestyles.

Each European birth cohort has its own specific objectives such as the analyses of the determinants of respiratory diseases like asthma, rhinitis or allergy (as the BAMSE (Lagrelius et al., 2015) and MAS (Gough et al., 2015) cohorts and the PIAMA (Ruijsbroek, Wijga, Gehring, Kerkhof, & Droomers, 2015) project), the study of preterm births (the Greek cohort RHEA (Chatzi et al., 2009)) or the study of the causes related to morbidity and infant mortality (the BiB (Wright et al., 2013) cohort). Data coming from some of these cohorts have already been used to explore the association between maternal smoking habits during pregnancy and the first years of newborns' life and their cognitive, socio-emotional development (as it is done in the EDEN (Galéra et al., 2015; Melchior et al., 2015) cohort).

One of the main topics recently discussed is the effects of air pollution exposure during pregnancy: for example, the ESCAPE (Mònica Guxens et al., 2016) study is a project built on different cohort-based datasets which has the objective to evaluate the impact of the atmospheric air pollution on infant autism disease.

Some of these European birth cohorts are created to collect not only mere data, but also biological samples from the gestational period, at the moment of delivery and sometimes during clinical visits. The biological samples will then allow different kinds of analyses which may further contribute to the development of genetic studies, and also to understand the relation between exposures and the onset of different kinds of diseases.

In Italy, the use of birth cohorts is becoming more frequent, and in the last years several birth cohorts have been created, such as the cohorts of newborns in Bologna (D., Porta, M.P. Fantini, 2006) and Trieste (Vecchi Brumatti et al., 2013), the national birth cohort in the NINFEA study (Richiardi, Pizzi, Rusconi, & Merletti, 2015), the Piccolipiù cohort (Farchi et al., 2014), that is a young cohort of children from five different cities in Italy (i.e., Rome, Florence, Turin, Trieste and Viareggio) and the GASPII cohort used in this study.

3.2 Study population

The project "*Genetics and Environment: Prospective Study on Childhood in Italy*" (known as GASPII) started in June 2003 in Rome. It was created by the Department of Epidemiology of the Lazio Regional Health Service - Lazio Region, with the aims of establishing a cohort of children enrolled at the moment of birth and collecting data during a number of follow-up points (Porta, Forastiere, Di Lallo, & Perucci, 2007). As a longitudinal study, the GASPII is a survey composed of different waves, called here follow-ups (or follow-up points).

Children's enrolment in the GASPII cohort started in June 18th, 2003 and it was completed in November 5th, 2004 with an extra four-month extension as against to what had been planned at the beginning. The deadline extension was due to the high number of mothers that refused to take part in the project at the moment of the enrolment, causing a reduction in the cohort dimensions. Therefore, the extension was aimed at obtaining a satisfactory number of participants. To further advertise the project, leaflets and posters were printed and distributed in the gynaecologist wards of the hospitals involved in the recruitment. The area considered for the enrolment of the newborns is the local health units (ALS) Rome E, which was chosen for the presence of two big hospital centres: namely, the hospital Cristo Re and the Policlinico Agostino Gemelli. The GASPII cohort is a valuable prospective study which allows to assess the associations between different exposures and outcomes. Despite its internal validity, it is not representative of all the births in Rome.

To be eligible, newborns had to be born alive in one of the two hospitals mentioned before, without being transferred to other centres after birth. The eligible population includes infants whose mothers were older than 18 years old at the time of recruitment, and living in the area of the ASL Rome E (counting about 500,000 inhabitants). The mothers who decided

not to participate in the project were asked to give basic demographic information for a secondary assessment of potential selection biases at the time of enrolment. All this information was collected and anonymized.

At the time of enrolment, mothers were given information about objectives and methodologies of the study by the doctors, also clarifying all the aspects related to data collection privacy. The medical doctors asked parents (mothers and fathers, if the latter were also present) to subscribe some informed consents, including mothers', fathers' and children's, in order to confirm their participation in the project. For collecting children's data only one parental signature was needed, while both parents had to sign their consents to the treatment of maternal and paternal data.

At a later time, a number of planned interviews were carried out to collect the first information about pregnancy. The first questionnaire was administered by an interviewer, and mothers were asked to answer questions about their socio-demographic status, clinical history, current and previous pregnancies, emotional status during pregnancy, environmental exposures, anthropometric measurements before and after pregnancy, lifestyles and household environment (questionnaire M-1: *The mother: environment, lifestyle, health and pregnancy, La madre: ambiente, stile di vita, salute e gravidanza***)**. The second questionnaire was filled out by the mothers and was aimed at collecting information on their diets and eating habits during the gestational period (questionnaire D-2: *The mother: diet during pregnancy, La madre: la dieta in gravidanza*). Another questionnaire was filled by the medical doctor in the birth centre and it collected basic information on the delivery. This information was extracted from the medical record or sometimes asked directly to the mothers (questionnaire M-2: *The mother: the delivery, La madre: il parto*). Fathers' basic information was collected after the delivery with a specific questionnaire similar to mothers' basic one (questionnaire P-1: *The father: environment, lifestyle and health, Il padre: ambiente, stile di vita e salute*), regarding socio-demographic information, clinical and medical history, lifestyle and household environment. Moreover, another questionnaire was administered to neonatologists at the moment of discharge from the hospital in the very first days after the delivery, in order to collect newborns' characteristics at their birth (questionnaire B-1: *The child: birth and first days of life, Il bambino: la nascita e i primi giorni*).

The GASPII cohort, as most of other European birth cohorts, has its own biological bank where several kinds of biological samples of the subjects participating in the study are

stored. In the Cristo Re hospital, cord blood samples of the newborns were collected at birth, while in the Policlinico Gemelli hospital blood samples were collected in the day of discharge from the hospital. In both cases, the biological samples would be used for genetics analyses with children's DNA. In addition to children's biological samples, maternal blood samples were also collected with different methods depending on the birth centre: at the Cristo Re hospital maternal blood was collected before mothers and children's discharge from the hospital, while at the Policlinico Gemelli hospital blood samples were collected during a first visit after 10-15 days from the moment of delivery. As for newborns' blood samples, maternal biological samples would also be used for genetics analyses and DNA extrapolation. All blood samples collected in the two hospitals were carried to the Genetics Institute every 24 hours for treatment and storage. If previously-enrolled mother-child pairs decided to drop out from the study, their biological samples would be destroyed.

Further information about children's development, health status and growth were collected at different follow-up points after delivery. The first follow-up was done 10-15 days after delivery (questionnaire B-2: *The child: first visit after 10-15 days from birth, Il bambino: prima visita a 10-15 giorni dalla nascita*). The clinical visit took place in the same birth centre, and different kinds of information on weight, length, head circumference, breastfeeding and sleep were collected. In the case of families' unavailability to go to the hospital for the visit, families' paediatricians were involved to collect the necessary information.

A second follow-up was done when children were 6 months old (questionnaire B-3: *The child: the follow-up at 6 months from birth, Il bambino: il follow-up a 6 mesi dalla nascita*). Mothers were contacted on the telephone by interviewers (often if previously agreed so) and were administered a questionnaire focusing on dietary habits, breastfeeding and children's weaning, housing environment, health status (particularly in relation to falls, access to the emergency room, hospitalization, information about respiratory diseases or allergies, vaccinations and drugs), psychomotor development, sleeping habits and so on. Moreover, information about mothers' emotions after delivery was collected because they are important factors for the relationship between mothers and children during the first months after birth.

A third follow-up was then conducted when the children were 15 months old through a telephone interview by some trained personnel (questionnaire B-4: *The child: the follow-up at 15 months from birth, Il bambino: il follow-up a 15 mesi dalla nascita*). The information

collected during this follow-up focussed on children's dietary patterns, children's living environment, grandparents' role as caregivers or the presence of siblings, health status (as in the 6-month follow-up, particularly related to falls, access to the emergency room, hospitalization, information about respiratory diseases or allergies, vaccinations and drugs etc.), and their screen habits. A few questions directly asked mothers about their emotive status, the latter deriving from the relationship between mothers and children during their first 12 months of life. Finally, mothers were asked to book a clinical visit with a paediatrician from the same birth centre before children were 18 months old. During these visits, paediatricians filled in the questionnaire (questionnaire B-5: *The child: the clinical follow-up at 15 months from birth, Il bambino: il follow-up clinico a 15 mesi dalla nascita*) with information on anthropometric measurements (e.g., weight, height, head circumference etc.), physiological data (e.g., cardiac and respiratory frequencies etc.) and exams on minor malformations. If this was the case, a psychomotor development test (Denver II) was carried out to check children's motor and language developments.

A fourth follow-up was planned when children were 4 years old (questionnaire B-6: *The child: the follow-up at 4 years, Il bambino: il follow-up a 4 anni*). As for the other follow-ups, the main questions included dietary habits, sleeping habits, screen time per day, lifestyle factors, health status and clinical history, number of siblings, grandparents' role as caregivers and children's motor development. Furthermore, mothers were also asked to answer questions about their relationship with their children and to give information about their emotional status. Finally, anthropometric measurements such as children's weight and height were collected by some trained personnel.

Afterwards, a follow-up was done when children were 7 years old (questionnaire B-7: *The child: the follow-up at 7 years, Il bambino: il follow-up a 7 anni*). Questions focussed on the same information collected during the previous follow-ups, plus some others about their physical activity. Anthropometric measurements of weight and height were also collected such as systolic and diastolic blood pressures.

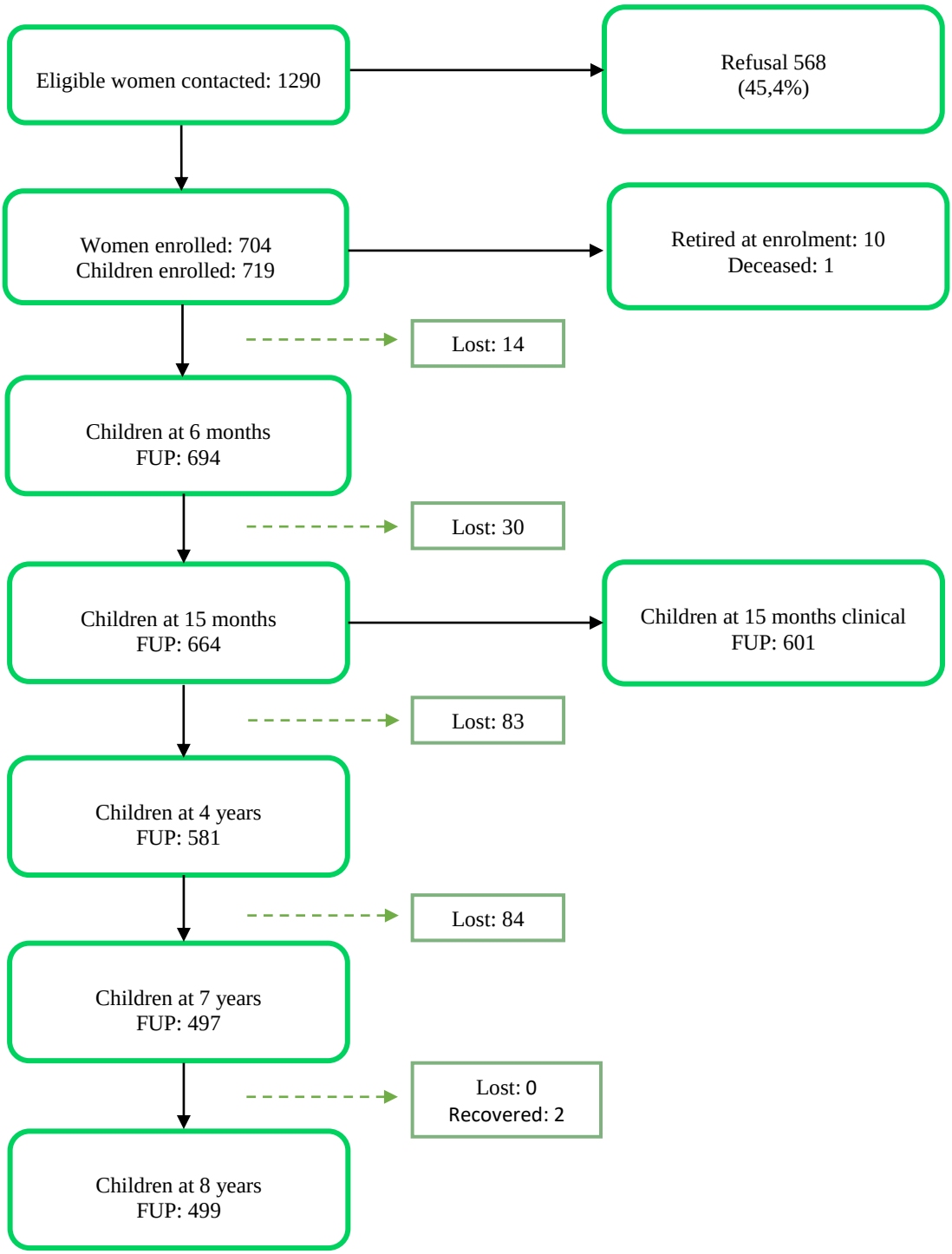
The last survey was conducted when children were 8 years old (questionnaire B-8: *The child: the clinical follow-up at 8 years, Il bambino: il follow-up clinico a 8 anni*). Once again, mothers were asked the same questions as in the previous questionnaires, including children's eating habits, physical activity, sleeping habits, screen time, presence of siblings and grandparents. Moreover, a focus on respiratory diseases and respiratory allergies was also

included in the questionnaire. In this case, anthropometric measurements were directly collected with a clinical visit. Waist and hip circumferences were collected together with weight and height of standing children, and using standardized procedures to the nearest 0.1 cm. Moreover, blood samples were collected to store information about blood lipids and blood count. Blood samples were transferred to the central laboratory where total and HDL cholesterols were analysed. The concentrations of cholesterol were measured with plasma samples (namely, Li-heparin plasma) with standard enzymatic methods (such as the Cobas c systems or the Roche Diagnostics), following manufacturers' instructions.

For a clear and rapid understanding of the GASPII project and its phases, Figure 6 illustrates its main passages through the different follow-ups and the number of children involved in the study. The total number of women contacted during the enrolment were 1,291, but only 704 of them decided to take part in the project, that is a refusal percentage of 45.4%. At the moment of enrolment, 10 mother-child pairs interrupted their participation in the study, and one child also died. The number of children at the time of enrolment were 719, and it differs from the number of mothers because there were 12 twins couples and one triple birth. At the different follow-ups, the number of children intervening are as follows: 694 children for the 6-month follow-up; 664 children for the 15-month follow-up; 601 children for the 15-month clinical follow-up581 children for the 4-year follow-up; 497 children at the 7-year follow-up; and finally 499 children at the 8-year one. As can be noticed, the number of children has decreased between the moment of enrolment (719 children) and the 8-year follow-up (499 children), showing the main limitations of a longitudinal and prospective study where enrolled participants can decide to drop-out at a certain point in time.

At the same time, it can happen that children do not participate in the 6-month follow-up and may equally continue to be part of the study, as it happens for the 7- and the 8-year follow-ups: as a matter of fact, the total number of children at the 7-year follow-up are 497, while there are two children more at the last one (499 children). Considerations about the total numbers of children participating in the study and the ones missing during certain follow-up points will be discussed in Chapter 4, while paragraph 3.3.4 of this Chapter will illustrate the methodology used in the thesis to account for missing data.

Figure 6: Flow chart of the enrolment and follow-ups of the population at study in the GASPII birth cohort project



3.3 Overview of methods

This paragraph focuses on the models and methods used in this thesis to analyse the main determinants of being overweight/obese during childhood, and to study the effects of different types of exposures on children's ponderal excess.

Before discussing about the methodology, a brief description on the construction of the main outcomes is provided. As said before, calculating children's BMI is not as simple as in the case of adults' BMI, because both children's sex and age (in months and in years) should be considered. On the WHO website there is a SAS program where it is possible to calculate the BMI Z-scores or percentiles of the population at study, according to the WHO standards. When the BMI Z-scores (or the percentiles) have been calculated for each child, a categorical variable is created, that follows the WHO thresholds to differentiate between normal weight and overweight/obese statuses. The threshold changes by age and in this case, it was considered the threshold below and above age 5 years old: from birth to age 5, all children having a BMI Z-score higher than 2 standard deviations above the WHO growth standard median are considered overweight/obese. Children older than 5 years are also considered overweight/obese if their BMI Z-score is higher than 1 standard deviation above the WHO growth standard median.

The BMI Z-score calculations were then performed for the 15-month, 4-year and 8-year follow-ups. All three follow-up points will be used in the first part of the thesis, together with the analyses of the possible determinants of the ponderal excess status. In the second and third parts of the thesis (both presented in the form of a scientific article), only 4- and 8-year follow-ups will be considered, because of an inconsistency for both analyses in the results obtained for the 15-month follow-up.

In the next paragraph, the models used to analyse the data are presented. At the beginning, the stepwise logistic and regression models are described, according to the nature of the outcome variable considered. For each measure of ponderal excess, a different model will be implemented, according to the well-thought-out different sets of determinants. Afterwards, the exposures to air pollution and to the SEP levels (which are considered as two separate exposures) will be evaluated using the Generalized Linear Model (GLM). The GLM model allows to estimate the impact of different exposures according to a cross-sectional approach. Furthermore, a Generalized Estimating Equation (GEE) model will be used to

estimate the impact of these two exposures from a longitudinal point of view, and its main characteristics will be presented. In a paragraph of this Chapter a statistical methodology called Inverse Probability Weighting will be presented as a possible solution to the missing data because of the refusals at the time of enrolment and for continuing the study. All the analyses in this thesis are conducted with SAS and STATA software, version 9 and 13.

3.3.1 Stepwise Models

The stepwise regression model is a procedure that is usually used to find the best set of determinants in explaining the outcome/condition at study. The idea behind this type of statistical procedure is to build the best model with a number of variables from a set of eligible units which turn out to be the best determinants for the outcome at study. The purpose of this methodology is clearly to build a useful regression/logistic model, considering from the beginning all the possible determinants of the outcome at study. In fact the main rule of the stepwise analysis is to include all the variables that may predict a certain response, otherwise the final model will be misleading and underspecified.

The stepwise regression is an automated procedure, and is used most times when the number of determinants is large. Before running the model, a conceptual selection made by the researchers identifies the initial set of potential determinants. Afterwards, the potential determinants will be used to run the model, which will result in a specific selection of variables. The model runs this "mechanical" selection according to a p-value threshold (in most cases corresponding to pr(0.20)), which is set a priori. Two things can happen when the threshold is passed: either the routine stops and the analysis is completed or the variable with the pr>0.2 is removed from the model (it depends on the type of selection model performed).

There are different kinds of stepwise models, which differ in the rules applied to keep the variables in the model, or to remove them from it. The most common stepwise models are as follows:

- the forward selection
- the backward elimination
- the stepwise selection.

In this thesis, it has been used the backward elimination stepwise model in this thesis, that results in either a linear or a logistic regression, according to the nature of the outcome at study. It has been decided to use this procedure instead of the other two because the amount of determinants in the analyses is not too much wide. Another reason why the backward elimination process has been selected comes from the fact that in the forward selection a determinant added in an earlier step may become redundant when another determinant is included in the model. The forward-backward selection which is based on both methods does not account for this problem (since a variable is removed if it becomes redundant), but it is based on longer procedures compared to the backward elimination.

The backward elimination procedure starts considering all the possible determinants together in a full least squares model. The variables are then removed one by one through the different steps, according to the pr>0.20 removal criteria. The backward elimination process should be mainly used when the number of variables in the model is lower than the number of units at study. In this specific procedure the exclusion criteria (and not the inclusion ones) allow the method to remove one variable at a time. The process begins with the full model, and the first variable which is higher than the threshold (p-value) is removed (it means that statistically speaking it is the least significant variable). The new model without the removed variable is tested, and once again the variable with a higher p-value will be removed. The mechanism continues to run until there is not any variable with a p-value higher than the threshold set.

In general, the original model is as follows:

$$Y = \beta_0 + \beta_1 X_1 + \cdots + \beta_j X_j + \cdots + \beta_p X_p + \varepsilon$$

The equation shows the full model at the beginning of the analysis. When p-value of the first variable (for example, X_j) is higher than the threshold, it is removed from the original model (let's say for example that the p-value of $\beta_j X_j$ is higher than the threshold). The new model would then be as follows:

$$Y = \beta_0 + \beta_1 X_1 + \cdots + \beta_{j-1} X_{j-1} + \beta_j X_j + \cdots + \beta_p X_p + \varepsilon$$

As stated before, the backward procedure is used in this thesis for binomial and linear outcomes. Therefore, the backward elimination models implemented here will be logistic or linear models according to the nature of the outcome variables considered.

3.3.2 Generalized Linear Models (GLM)

Ordinary linear regression models imply that a constant change in a determinant leads to a constant change in the outcome variable. A general linear model can be written as follows below:

$$y_i = \beta_0 + \beta_1 x_i + \varepsilon_i \qquad \varepsilon_i \sim N\,(0, \sigma^2)$$

It means that y_i is a linear function of explanatory variables (x_i), it is continuous and it can therefore assume positive and negative values, or it can be equal to zero. The errors (ε_i) are independent and identically distributed as shown above. An extension of the traditional linear regression model is the Generalized Linear Model (GLM), which is often used for nominal or binary outcomes. The term GLM refers to a big class of models where the random component (the probability distribution of the response variable Y_i) may have a normal or a binomial distribution. The systematic component of the model specifies the explanatory variables $X_1, X_2, \ldots, X_p$, which are combined in the determinants function, expressed as a linear combination like:

$$\eta_i \sim \beta_0 + \beta_1\, x_{1i} + \cdots + \beta_p x_{pi}$$

The random and systematic components in the model are connected by a third component of the GLM models, a link function that should always be specified:

$$g(\mu_i) = \eta_i$$

The link function $g(\mu_i)$ is also called *canonical link* function, which corresponds to the inverse of the conditional mean function, and expresses the transformation that should be applied to the dependent variable. In addition to the link function, the family of the dependent variable must also be specified. The GLM models are essentially based on outcome variables which assume a distribution within the exponential family. They cover different kinds of distributions, which can also include binary and continuous data. Each family has usually its own canonical link function.

Differently from the traditional regression (OLS), the GLM models do not need to transform the outcome variable in order to obtain a normal distribution. The GLM models are more flexible because of the presence of the canonical link function, which should be selected separately from the random component. Within the GLM, model checking tools such as the Likelihood ratio test, overdispersion, confidence interval, and Wald test can be used in addition to AIC and BIC criteria.

According to the nature of the outcome variables in this thesis, the GLM models have here the following characteristics:

- for the continuous outcomes, family (Gaussian) and link (identity)
- for the binary outcomes, family (Poisson) and link (log)

Among all the families that can be specified for the binary outcomes, the reason why a family (Poisson) and link (log) combination is used in these analyses depends on the way the results are expressed. With this particular combination, instead of the Odds Ratio (OR) the results have been expressed as Relative Risk (RR). OR's and RR's are usually comparable when the outcome at study is a rare condition. Nevertheless, when the magnitude of the phenomenon is not that rare, the OR's might overestimate the risks and therefore diverge from the RR's. Usually the RR's are used in statistical analyses of data coming from cohort studies, and are also easier to calculate, understand and interpret.

Moreover, in an article by Zou Guangyong in 2004 (Zou, 2004) it was demonstrated that a Poisson regression with a robust error variance (called *modified Poisson regression* approach by the author) may directly estimate the relative risks. The most popular model used when the outcome at study is dichotomous is the logistic regression model, which gives results expressed as OR's. Given all the reasons discussed above, interpreting the OR's as RR's may lead to an exaggeration of the results obtained. Therefore, a binomial regression or

a Poisson regression can be solutions to the problem, even though neither of them are fully satisfying: binomial regression model often leads to convergence problems, while Poisson regression model may provide conservative results. For these reasons, Zou Guangyong demonstrated the validity of this *modified Poisson regression* model, which works with a robust error variance (also called sandwich estimator), essential not to produce overestimated RR's when applying the Poisson regression model to binomial data. In the end, the author showed that the results were reliable also in a limited simulation study, with a 100-individual sized sample.

In the STATA software, the specific commands to obtain the analyses of the binary and the linear outcomes have been written above. In both cases, the commands for obtaining the sandwich estimators have been used.

3.3.3 Generalized Estimating Equations Models (GEE)

The GASPII project is a prospective birth cohort project which precisely allows researchers to collect data on one individual at different moments in time. A number of different measurements are then gathered, and a longitudinal approach like the Generalized Estimating Equations (GEE) is needed to analyse their correlation. A specificity of the GEE model is that it takes into account the dependency of the observations, specifying the "working correlation structure" among information from different moments in time.

The GEE model is an extension of the GLM's, and it provides a semi-parametric approach to longitudinal data and their analyses. The GEE equation can be written as the equation of a GLM model, but the specification of the joint distribution is not required; therefore, either the likelihood function. As the GLMs, GEE models have a response variable (Y) which may be either continuous or categorical, a set of explanatory variables that can be discrete, continuous or a combination of both types ($X_1, X_2, \dots, X_p$), a link function and a family distribution, that should be specified according to the nature of the outcome variable at study. The link functions and the families that can be used in GEE models are basically the same as in the GLM ones.

Compared to the GLMs' approach, GEE models present another fundamental component to take into consideration. Since they model repeated measurements in time, it is

important that the dependency of the observations are either correlated or nested. Data's covariance structure must be specified to get reasonable estimates and standard errors. The structure of the correlation depends on the type of measurement data, and therefore it may easily vary.

The four most popular structures are as follows below:

- Independence
- Exchangeable (defined also as Compound Symmetry)
- Autoregressive of Order 1
- Unstructured

The within-subject correlation is assumed a priori, so the type of correlation structure of the repeated measurements might not be correctly specified. Despite that, GEE models are quite robust against potential wrong choices for the correlation matrix (still, coefficient estimates will be consistent). As in other kinds of models, GEE models have many selection criterion measures as to understand which final model is the best candidate. AIC and BIC are two traditional model selection criteria, that cannot be used in the selection of the GEE models because they are likelihood-based; as said before, full multivariate likelihoods are not available for GEE models. The QIC is another valid tool that can be used in the same way of the AIC criterion. QIC measures are used to compare models with different means or covariance structures, and they are used in this thesis to select the working correlation structure of the data. The QIC's results show that the best correlation structure for the data used in this thesis, is the exchangeable structure. Therefore, every GEE model (also those not reported here) is specified along its exchangeable correlation structure (that is homogenous correlations between different elements).

GEE models can be used when unmeasured dependences of the outcomes at study occur during the research, and this is exactly one of the reasons why are they are frequently used in analyses of data coming from cohort studies. Moreover, missing data are not a problem for GEE models, since they use all the available pairs plus the non-missing observations for each subject present.

The results of the backward elimination models for each outcome at study will be presented and discussed in the following chapter, while the results of the GLM and GEE models on the exposures considered in this thesis (i.e., air pollution and families'

socioeconomic position) will be presented in the shape of two scientific articles in the last two chapters.

3.3.4 Inverse Probability Weighting (IPW) methodology

One important limitation of cohort studies is related to the likelihood of biased results because of scarce numbers of recruited participants and the drop-out events at each follow-up. In fact, all the individuals deciding not to participate in the study may have specific characteristics with consequent specific effects on the final results. Furthermore, anyone deciding to leave the project at a certain moment in time may be part of a subgroup of the population and may cause a non-random lack of observations. In order to avoid these problems, there are different methodologies that can be applied to the analyses. In this thesis, the Inverse Probability Weighting (IPW) methodology is used to account for the lack of information (Narduzzi, Golini, Porta, Stafoggia, & Forastiere, 2014; Robins, 1997; Rotnitzky & Robins, 1997). This methodology is a statistical procedure producing unbiased results, calculating weights, improving efficiency and reducing selection biases. Therefore, the analyses can be corrected weighting all the available observations with the probability of being selected. This procedure is based on the calculation of a weight for each subject, where more weight is given to the subjects with similar information to the individuals who refused to be enrolled (or decided to leave the project). This way, the analyses are corrected without introducing further errors, since the results are based on the probability of being "selected" at one precise stage during the study. In addition, this is a methodology based on the assumption that the inclusion probability is related to observed information, that should also be collected for the nonrespondents or the ones who are not enrolled.

Weights are related to the participation of the eligible population, and are calculated using a logistic regression model where the response variable represents the participation or not in the study (0= not participating, 1= participating). The covariates of this regression model are the main information (and variables) collected at the moment of enrolment, and they must also be available for those subjects who refused to join the study. The covariates are selected according to their importance in the light of the selection process. In the end, weights are calculated as the inverse of the probability factors obtained in the predictive model. The mean value of these weights should approximately be close to 1: if it is not the

case, a penalized set of weights is calculated, in order to reduce the influence of the extreme weights. The penalized IPW is the inverse of the ratio between the probabilities obtained within the first (and complete) model, and the probabilities obtained within a second predictive model that considers the most predictive variable in the first model as one covariate. In this way, the distribution of the set of penalized weights will be symmetric and the mean will be close to 1.

According to the flow chart presented in Figure 7 and all the follow-ups, there are four different selection processes: the first process is the one at the moment of recruitment, while the second, third and fourth ones are respectively related to the follow-up visits at ages 15 months, 4 years and 8 years old.

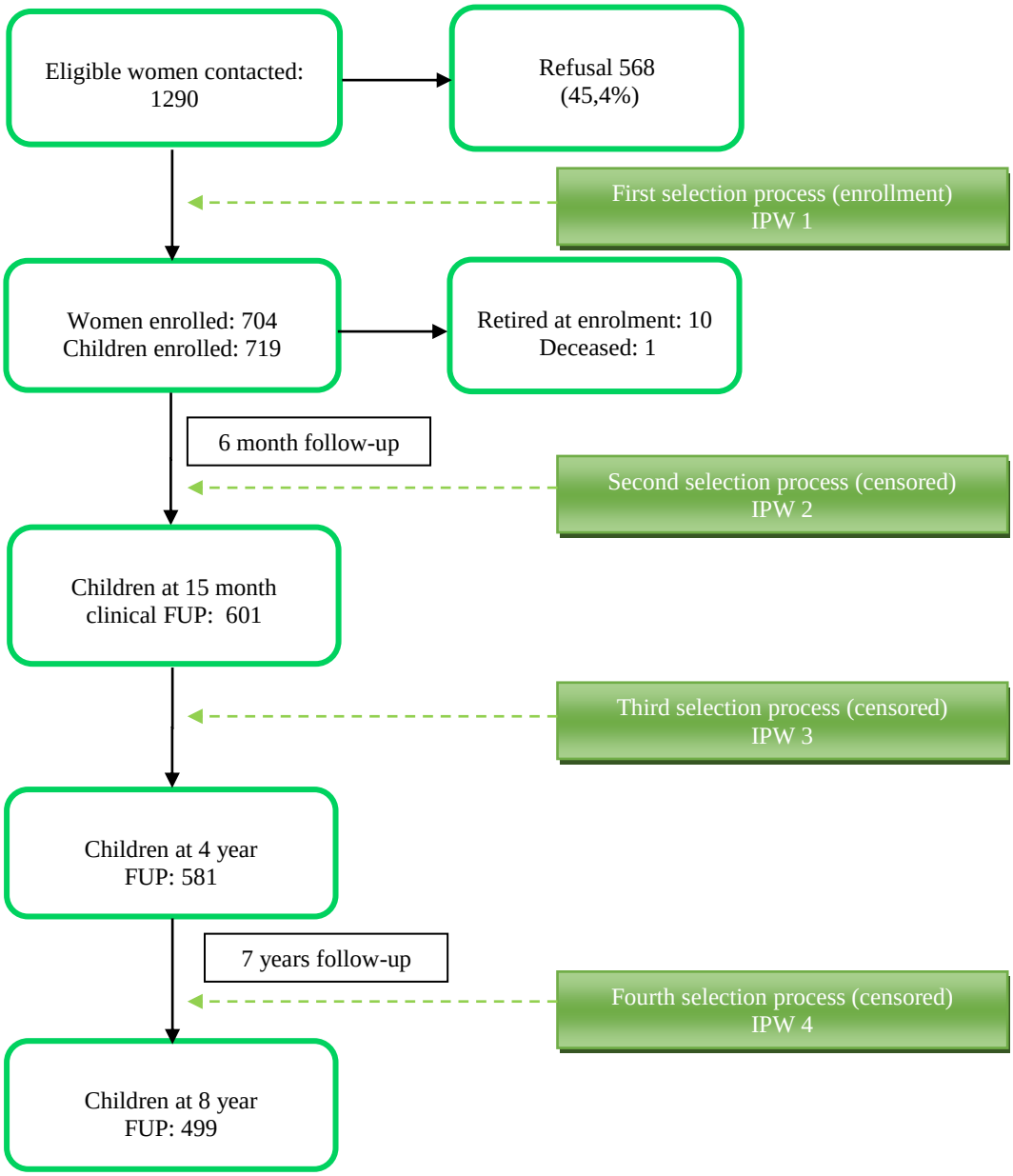
As already done in Porta et al. in 2016 (Porta et al., 2016), different regression models are performed to take into account the different selection processes. The first selection process takes place at the moment of enrolment, with a refusal percentage of 45%. A logistic regression model is performed on the number of all the mothers contacted at the beginning (1290 units), using as outcome the dichotomous variable participation (yes=1, no=0). The set of covariates considered is composed by the number of previous pregnancies, the maternal age at delivery, the maternal educational level, children's gestational age and the type of delivery.

According to a backward elimination strategy ($p<0.20$) the covariates selected for the logistic model were the number of previous pregnancies and the maternal educational level. After performing the first logistic regression model, the mean of the weights was higher than 1. Therefore, a second logistic regression was performed, only considering the maternal educational level as a covariate. The first set of weights was consequently obtained calculating the inverse of the ratio between the probabilities of the first model (the complete one) and the probabilities of the second model (with one covariate). In this way, the set of penalized weights had a lower variability and a mean close to 1. These weights were afterwards used to account for the selection process at the moment of recruitment.

The second selection process included all the children enrolled at birth, supposedly completing their 15-month follow-up visit. At first, a dichotomous variable assessing if children had completed or not the follow-up was created. A logistic regression model was performed with the following covariates: a) the number of previous pregnancies; b) the maternal age at delivery; c) the maternal educational level; d) children's gestational age; and

e) maternal smoking habits during pregnancy. With a backward elimination strategy and a p-value threshold of 0.20, the covariates kept in the model were only the maternal age at delivery and the maternal educational level.

Figure 7: Flow chart of the not enrolled and of the lost at follow-up visits, in the GASPII birth cohort



With the aim of reducing the variability of the calculated weights, a second logistic regression model was performed, using the maternal age at delivery as covariate. The set of

penalized weights was calculated by doing the inverse of the ratio of the probabilities of the first and complete model and the probabilities of the second model. At the end, these weights were considered during the analyses of the 15-month follow-up. The third and the fourth selection processes were also conducted on these children completing both the 4- and 8-year follow-ups. The logistic regression models are the same as in the 15-month selection process, with the assumption that those variables playing a role when mothers and children left the project were still the same. Therefore, the mechanisms of the variables selection and the weights calculation (both basic and penalized weights) are the same as in the 15-month questionnaire. Moreover, the variables selected at each 4- and 8-year models were the same as in the 15-month analyses. This is probably due to the lack of reasonable motivations why mothers decided to leave the project or not to complete their follow-up visits.

Finally, to account for the different selection processes, the weights of the enrolment selection and of the follow-up selection processes must be multiplied. By multiplying the weights, it has been assumed that the selection processes are independent one from the other. This way, a final set of weights can be introduced in the analyses to correct for the potential biases. Not only the weights should be included in the main analyses, but also the covariates used to calculate the weights should be part of the final model. In fact, putting these variables in the predictive model (which is used to calculate the weights) does not account for confounding in the final model.

4. Determinants of being overweight/obese

4.1 Selection of variables

This chapter describes the variables selected for analysing the possible determinants of ponderal excess in children. After an overview of these variables, an analysis of the factors which may potentially determine a status of overweight/obesity in children (measured at each follow-up) follows. Finally, an analysis of the possible determinants of change in children's ponderal status through the various follow-ups concludes this chapter.

The relevant measurements of children's ponderal excess are extracted from the clinical data of follow-ups at ages 15 months, 4 years and 8 years. BMI depends on weight, height and age measurements collected during the three follow-up visits. The calculation of the BMI Z-score, standardized according to the WHO recommendations, and the classification of the values obtained in the categorical variable "overweight/obese" yes vs. no are described in Chapter 3, paragraph 3.3. During the clinical examinations in the third follow-up, other indicators of ponderal excess are collected such as waist circumference, waist-to-hip ratio, total cholesterol and HDL cholesterol. All these measures are additional indicators of children's ponderal excess status in the analyses that follow.

In Table 2 the variables selected as potential determinants of ponderal excess are reported. This table shows when the variables are collected, specifying their use in the analyses, according to the different follow-ups. The first variable to be collected is the maternal age at birth. It is used as a categorical variable and is divided in three categories according to the distribution of a continuous variable (<= 30 years, between 30 and 35, and => 35 years). Another mother-related variable is the pre-pregnancy maternal BMI, which is classified according to the standard categorization for adults: mothers with BMI < 25 kg/m^2 are classified as underweight/normal weight; mothers with BMI between 25 and 30 kg/m^2 are classified overweight; finally, mothers with BMI over 30 kg/m^2 are considered obese.

Table 2: List of variables considered as possible determinants, available in each follow-up points

	At birth	15 months	4 years	8 years
Available variables				
Maternal age at birth	x			
Maternal pre-pregnancy BMI	x			
Gestational age	x			
Maternal smoking habits during pregnancy	x			
Maternal educational status	x			
Paternal educational status	x			
Breastfeeding duration (in months)	x			
Weaning (in months)	x			
Post-partum depression	x			
Additional variables				
Screen habits		x		
Screen time (per day)			x	x
Presence of grandparents		x	x	x
Number of siblings		x	x	x
Diet			x	x
Child eating habits			x	x
Sleeping habits (hours per day)			x	x
Physical activity (per week)				x

Children's gestational age is used as a continuous variable, while the information about mothers' smoking habits during pregnancy is classified as smokers vs. no smokers. Maternal and paternal educational level is categorized as follows: a) higher level for a university degree; b) medium level for a high school degree (secondary school); and c) low level for education from the elementary until the junior high schools. For calculating the duration of breastfeeding, information from three follow-ups (respectively at ages 6 months, 15 months and 4 years) is collected. A continuous variable is created with data extracted from various questionnaires, which is monthly-measured and classified in four different categories: a) never breastfed; b) breastfed for less than 4 months; c) breastfed from 4 to 6 months; and d) breastfed for more than 6 months. In case of premature weaning measured in months, information about all other kinds of food is collected for analysing its effects and placing it in time. The continuous variable measuring the duration of weaning is a combination of the information on the alternative food in the 6-month follow-up. The classification of the

variable follows its distribution in time and aims at defining the likelihood of the ponderal excess if children are weaned before/after they are 4 and 6 months old. The variable is classified as follows: a) weaned within the first 4 months; b) weaned in a 2-month timespan between ages 4 and 6 months old; and c) weaned beyond age 6 months old. One last variable collected at the delivery is the post-partum depression. It is measured through a score calculated from the Edinburgh Postnatal Depression Scale (EPDS), which is dichotomized depending on the presence or absence of depressive symptoms.

All the other variables refer to different times in children's life. A screen habits variable is also included to know if 15 month-old children used to watch television during the day. In the 4- and 8-year follow-ups, information about the amount of time spent playing with the computer, with videogames and watching television are collected through direct observation of children's habits. These variables are collected as continuous variables, but they are then dichotomized with a cut-off set at 9 hours per day. Furthermore, another variable indicating children's grandparents as family caregivers is collected during all the follow-ups. The variables in the questionnaire differentiate between maternal and paternal lineages, but a third variable is also created for measuring the presence of caregivers in general, regardless of the family's branches. Information about children's siblings is also calculated as a continuous variable summing up all younger and older siblings. It is then classified as: a) no siblings; b) one brother/sister; and c) two or more.

In the last two follow-ups (ages 4 and 8), data on children's diet are collected. The Kidmed index is also constructed, which registers a set of information and results from the sum of "good diet habits" and "bad diet habits". The index evaluates the conformity of children's diets to the Mediterranean standards, with its final score used as a continuous variable. The higher the variable, the more "optimal" the diet. Besides the information about children's diet quality, other eating habits are registered: for example, parents are asked whether or not their children used to have food between their main meals. The dichotomous variable can describe children's eating habits, therefore it indirectly indicates if children used to eat more than "normal" or if they had an unbalanced diet.

As said before, children's sleeping habits are also important health indicators. Information about sleep duration at night is also collected in the 4- and 8-year follow-ups. The two variables are collected as continuous and used accordingly in the first set of analyses. Instead, the two articles inserted in this thesis follow the National Sleep Foundation

guidelines. Recommendations on sleep duration change depending on children's age. Children between 3 and 5 years old are recommended to sleep from 10 to 13 hours per night, but a minimum 8/9 hours and a maximum 14 hours per night are also considered appropriate. Children between 6 and 13 years old are recommended to sleep from 9 to 11 hours per night, while a minimum 7/8 hours and a maximum 12 hours per night are both considered appropriate. Eventually, a 9-hour cut-off is used for harmonizing the two variables and because of their distribution, also because 9 hours of sleep per night is acceptable for children aged 4 and recommended for children aged 8. Both variables refer to the number of hours slept per day at night.

The last variable in Table 2 is only related to the 8-year follow-up, and it measures the time spent doing physical activity during the week. This variable is constructed taking into account a set of information about the type of physical activity, the number of hours of physical activity and the amount of days per week. The questionnaire reports how many physical activities children might be involved in and the relevant duration in hours per time and in days per week. Due to the large amount of information, a new variable is created which refers to the number of hours per week devoted to physical activity. All other activities such as walks with parents on Sunday or weekend training at the park are excluded from this analysis because of the inconsistency of the reported time.

4.2 Descriptive analyses

This paragraph introduces the descriptive statistics of the outcomes and variables used in this thesis. Firstly, the outcomes' basic information for assessing children's ponderal status is shown. Secondly, the distribution of the selected variables is presented, according to the dichotomous outcome "overweight/obese" yes/no. The tables of the distribution of the selected variables, according to the additional outcomes, are included in Appendix A.

Table 3a shows the values of the dichotomous variable used as main outcome in this thesis. The prevalence of overweight/obese children is increasing as children grow: while 3.49% of children have a condition of ponderal excess when they are 15 months old, the prevalence rose to 9.29% when they are 4 years old, reaching 36.9% of children aged 8 years old. Table 3b reports the other four outcomes considered as alternative measures of the ponderal excess. The first outcome is the BMI Z-score, which is calculated as shown in

Chapter 3, paragraph 3.3, and considered as a continuous variable. It can be noticed that the mean value of the BMI Z-score tends to increase between the 15-month and 4-year follow-ups, and between the ones at ages 4 and 8.

As it can be noticed, the percentages for each variable change during the different follow-ups because of missing data for the overweight/obese "yes/no" variables. Amongst all 15-month-old children, 4.33% do not have information about their ponderal status. The percentage is similar for 4-year-old children (3.79%). Finally, there are not missing data on this outcome variable for children aged 8 years old.

Table 3a: Description of the main outcome collected at the different follow-up points

	15 months		**4 years**		**8 years**	
	N	**%**	**N**	**%**	**N**	**%**
Normal Weight	554	92.2	505	86.9	315	63.1
Overweight/Obese	21	3.49	54	9.29	184	36.9
Missing	26	4.33	22	3.79	0	0
Total	601	100	581	100	499	100

A brief explanation of the calculation methods for this variable is provided here to better understand the missing data on the outcome considered. Overweight/obese "yes/no" variables are created as a combination of three variables (according to the WHO guidelines), as explained before (Chapter 3, paragraph 3.3). Therefore, it was sufficient to have one variable between weight, length, and children's age in months/years to obtain the missing data for these same variables. For example, since it is difficult to measure children's length when they are 15 months old, there are missing data at this follow-up that derive precisely from this lack of information. Furthermore, the trained personnel in the 4-year follow-up did not report the exact date of the measurements, so again there is a lack of information to calculate 4-year-old children's ponderal status. To better understand the pattern of the outcomes' missing data, a check of the potential differences between missing and not missing data is carried out, showing no significant deviation.

The previous observations on a potential pattern and on the reasons for these missing data in the outcome variables mean that the propensity of becoming "missing values" may be not related to the unobserved value itself. At the same time, the proportion of missing data for

the two outcomes is small and it should not matter too much. Furthermore, other two issues causing an additional kind of missing data need be considered: as discussed before, several subjects have decided not to participate in the project, and others have not completed all the follow-ups. Therefore, their missing information may impact on the results of the analyses. The solution is the implementation of the IPW methodology (as discussed in Chapter 3, paragraph 3.3.4).

The other four outcomes in Table 3b are only collected in the last follow-up: two are measures of the abdominal fat and two of the blood lipids' level. The waist circumference and the hip circumference are measured to calculate the waist-to-hip ratio, another good measure for assessing the abdominal fat. Waist circumference has a mean of 60.0 and an SD of 6.18, while the waist-to-hip circumference has a mean of 0.91 and an SD of 0.04.

Table 3b: Description of the additional outcomes collected at the different follow-up

	15 months			**4 years**			**8 years**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
BMI Z-score	575	0.44	0.91	559	0.69	1.07	499	0.65	1.18
Waist circumference	-	-	-	-	-	-	499	60.0	6.18
Waist -to-hip ratio	-	-	-	-	-	-	499	0.91	0.04
Total cholesterol	-	-	-	-	-	-	412	162.3	25.1
HDL cholesterol	-	-	-	-	-	-	412	59.2	15.2

There are as many children with information about their BMI Z-score, waist circumference and waist-to-hip ratio as many completing the 8-year follow-up. The two measures of the blood lipids (i.e., total and HDL cholesterol) have respectively a mean of 162.3 and 59.2 and a standard deviation of 25.1 and 15.2. For both variables, the number of children with the relevant information is lower (412) if compared to the number of children whose information is collected when they are 8 years old (499). These five additional outcomes are used as continuous variables in all the thesis.

Table 4 illustrates the variables collected at the baseline, namely the moment of delivery. The variables are listed here: a) maternal age at delivery; b) maternal pre-pregnancy BMI; c) children's birth's weight; d) gestational age; e) maternal smoking habits during pregnancy; and f) parents' educational level. The distribution of the variables is shown

according to children's ponderal status for each questionnaire at ages 15 months, 4 years and 8 years old. In general most mothers were aged 30-35 at delivery, and are classified as "normal weight" according to the BMI pre-pregnancy classifications. 14.3%[1] of obese mothers have a 15-month-old overweight/obese child, compared to 4.7% of normal weight children with mothers in the same ponderal status.

For children aged 4 years old, the percentage of obese mothers having children with weight problems is higher than the percentage of obese mothers whose children do not have any weight issue (respectively 9.3% and 4%). A lower percentage of overweight/obese children, compared to normal weight children, is related to obese mothers in the 8-year follow-up (3.8% vs. 5.1%). Nearly all the children in the cohort were born at term, and most of them had a birth weight between 2,500 g and 3,999 g. A low percentage of mothers used to smoke during pregnancy. Around 4.8% of 15-month-old overweight/obese children have mothers who used to smoke during pregnancy, against 11% of normal weight children. An inverse result is showed instead for the 4- and 8-year follow-ups: there are more overweight or obese children compared to normal weight children with mothers that used to smoke during pregnancy (10.7% vs. 11.1 when they are 4 years old and 9.8% vs. 13.6% when they are 8 years old). Most mothers have a secondary school diploma or a university degree, and a similar result is true for fathers: most of them have a secondary school diploma.

Table 5 which is presented below, illustrates the selected characteristics for the 6-month follow-up. Information is shown about the duration of the breastfeeding, calculated in months: overall, most children were breastfed beyond their sixth month of life. The majority of children with an excessive ponderal status (amongst all those with corresponding questionnaire when they were 15 months old, 4 years old and 8 years old) are breastfed for more than six months, with percentages of 1.66%, 4.99% and 16.6% respectively in the 15-month, 4-year and 8-year follow ups.

[1] In this case the percentage is calculated according to the absolute value presented in Table 4. When 15 months old, the number of children OW/OB with an obese mother is 3. The total number of OW/OB children at that moment is 21. The calculation is: $\frac{3}{21} * 100 = 14.3\%$.

Table 4: Descriptive statistics of the baseline characteristics, analysed at each follow-up [2]

	15 months follow-up								4 years follow.up								8 years follow-up					
	N W		OW / OB		Missing		Total		N W		OW / OB		Missing		Total		N W		OW / OB		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	554	92,2	21	3,49	26	4,33	601	100	505	86,9	54	9,29	22	3,79	581	100	315	63,1	184	36,9	499	100
Baseline characteristics																						
Maternal age at birth																						
< 30 years	149	24,8	6	1,00	10	1,66	165	27,5	133	22,9	12	2,07	8	1,38	153	26,3	82	16,4	45	9,0	127	25,5
30-35 years	247	41,1	9	1,50	12	2,00	268	44,6	219	37,7	27	4,65	11	1,89	257	44,2	135	27,1	80	16,0	215	43,1
> 35 years	158	26,3	6	1,00	4	0,67	168	28,0	153	26,3	15	2,58	3	0,52	171	29,4	98	19,6	59	11,8	157	31,5
Maternal BMI pre-pregnancy																						
Underweight/Normal weight	462	76,9	17	2,83	19	3,16	498	82,9	428	73,7	40	6,88	20	3,44	488	84,0	271	54,3	143	28,7	414	83,0
Overweight	65	10,8	1	0,17	7	1,16	73	12,1	56	9,64	9	1,55	2	0,34	67	11,5	28	5,61	33	6,61	61	12,2
Obese	26	4,33	3	0,50	0	0	29	4,83	20	3,44	5	0,86	0	0	25	4,30	16	3,21	7	1,40	23	4,61
Missing	1	0,17	0	0	0	0	1	0,17	1	0,17	0	0	0	0	1	0,17	0	0	1	0	1	0,20
Birth weight																						
< 2499 gr	38	6,32	19	3,16	2	0,33	59	9,82	32	5,51	2	0,34	1	0,17	35	6,02	21	4,21	13	2,61	34	6,81
2500-3999 gr	468	77,9	2	0,33	21	3,49	491	81,7	436	75,0	43	7,40	18	3,10	497	85,5	274	54,9	148	29,7	422	84,6
>4000 gr	48	7,99	0	0	3	0,50	51	8,49	37	6,37	9	1,55	3	0,52	49	8,43	20	4,01	23	4,61	43	8,62
Gestational age																						
<37 week	40	6,66	0	0	0	0	40	6,66	28	4,82	1	0,17	4	0,69	33	5,68	17	3,41	12	2,40	29	5,81
>=37 week	512	85,2	21	3,49	26	4,33	559	93,0	475	81,8	53	9,12	18	3,10	546	94,0	296	59,3	172	34,5	468	93,8
Missing	2	0,33	0	0	0	0	2	0,33	2	0,34	0	0	0	0	2	0,34	2	0,40	0	0	2	0,40
Maternal smoking habits during pregnancy																						
No	490	81,5	20	3,33	23	3,83	533	88,7	447	76,9	48	8,26	20	3,44	515	88,6	282	56,5	157	31,5	439	88,0
Yes	61	10,1	1	0,17	3	0,50	65	10,8	54	9,29	6	1,03	2	0,34	62	10,7	31	6,21	25	5,01	56	11,2
Missing	3	0,50	0	0	0	0	3	0,50	4	0,69	0	0	0	0	4	0,69	2	0,40	2	0,40	4	0,80
Maternal educational status																						
University degree	202	33,6	8	1,33	13	2,16	223	37,1	190	32,7	19	3,27	8	1,38	217	37,3	120	24,0	64	12,8	184	36,9
Secondary school	281	46,8	11	1,83	10	1,66	302	50,2	257	44,2	25	4,30	10	1,72	292	50,3	150	30,1	98	19,6	248	49,7
Primary school	71	11,8	2	0,33	3	0,50	76	12,6	58	10,0	10	1,72	4	0,69	72	12,4	42	8,42	22	4,41	64	12,8
Paternal educational status																						
University degree	164	27,3	5	0,83	11	1,83	180	30,0	167	28,7	10	1,72	6	1,03	183	31,5	95	19,0	57	11,4	152	30,5
Secondary school	227	37,8	11	1,83	9	1,50	247	41,1	200	34,4	23	3,96	11	1,89	234	40,3	133	26,7	67	13,4	200	40,1
Primary school	118	19,6	3	0,50	6	1,00	127	21,1	101	17,4	19	3,27	3	0,52	123	21,2	63	12,6	48	9,62	111	22,2
Missing	45	7,49	2	0,33	0	0	47	7,8	37	6,37	2	0,34	2	0,34	41	7,06	24	4,81	12	2,40	36	7,21

[2] N W stands for “Normal Weight” and OW / OB stands for “Overweight/Obese”

Table 5: Descriptive statistics of the characteristics collected at the six month follow-up, analysed at each follow-up

	15 months follow-up								4 years follow.up								8 years follow-up					
	N W		OW / OB		Missing		Total		N W		OW / OB		Missing		Total		N W		OW / OB		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	554	92,2	21	3,49	26	4,33	601	100	505	86,9	54	9,29	22	3,79	581	100	315	63,1	184	36,9	499	100
Six months characteristics																						
Breastfeeding duration (in months)																						
Never been breastfed	66	11,0	1	0,17	2	0,33	69	11,5	68	11,7	5	0,86	0	0	73	12,6	38	7,62	22	4,41	60	12,0
Until 4 months	132	22,0	6	1,00	8	1,33	146	24,3	111	19,1	14	2,41	11	1,89	136	23,4	64	12,8	45	9,02	109	21,8
Between 4 and 6 months	114	19,0	4	0,67	5	0,83	123	20,5	99	17,0	6	1,03	2	0,34	107	18,4	61	12,2	34	6,81	95	19,0
Beyond 6 months	242	40,3	10	1,66	11	1,83	263	43,8	227	39,1	29	4,99	9	1,55	265	45,6	150	30,1	83	16,6	233	46,7
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0,40	0	0	2	0,40
Weaning (in months)																						
Until 4 months	395	65,7	17	2,83	20	3,33	432	71,9	357	61,4	40	6,88	16	2,75	413	71,1	224	44,9	124	24,8	348	69,7
Between 4 and 6 months	119	19,8	1	0,17	5	0,83	125	20,8	114	19,6	5	0,86	6	1,03	125	21,5	71	14,2	42	8,42	113	22,6
Beyond 6 months	32	5,32	3	0,50	1	0,17	36	5,99	28	4,82	8	1,38	0	0	36	6,20	14	2,81	16	3,21	30	6,01
Missing	8	1,33	0	0	0	0	8	1,33	6	1,03	1	0,17	0	0	7	1,20	6	1,20	2	0,40	8	1,60
Post-partum depression																						
No	464	77,2	19	3,16	20	3,33	503	83,7	423	72,8	45	7,75	19	3,27	487	83,8	260	52,1	156	31,3	416	83,4
Yes	86	14,3	2	0,33	6	1,00	94	15,6	79	13,6	9	1,55	3	0,52	91	15,7	51	10,2	28	5,61	79	15,8
Missing	4	0,67	0	0	0	0	4	0,67	3	0,52	0	0	0	0	3	0,52	0	0	0	0	0	0

Considering the moment of weaning, most children were weaned before they were four months old. For mothers with symptoms of distress, the percentages of overweigh/obese children in the 15-month and 8-year follow-ups are lower if compared to the number of children with a normal ponderal status. On the contrary, it is almost the opposite for age 4 follow-up (15.6% and 16.6% for normal weight vs. overweight/obese children aged 4 years old).

Table 6 shows the variables collected in the 15-month follow-up. The first variable measures whether or not 15-month-old children used to spend time watching TV. The majority did not watch television at all, but the percentages of children in ponderal excess status are similar for both groups: 52.4% of children watched TV during the day, while 47.6% of them did not.

Table 6: Descriptive statistics of the characteristics collected at the fifteen month follow-up

	15 months follow-up							
	N W		**OW / OB**		**Missing**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Total	554	92,2	21	3,49	26	4,33	601	100
Fifteen months characteristics								
Screen habits								
No	223	37,1	10	1,66	10	1,66	243	40,4
Yes	328	54,6	11	1,83	16	2,66	355	59,1
Missing	3	0,50	0	0	0	0	3	0,50
Presence of grandparents								
No	241	40,1	5	0,83	13	2,16	259	43,1
Yes	312	51,9	15	2,50	13	2,16	340	56,6
Missing	1	0,17	1	0,17	0	0	2	0,33
Number of siblings								
No one	318	52,9	15	2,50	19	3,16	352	58,6
One	200	33,3	5	0,83	7	1,16	212	35,3
Two or more	35	5,82	1	0,17	0	0	36	5,99
Missing	1	0,17	0	0	0	0	1	0,17

Information on grandparents being caregivers shows that in this follow-up more than the half of the children spent time with their grandparents during the day. 71.4% of overweight/obese children spent time with their grandparents, against a lower percentage (23.8%) of children with the same ponderal status who did not spend time with them. Data collected from the 15-month questionnaire show that 58.6% of children in the 15-month follow-up are only child. More than 35% have one sibling, and only a small percentage of children have more than two siblings (around 6%).

Variables collected at the 4-year follow-up are presented in Table 7. Sixty seven percent of children usually watch television for more than one hour per day, and 77.8% of them are overweight/obese. Only 22.2% of overweight/obese children do not usually watch TV for more than one hour per day.

Table 7: Descriptive statistics of the characteristics collected at the four year follow-up

	4 years follow-up							
	N W		OW / OB		Missing		Total	
	N	%	N	%	N	%	N	%
Total	505	86,9	54	9,29	22	3,79	581	100
Four years characteristics								
Screen time (per day)								
< 1 h	171	29,4	12	2,07	8	1,38	191	32,9
>= 1 h	333	57,3	42	7,23	14	2,41	389	67,0
Missing	1	0,17	0	0	0	0	1	0,17
Presence of grandparents								
No	169	29,1	18	3,10	10	1,72	197	33,9
Yes	336	57,8	36	6,20	12	2,07	384	66,1
Number of siblings								
No one	150	25,8	18	3,10	8	1,38	176	30,3
One	292	50,3	28	4,82	11	1,89	331	57,0
Two or more	62	10,7	8	1,38	3	0,52	73	12,6
Missing	1	0,17	0	0	0	0	1	0,17
Diet								
Optimal Mediterranean diet	82	14,1	8	1,38	2	0,34	92	15,8
Improvement needed	282	48,5	32	5,51	5	0,86	319	54,9
Very low diet quality	17	2,93	3	0,52	1	0,17	21	3,61
Missing	124	21,3	11	1,89	14	2,41	149	25,6
Child eating habits								
Main meal	325	55,9	26	4,48	15	2,58	366	63,0
Also between meal	180	31,0	28	4,82	7	1,20	215	37,0
Sleeping habits (hours per day)								
<= 9 h	409	70,4	46	7,92	16	2,75	471	81,1
>9 h	95	16,4	8	1,38	5	0,86	108	18,6
Missing	1	0	0	0	1	0,17	2	0,34

In the 4-year follow-up the percentage of children spending time with their grandparents during the day increases (66.1%), if compared to the percentages in the 15-month follow-up. 66.7% of children in ponderal excess usually spend time with grandparents. In the 4-year follow-up, 57% of children have at least one brother/sister, while 30.3% are only children. The information about children's diet shows that 54.9% of children need an improvement in their diet, and that only 15.8%

have an optimal one. 14.8% of overweight/obese children have an optimal Mediterranean diet, while 59.3% need some improvements. Children's eating habits include their main meals and others possible during the day. In general, 63% of children eat only at the main meals. Children in ponderal excess status that only eat during the main meals are 48%, while overweight/obese children eating without rules are almost 52%. The last variable in this follow-up is children's sleeping habits, measured in hours slept per night. Most children usually sleep less than 9 hours (81.1%) per night, and 85.2% of them are overweight/obese.

In the first part of Table 8 the variables of the 7-year follow-up are listed, while in the second part the variables refer to the 8-year follow-up. The percentage of children spending time with their grandparents remain quite stable if compared with the same variable from the other follow-ups (56.7%). More than 59% of them are overweight or obese. The percentage of children with two or more siblings increases a bit, if compared to the 4-year follow-up (15.8%). Nevertheless, the majority of children have only one brother/sister (54.5%). In addition, the majority of children in ponderal excess have one sibling (21.6%). Talking about eating habits, 35% of children in the 7-year follow-up eat also between one main meal and the other. 54.3% of overweight/obese children only eat during the main meals, while 36.4% of them also eat some snacks.

In both 4-year and 8-year follow-ups, data about the time spent in front of a screen (i.e., TV and/or computer) are collected. In the latter follow-up, 88.8% of children watch television (or play videogames) for less than seven hours, and 83.7% of them are overweight/obese. The percentage of children in ponderal excess watching television for more than seven hours per day is 16.3%, which is higher than the percentages for normal weight children with the same screen habits (8.25%). The information about children's diet is also included in this table. In this follow-up, 61.3% of all children need some improvements in their daily diet, and only 29.1% follow an optimal quality diet. 26.1% overweight/obese children have an optimal diet, 65.8% need some improvements, while 8.15% have a low quality one. Finally, this is the only follow-up including also the information on children's physical activity: 34.5% spent less than 2 hours per week doing physical activity, 34.1% spent from 2 to 4 hours, and 20.6% spent more than 4 hours per week. Furthermore, it is easy to observe that overweight and obese children have a lower percentage corresponding to the higher category of hours spent doing physical activity (21.9% and 18.4% for normal weight and overweight/obese children, respectively). The last variable measures children's sleeping habits. 69.3% of children sleep less than 9 hours per night, and 73.4% of them are also overweight/obese.

Table 8: Descriptive statistics of the characteristics collected at the seven and eight year follow-ups

	8 years follow-up					
	N W		OW / OB		Total	
	N	%	N	%	N	%
Total	315	63,13	184	36,87	499	100
Seven years characteristics						
Presence of grandparents						
No	117	23,4	58	11,6	175	35,1
Yes	174	34,9	109	21,8	283	56,7
Missing	24	4,81	17	3,41	41	8,22
Number of siblings						
No one	68	13,6	36	7,21	104	20,8
One	164	32,9	108	21,6	272	54,5
Two or more	56	11,2	23	4,61	79	15,8
Missing	27	5,41	17	3,41	44	8,82
Child eating habits						
Main meal	183	36,7	100	20,0	283	56,7
Also between meal	108	21,6	67	13,4	175	35,1
Missing	24	4,81	17	3,41	41	8,22
Eight years characteristics						
Screen time (per day)						
<= 7 h	289	57,9	154	30,9	443	88,8
> 7 h	26	5,21	30	6,01	56	11,2
Diet						
Optimal Mediterranean diet	97	19,4	48	9,62	145	29,1
Improvement needed	185	37,1	121	24,2	306	61,3
Very low diet quality	32	6,41	15	3,01	47	9,42
Missing	1	0,20	0	0	1	0,20
Physical activity (per week)						
<=2 h	111	22,2	61	12,2	172	34,5
2-4 h	104	20,8	66	13,2	170	34,1
>= 4 h	69	13,8	34	6,81	103	20,6
Missing	31	6,21	23	4,61	54	10,8
Sleeping habits (hours per day)						
<= 9 h	211	42,3	135	27,1	346	69,3
> 9 h	104	20,8	49	9,82	153	30,7

4.3 Cross-sectional Backward Stepwise Analyses

In this paragraph, the main possible determinants of the condition of overweight/obesity, measured during three follow-ups are presented and discussed. Analyses are carried out with the methodology of the Inverse Probability Weighting (IPW) which accounts for possible selection

biases at the time of enrolment and follow-up visits. The IPW is presented in Chapter 3, paragraph 3.3.4.

As explained in methodology, Chapter 3 paragraph 3.3.1, the stepwise backward analysis aims at catching the variables for children's ponderal status. As first thing, researchers choose one set of possible determinants among literature contents. Secondly, a "mechanic" process of variables selection is conducted by the backward model. Finally, the results of this logistic regression are checked and commented.

The first analysis uses data from the 15-month follow-up. Here follows the conceptual selection of possible determinants which are considered:

- maternal age at delivery
- maternal educational level
- paternal educational level
- maternal pre-pregnancy BMI
- maternal smoking habits during pregnancy
- gestational age of the infant
- birth weight of the infant
- breastfeeding duration in months
- weaning in months
- maternal post-natal depression (when children are 6 months old)
- number of siblings (when children are 15 months old)
- presence of grandparents as alternative caregivers (when children are 15 months old)
- screen habits of the child (when children are 15 months old).

In Table 9, the results of the stepwise backward logistic analysis in the 15-month follow-up are showed. As can be noticed, only four determinants in this analysis are not excluded by the pr (0.20) inclusion criteria: maternal BMI before pregnancy, grandparents as caregivers in the family, gestational age of the new-born and the weaning phase measured in months.

Maternal BMI is the only variable contributing significantly to the ponderal excess status of 15-month-old children. Nevertheless, it should be specified that the variable is not correlated to the ponderal excess through its all modalities. In fact, maternal pre-pregnancy BMI is a determinant only when mothers were obese during the pre-pregnancy period (OR=5.14).

Table 9: Odds Ratio and 95% confidence intervals from the stepwise backward logistic model estimating the possible determinants of being overweight/obese at 15 months

	15 months	
	OR	**IC 95%**
Maternal pre-pregnancy BMI		
Underweight/Normal weight (Ref.)	1.00	
Overweight	0.58	(0.08, 3.95)
Obese	**5.14**	**(1.31, 20.1)**
Presence of grandparents		
No (Ref.)	1.00	
Yes	3.09	(0.97, 9.88)
Gestational age		
Continous	1.31	(0.91, 1.89)
Weaning (in months)		
Until 4 months (Ref.)	1.00	
Between 4 and 6 months	0.25	(0.03, 2.05)
Beyond 6 months	3.15	(0.81, 12.3)

For the 4-year follow-up, the determinants chosen from literature for the backward logistic model are quite similar to the ones described above and only a few more have been added. The list of determinants similar to the previous analysis' are as follows:

- maternal age at delivery
- maternal educational level
- paternal educational level
- maternal pre-pregnancy BMI
- maternal smoking habits during pregnancy
- gestational age of the infant
- birth weight of the infant
- breastfeeding duration in months
- weaning in months.

Four variables which are not included in the previous analysis (i.e., maternal post-natal depression, number of siblings, presence of grandparents as alternative caregivers and screen habits of the child) are considered determinants in the 4-year follow-up:

- maternal post-natal depression (when children are 15 months old)
- number of siblings (when children are 4 years old)

- presence of grandparents as alternative caregivers (when children are 4 years old)
- screen habits of the child (when children are 4 years old).

The set of new variables added at this stage of the research are as follows:

- sleeping time (when children are 4 years old)
- dietary habits (when children are 4 years old)
- children eating habits (when children are 4 years old)

As reported in Table 10, less than half of these variables are automatically selected by the model, always following the pr (0.20) permanence criteria.

Table 10: Odds Ratio and 95% confidence intervals from the stepwise backward logistic model estimating the possible determinants of being overweight/obese at 4 years

		4 years	
		OR	**IC 95%**
Weaning (in months)			
	Until 4 months (Ref.)	1.00	
	Between 4 and 6 months	0.66	(0.25, 1.79)
	Beyond 6 months	2.40	(0.80, 7.22)
Maternal pre-pregnancy BMI			
	Underweight/Normal weight (Ref.)	1.00	
	Overweight	1.47	(0.58, 3.72)
	Obese	**3.14**	**(1.01, 9.76)**
Gestational age			
	Continous	1.17	(0.93, 1.47)
Screen time			
	< 1 hours (Ref.)	1.00	
	>= 1 hours	2.29	(0.96, 5.46)
Eating habits			
	Main meal (Ref.)	1.00	
	Also between main meal	**2.09**	**(1.06, 4.14)**

The selection includes: children's weaning time; maternal pre-pregnancy BMI; gestational age; children's screen habits and children's eating habits. Amongst these, only maternal pre-pregnancy BMI and children's eating habits are the only two variables having some significant association with overweight/obesity at age 4. Pre-pregnancy obese mothers can be a determinant of 4-year-old children's ponderal excess (OR=3.14). Furthermore, children's bad eating habits (e.g.,

having food between the main meals) double the risk of being overweight/obese at age 4, if compared to regularly-eating children (OR=2.09).

The last one is the backward stepwise analysis for the 8-year follow-up. Again, the set of possible determinants only includes a few variables from the previous analysis, and it adds some others. Below follows the list of variables from the 4-year follow-up:

- maternal age at delivery
- maternal educational level
- paternal educational level
- maternal pre-pregnancy BMI
- maternal smoking habits during pregnancy
- gestational age of the infant
- birth weight of the infant
- breastfeeding duration in months
- weaning in months
- maternal post-natal depression (when children are 15 months old).

Six variables from the 7- and 8-year follow-ups replace six others from the questionnaire at age 4. The new variables follow below:

- number of siblings (when children are 7 years old)
- presence of grandparents as alternative caregivers (when children are 7 years old)
- screen habits of the child (when children are 8 years old)
- children eating habits (when children are 7 years old)
- sleeping time (when children are 8 years old)
- dietary habits (when children are 8 years old).

One variable is added here:

- time spent doing physical activity (when children are 8 years old).

These last variables differ a little from the previous ones (for example, the time spent doing physical activity is introduced). Table 11 shows the results of the backward stepwise analysis at age 8. The number of siblings, the presence of grandparents as caregivers, the amount of time spent doing physical activity, the weaning time measured in months, pre-pregnancy maternal BMI and screen habits are automatically kept by the backward selection model. Finally, the existence of

siblings and maternal pre-pregnancy BMI are significant determinants of 8-year-old children's ponderal excess.

Table 11: Odds Ratio and 95% confidence intervals from the stepwise backward logistic model estimating the possible determinants of being overweight/obese at 8 years

		8 years	
		OR	**IC 95%**
Number of siblings			
	No one (Ref.)	1.00	
	One	1.18	(0.70, 1.99)
	Two or more	**0.48**	**(0.22, 0.99)**
Presence of grandparents			
	No (Ref.)	1.00	
	Yes	1.41	(0.90, 2.22)
Physical activity			
	Continous	1.08	(0.96, 1.22)
Weaning (in months)			
	Until 4 months (Ref.)	1.00	
	Between 4 and 6 months	1.21	(0.70, 2.11)
	Beyond 6 months	2.43	(0.99, 6.05)
Maternal pre-pregnancy BMI			
	Underweight/Normal weight (Ref.)	1.00	
	Overweight	**2.80**	**(1.41, 5.56)**
	Obese	1.30	(0.40, 4.26)
Screen time			
	Continous	1.64	(0.78, 3.46)

Specifically, the number of sibling contributes "negatively" to the ponderal excess, and the OR is less than one for children having at least two brothers/sisters (OR=0.48). Having one brother/sister seems not to affect at all the OR. In opposition with the previous results, only overweight mothers (therefore, not the obese) contribute to the development of ponderal excess in 8-year-old children (OR=2.80). Weak evidence for obese mothers may derive from the small number of overweight/obese children in the follow-up whose mothers were obese before pregnancy.

Additional backward stepwise analyses have been then performed because of the other variables used for measuring children' ponderal excess. They are children's waist circumference, waist-to-hip ratio, HDL and total cholesterol. These additional analyses also include the determinants of age 8 follow-up, and are connected to the backward stepwise model. Nevertheless,

the model is a linear model, instead of a logistic one: this is because of the continuous-nature of the variables in the outcomes.

The set of possible determinants used in these analyses is the same of the 8 years analysis. The results of the analysis of the waist circumference are reported in Table 12.

Table 12: Odds Ratio and 95% confidence intervals from the stepwise backward logistic model estimating the possible determinants of increasing waist circumference at 8 years

	8 years - Waist Circumference	
	Coeff	**IC 95%**
Maternal pre-pregnancy BMI		
Underweight/Normal weight (Ref.)	1.00	
Overweight	**4.55**	**(2.68, 6.43)**
Obese	0.29	(-2.95, 3.53)
Maternal smoking habits		
No (Ref.)	1.00	
Yes	1.88	(-0.06, 3.82)
Sleeping time (hours)		
Continous	-0.70	(-1.52, 0.11)
Physical activity		
Continous	0.30	(-0.20, 0.63)
Presence of grandparents		
No (Ref.)	1.00	
Yes	0.98	(-0.23, 2.19)
Gestational age		
Continous	0.25	(-0.09,0.60)
Weaning (in months)		
Until 4 months (Ref.)	1.00	
Between 4 and 6 months	-0.68	(-2.19, 0.82)
Beyond 6 months	**2.60**	**(0.19, 5.00)**
Screen time		
Continous	1.38	(-0.50, 3.26)

As is clear now, the variables kept in the model are as follows: pre-pregnancy maternal BMI; maternal smoking habits; children's sleeping habits; time for physical activity; the presence of grandparents as caregivers; gestational age; weaning and screen habits.

Finally, the real two determinants are pre-pregnancy mothers' BMI and the time of weaning. The results of the maternal BMI do not change a lot from before, since only one modality

"overweight" of the variable is considered for measuring children's ponderal excess (Coeff=4.55), and also here obese mothers seem not to be associated with the increase in children's abdominal excess. This may be because of the small amount of big-waist children with obese mothers during pregnancy. As in age 8 cross-sectional analysis of overweight/obesity, being weaned after six months may result in a larger waist circumference (Coeff=2.60).

Table 13 shows the results of an increased waist-to-hip ratio. The subset of variables chosen by the model are quite similar to the ones of the waist circumference outcome, such as children's eating habits, maternal education, dietary habits, gestational age and screen habits. No variable of ponderal excess contributes significantly to the increased waist-to-hip ratio.

Table 13: Odds Ratio and 95% confidence intervals from the stepwise backward logistic model estimating the possible determinants of increasing waist-to-hip ratio at 8 years

	8 years - Waist-to-hip Ratio	
	Coeff	**IC 95%**
Eating habits		
Main meal (Ref.)	1.00	
Also between main meal	-0.11	(-0.20, 0.02)
Maternal educational level		
University degree (Ref.)	1.00	
Secondary school	-0.08	(-0.17, 0.02)
Primary school	0.03	(-0.12, 0.02)
Diet		
Continous	-0.01	(-0.03, 0.01)
Gestational age		
Continous	-0.02	(-0.04, 0.01)
Screen time		
Continous	-0.09	(-0.23, 0.05)

Similar results are obtained for the analyses of the blood lipids in Table 14 and Table 15. For the total cholesterol levels, breastfeeding duration is kept as variable after the backward stepwise regression, even though it does not seem to be significantly responsible of 8-year-old children's increased levels of total cholesterol. The results in Table 15 show that the three variables kept in the model are screen habits, maternal smoking habits during pregnancy and the children's

diet. Again, no variable contributes significantly to 8-year-old children's increased levels of HDL cholesterol.

Table 14: Odds Ratio and 95% confidence intervals from the stepwise backward logistic model estimating the possible determinants of increasing total cholesterol levels at 8 years

	8 years - Total Cholesterol	
	Coeff	**IC 95%**
Breastfeeding duration (months)		
Never been breastfed (Ref.)	1.00	
Until 4 months	1.01	(-9.52, 11.5)
Between 4 and 6 months	-3.87	(-14.4, 6.68)
Beyond 6 months	-8.72	(-18.1, 0.67)

Table 15: Odds Ratio and 95% confidence intervals from the stepwise backward logistic model estimating the possible determinants of increasing HDL cholesterol levels at 8 years

	8 years - Cholesterol HDL	
	Coeff	**IC 95%**
Screen time		
Continous	-5.54	(-11.4, 0.34)
Maternal smoking habits		
No (Ref.)	1.00	
Yes	-4.71	(-10.8, 1.40)

In general, it seems that the most important determinant of fat accumulation is the late weaning variable. In fact, in this cohort being weaned after six months is correlated to 8-year-old children's ponderal excess status. Wrong eating habits also constitute a crucial determinant of children' ponderal excess status. Even with borderline results, having two or more brothers/sisters leads to a decreased OR value at age 8. The analysis of the waist circumference at age 8 confirms the results for maternal BMI before pregnancy, and for the time of weaning, while the three alternative measures are inconclusive due to the lack of results.

4.4 Trajectories Stepwise

This paragraph presents children's changes in ponderal status through time, with the aim of catching the determinants of ponderal excess variations from one follow-up to the other. Modelling the risk of becoming overweight/obese at different ages completes the previous cross-sectional analyses with some longitudinal investigation. The trajectories of children's changes in the GASPII birth cohort are shown in Table 16a and Table 16b.

Table 16 a: Tracking of the ponderal change in children from 15 months to 4 years[3]

	BMI 4 years							
	Normal weight		**Overweight/Obese**		**Missing**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
BMI 15 months								
Normal weight	434	60.4	39	5.42	81	11.3	554	77.1
Overweight/Obese	9	1.25	11	1.53	1	0.14	21	2.92
Missing	62	8.62	4	0.56	78	10.8	144	20.0
Total	505	70.2	54	7.51	160	22.3	719	100

Table 16a shows children's ponderal status (normal weight vs. overweight/obese) at ages 15 months and 4 years. Most children are classified as normal weight (60.4%) at both ages and only a small part (1.25%) is overweight/obese at age 15 months. 7.04% of 15-month-old normal weight children change their status when they are 4 years old, while 52.4% of children stay overweight/obese through all the two follow-ups. Table 16b includes children's ponderal excess data between ages 4 and 8. The majority of children are still normal weight (56.6%), while only 16.7% of overweight/obese children at 4 become normal weight at 8. 26.9% of overweight/obese children at 8 is normal weight at 4, and 59.3% of them already suffer from a condition of ponderal excess at 4.

A large amount of data is missing in both Table 16a and Table 16b, mostly because of the dropped-out subjects from one follow-up to the other. In fact, the Inverse Probability Weighting (IPW) methodology will account for this type of missing data. Only small parts are related to the scarce information about the outcome. As one can see in Table 3a, paragraph 4.2 of this Chapter,

[3] The percentages considered in both tables are referred to the 719 enrolled infants in the GASPII project. Therefore, the prevalence of children overweight/obese are lower compared to the real amount, due to the presence of lot to follow-up.

the percentages of children with no information on their ponderal status at ages 15 months and 4 years are respectively 4.33% and 3.79%, while children aged 8 do not miss any relevant data. As explained before, a small amount of missing data and the reasons for missing values at both follow-ups may lead us to assume that no greater change in results would happen if these data were not missing.

Table 16 b: Tracking of the ponderal change in children from 4 years to 8 years

	BMI 8 years							
	Normal weight		**Overweight/Obese**		**Missing**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
BMI 4 years								
Normal weight	286	39.8	136	18.9	83	11.5	505	70.2
Overweight/Obese	9	1.25	32	4.45	13	1.81	54	7.51
Missing	20	2.78	16	2.23	124	17.2	160	22.3
Total	315	43.8	184	25.6	220	30.6	719	100

Both "longitudinal" and cross-sectional analyses use one methodology. As explained in Chapter 3 paragraph 3.3.1, the possible determinants are chosen through two following steps. Firstly, researchers select their most plausible determinants. Secondly, the backward logistic model identifies the possible determinants. The aim here is to focus on the main determinants of change in children's ponderal excess status. Therefore, the analyses refer to subjects who are comprised in every model according to the specific condition at study.

For example, considering the changes in ponderal excess between ages 15 months and 4 years the focus is on 15-month-old not overweight children, who start gaining weight until they become overweight/obese at age 4. They are also compared to normal weight children at both follow-ups. In total, 473 children are included in this first analysis, 39 of whom change their ponderal status through time.

The results are presented in Table 17. The potential determinants here are the same variables used in the cross-sectional analysis at age 4. These are the variables kept by the model, also accounting for the exclusion criteria of pr (0.20): eating habits (when children are 4 years); paternal and maternal educational levels and screen habits (when children are 4 years).

Table 17: Logistic backward stepwise regression model estimating the possible determinants of changing ponderal status (trajectories between 15 months and 4 years), from normal to overweight/obese status

	15 months - 4 years	
	OR	**IC 95%**
Eating habits		
Main meal (Ref.)	1.00	
Also between main meal	**2.48**	**(1.11, 5.57)**
Paternal educational level		
University degree (Ref.)	1.00	
Secondary school	1.66	(0.53, 5.20)
Primary school	**4.22**	**(1.22, 14.6)**
Maternal educational level		
University degree (Ref.)	1.00	
Secondary school	0.43	(0.16, 1.19)
Primary school	0.90	(0.27, 3.00)
Screen time		
< 1 hours (Ref.)	1.00	
>= 1 hours	2.16	(0.82, 5.66)

On the one side, this analysis underlines the negative role of bad eating habits and low paternal education on the risk of developing a status of ponderal excess between ages 15 months and 4 years. On the other, mothers going back to work after delivery influence inversely the risk of developing overweight/obesity between the same ages. When children usually eat between the main meals, the OR is 2.48. Furthermore, there seems to be an association between paternal low educational level and ponderal excess in children aged 4 (OR=4.22).

A similar analysis for the time lapse between ages 4 and 8 is illustrated in Table 18. Out of a total of 422 children, 136 change their ponderal status from normal weight to overweight/obesity, while 286 are normal weight in both follow-ups. The set of variables in the backward stepwise cross-sectional analysis at age 8 are maintained (see paragraph 4.3), and only four variables are kept in the model by the backward selection process as showed in Table 18.

The number of siblings, maternal pre-pregnancy BMI, the time of weaning and physical activity can always be possible determinants in this model. In fact, having two or more brothers/sisters has a protective effect against overweight/obesity changes (OR=0.31). Furthermore, mothers' pre-pregnancy BMI (when mothers are overweight, OR is 2.29) and the time of weaning

(when children are weaned off after they are 6 months, OR is 3.17) mostly contribute to children's changes in ponderal status. Apparently, physical activity is not a significant determinant, despite of being kept within the model.

Table 18: Logistic backward stepwise regression model estimating the possible determinants of changing ponderal status (trajectories between 4 years and 8 years), from normal to overweight/obese

	4 - 8 years	
	OR	**IC 95%**
Number of siblings		
No one (Ref.)	1.00	
One	1.24	(0.70, 2.21)
Two or more	**0.31**	**(0.12, 0.82)**
Maternal pre-pregnancy BMI		
Underweight/Normal weight (Ref.)	1.00	
Overweight	**2.29**	**(1.08, 4.86)**
Obese	0.83	(0.17, 4.09)
Weaning (in months)		
Until 4 months (Ref.)	1.00	
Between 4 and 6 months	1.57	(0.88, 2.81)
Beyond 6 months	**3.17**	**(1.04, 9.71)**
Physical activity		
Continous	1.11	(0.97, 1.28)

A conclusive analysis for this chapter aims at studying the potential determinants of permanent overweight/obesity in children, and is conducted only between ages 4 and 8 because the results from the 15-month follow-up are irrelevant. The results are presented in Table 19.

Once again, the set of potential determinants is the same as those in age 8 cross-sectional analysis and in the trajectory longitudinal analyses between ages 4 and 8. The four variables kept in the model are the duration of weaning, maternal BMI before pregnancy, sleeping habits and physical activity. Apparently, the only variable responsible for a permanence in ponderal excess status is the number of months for weaning, when children are weaned off after 6 months. This underlines the importance of this variable for the outcome at study (OR=6.98).

According to these last results, the main determinants of children's ponderal changes (from normal weight to overweight/obesity) are the same as in the cross-sectional analyses, and they are

maternal pre-pregnancy BMI, the number of siblings, children's eating habits and the number of months for weaning.

Table 19: Logistic backward stepwise regression model estimating the possible determinants of changing ponderal status (trajectories between 4 years and 8 years)

	4 - 8 years	
	OR	**IC 95%**
Weaning (in months)		
Until 4 months (Ref.)	1.00	
Between 4 and 6 months	0.41	(0.09, 1.93)
Beyond 6 months	**6.98**	**(1.87, 26.0)**
Maternal pre-pregnancy BMI		
Underweight/Normal weight (Ref.)	1.00	
Overweight	1.94	(0.46, 8.21)
Obese	3.95	(0.85, 18.5)
Sleeping time (hours)		
Continous	0.53	(0.28, 1.01)
Physical activity		
Continous	1.23	(0.97, 1.56)

Overall, both the cross-sectional and the longitudinal analyses showed results quite in line with the literature. Pre-pregnancy maternal BMI is fundamental: as it is well known in literature, there is a strong association between maternal ponderal excess and offspring's health status, regardless of the severity of mothers' ponderal excess.

Eating habits from the first years deeply influence the development of the metabolism and a healthy growth. This is the reason why the time of weaning is a sensitive one. The WHO guidelines explain that the complementary feeding, that is anything else but breast milk, should only be introduced after children are 6 months old. The process of weaning should be a gradual one, where adequate amount of different kinds of food should be added to breast milk. This way the passage from exclusive breastfeeding to a complete diet without breast milk will be easier and children will be adequately fed, on a right frequency. Despite these guidelines inappropriate feeding practices are frequently adopted by families, and they may lead to metabolic disturbs and to ponderal excess at young ages. This is probably the case, where late weaning seems to increase the odds of being overweight/obese at age 8. There is certainly an association with bad weaning practices, that cannot be check due to the lack of further data.

Another unexpected result is related to the number of siblings. There are some studies in literature that show the importance of having siblings to grow healthy. The results suggest that having two or more brothers/sisters may have a positive impact for decreasing the risk of being overweight/obese. Probably this is due to the different habits of mothers and the other caregivers, or it can also be linked to the relation with brothers/sisters that makes them play or move more.

As stated before, all the analyses make use of the IPW methodology to account for the missing values from biased selections. The analyses conducted without this methodology give very similar results. The odds ratios are just a bit higher, and the confidence intervals are slightly larger. Tables in Appendix B show the results without the application of the IPW methodology. Since there are not important differences in the results of the two set of analyses, there seems not to be any selection bias at the time of enrolment and at the different follow-ups. Despite this, a comparison between the IPW and the un-IPW results will follow, in order to avoid any possible selection bias of the data.

5. Traffic-related air pollution and childhood obesity in an Italian birth cohort (Research paper[4])

In this chapter, data and analyses of the effects of air pollution exposure on the excess of weight in children are presented. In the last years, a number of epidemiological studies have evidenced the adverse health effects coming from the exposure to traffic-related air pollution. As a matter of fact, particulate matter, gaseous contaminants and vehicular traffic has rapidly become a public problem worldwide. The Global Burden of Disease (GBD) has recognized outdoor air pollution as one main cause of death and loss of disability-free life-years (Collaborators, 2015; Stephen S Lim, Theo Vos, Abraham D Flaxman, Goodarz Danaei et al., 2012). The effects of air pollution exposure have already been analysed in relation to respiratory symptoms and diseases, but in the last years the adverse effects of vehicular traffic exposure have also been observed on the cardiovascular system, on the central nervous system, on the reproduction and development systems, and also related to the onset of different kinds of cancer and metabolic outcomes.

There are studies suggesting that the exposure to air pollution operates on systemic inflammation in diabetes subjects (Rao, Patel, Puett, & Rajagopalan, 2015), and that a rapid weight gain both in foetuses and after birth is related to air pollution exposure during pregnancy (Fleisch et al., 2015; Lakshmanan et al., 2015). Evidently, the risk of being overweight/obese during childhood is strictly related to foetal growth and to weight gain after birth. Moreover, there are several studies demonstrating the relation between childhood obesity and the exposure to environmental pollutants (Dong et al., 2014; Jerrett M, McConnell R, C.C. Roger Chang, Wolch J, Reynolds K, Lurmann F, Gilliland F, 2010; Mao et al., 2016; Rundle et al., 2012). Michael Jerrett has created a conceptual framework describing all the possible ways for traffic-related air pollution to produce weight growth (Jerrett et al., 2014). This framework not only considers the medical and health-related parts of the exposure to air pollution, but also includes the individual and social ways to react to vehicular traffic all around children's houses. One study by Grassi et al. published in 2016 (Grassi et al., 2016) tried to evaluate the relation between vehicular traffic and ponderal excess in children. As discussed in the forthcoming article, they did not find any association between traffic exposure and the outcome considered, also admitting that their assessment methods were too much subjective. To

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my knowledge, there is no other Italian study at present trying to evaluate the association between traffic-related air pollution and overweight/obesity in children. Before introducing the results, a brief summary about data collection on air pollution will be presented.

5.1.1 Data collection on traffic-related air pollution

Air pollution has become a major problem all over the world, in America as much as in Europe, from which arises the need of different measures and models to collect information and to estimate the concentration of pollutants. One of the main methods for modelling pollution's concentrations is the Land Use Regression (LUR) model. It is a model that accounts for differences between cities where air pollution concentrations have to be estimated. This is one reason for its widespread use, the other one is due to its predictor variables coming from spatial and geographical information systems (GIS). Before using the LUR model, several monitors should first collect air pollution concentrations all around the city. These models can usually explain a large amount of spatial variability and are often used to collect information about air pollution around one's residential address (Beelen et al., 2013; Eeftens et al., 2012).

The data on air pollution concentration used in this thesis come from the European Study of Cohorts for Air Pollution Effects (ESCAPE), the aim of which is to study the effects of air pollution exposure on the health status of the population. The populations at study are usually comprised in existent cohorts, while the concentrations of air pollution are estimated at their residential addresses. In the ESCAPE project, measurements in different European cities were conducted between October 2008 and April 2011 according to a common manual (available on www.escapeproject.eu) to decide where to install the monitors; Rome is the city of interest here and measurements took place between January 2010 and April 2011. The selected sites for traffic modelling are classified by levels of traffic intensity; industries of major ports are considered geographical characteristics in these sites. Measurements are conducted during two weeks per each period considered, namely the warm, cold and intermediate seasons. The concentrations of six pollutants (i.e., PM_{10}, $PM_{2.5}$, $PM_{2.5\ absorbance}$, PM_{coarse}, NO_2 and NO_x) are estimated: specifically, PM is monitored with the Harvard impactors, while NO_2 and NOx with the Ogawa badges. The results from the seasonal measurements produce the annual averages from each site, and a centrally-located background reference site has been working during the whole year to adjust the average measurements to temporal variations. These temporal variations are the difference between the measurements from each single reference site and its annual mean. Afterwards, the corrections are

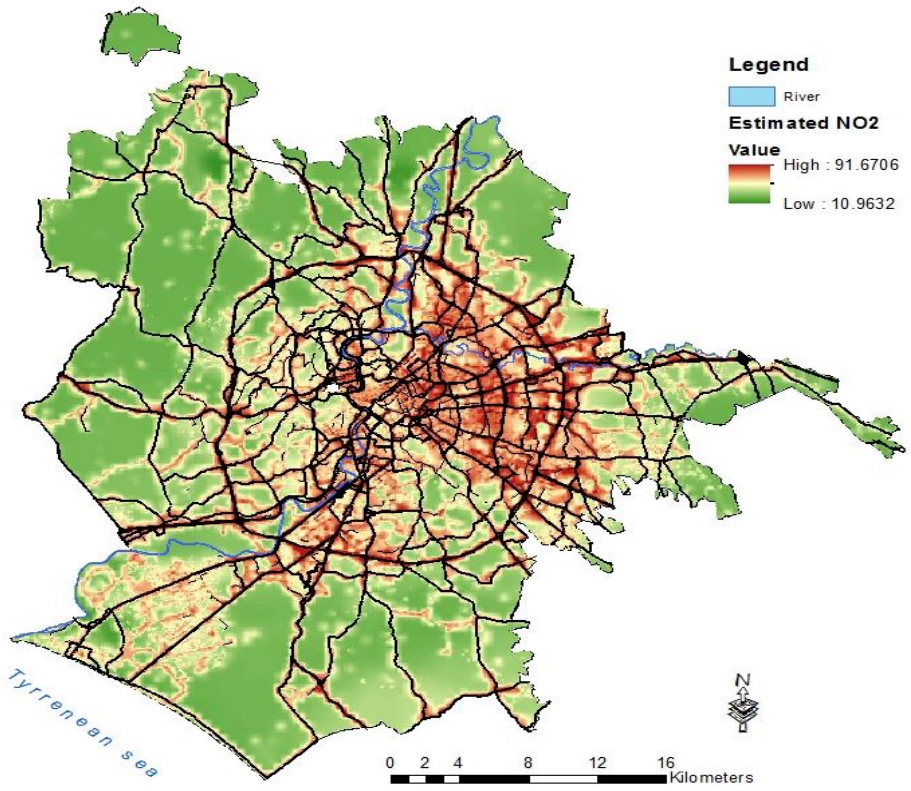
subtracted from all the measurements from that specific round. The positions of the measurement sites have been manually corrected in order to have a detailed map of the local areas. As mentioned before, the LUR models are based on predicted variables measured at each single site, using their coordinates and the digital GIS datasets. Buffers around the monitors with radii of 25, 50, 100, 300, 500 and 1,000 meters are used for traffic variables, while buffers for land use and population variables cover distances of 100, 300, 500, 1,000 and 5,000 meters. Data coming from GIS sources are related to a specific set of variables such as traffic intensity, road density, urban green and population density.

Univariate regression models are instead used in a stepwise procedure to define the predictor variables, and variables giving higher R^2 results are included in the final model. All the other variables are considered for improving each R^2 value according to their directions. Final steps include the use of the VIF value (namely, Variance Inflation Factor), which is higher than three, the p-value which is higher than 0.10 and Cook's D statistics to eliminate certain variables or detect influential observations. At the very end of the whole process, the model is validated with a leave-one-out cross validation and the Moran's I is used to calculate the spatial autocorrelation of the residuals. In Rome, that is the city where the GASPII cohort comes from, the highest R^2 is found for NO_2 concentrations (87%), while the lower one for PM_{coarse} (70%). At the same time, the R^2 values for the cross-validation models are all quite good, ranging from 79% of $PM_{2.5Abs}$ and 57% of PM_{coarse}. An example of pollutants' distribution is presented in Figure 8. In this specific case, the distribution of the estimated NO_2 values in Rome are reported. As one can see from the legend, red is used for the highest values, while green is for the lowest ones. This map also shows the main streets in Rome, where red and orange indicate the areas with more traffic. Additional measures used in the ESCAPE project are three traffic indices referring to children's residential addresses: the first variable measures traffic intensity (vehicles/day) in the road closer to one participant's residence. The other two variables are similar because both measure the traffic load of roads within a buffer of 100 meters away from the residence: it is the product of traffic intensity and the length of road fragments within a 100-m buffer. Nevertheless, while one variable measures the traffic load of major roads the second one can be applied to all roads.

These LUR models are used in the ESCAPE project to estimate the concentrations of traffic-related air pollution at the residential addresses of more than 30-cohort participants in all Europe. Model performances are overall quite satisfying, but some limitations include, for example, the scarce number of monitors (only 20 units) for the PM assessments. Another limitation is related to the position of the monitors, which can be problematic since the concentrations estimates refer to

the areas all around one's residential address, and do not consider different time patterns for activities and exposures which occur either outdoor or indoor. Despite these limitations, Cesaroni et al. have studied the stability of some measurements from the ESCAPE project in Rome, such as the NO_2 ones. In fact, they show that predicted levels of this pollutant using two LUR models which refer to different moments (with a 12-year temporal distance) remain stable during time (Giulia Cesaroni et al., 2012).

Figure 8: Map of the levels of NO_2 pollutant in the city of Rome



Source: Elaboration from the ESCAPE data for the city of Rome. Made by Chiara Badaloni, working at the Department of Epidemiology of the Lazio Regional Health Service (DEP)

The effects of air pollution exposure on overweight/obesity are assessed with data from the 4- and 8-year follow-ups. This part of the thesis is developed as a research paper, and it has been sent to the scientific journal *Environmental Research*. It was then accepted for publication on October 3rd, 2017 and it is now in production. Furthermore, Appendix C reports the Supplementary material of the paper.

Introduction

Over recent decades, the percentages of overweight and obese children have reached high levels all over the world. In 2013, the World Health Organization (WHO) estimated that around 42 million children under 5 years were overweight or obese (WHO, 2014).

Being overweight or obese during childhood can increase the risk of being overweight/obese, during adolescence or adulthood (Deckelbaum & Williams, 2001), and several complications and illnesses can arise from ponderal excess (Deckelbaum & Williams, 2001; Ebbeling, Pawlak, & Ludwig, 2002; Lobstein, Baur, & Uauy, 2004). There are several complications and diseases that can follow excess fat accumulation (Ebbeling et al., 2002), and adiposity excess is associated with increased risk of developing type 2 diabetes (Deckelbaum & Williams, 2001) and cardiovascular diseases (Franks et al., 2010; Lobstein et al., 2004). An obese child who remains obese throughout adolescence and adulthood, will have during his life an increased risk of elevated blood pressure, chronic inflammation, stroke (Deckelbaum & Williams, 2001; Ebbeling et al., 2002), and eventually an early death (Ebbeling et al., 2002; Franks et al., 2010). There is increasing evidence that factors underlying childhood obesity may be related to exposures that occurred during pregnancy (Al Mamun et al., 2006; Evagelidou et al., 2006; Linabery et al., 2013; Whitaker, 2004), the neonatal period, and the first years of life (Ebbeling et al., 2002; Potter, 2006). Gestational diabetes (Evagelidou et al., 2006), maternal weight gain (Linabery et al., 2013; Whitaker, 2004) or smoking (Al Mamun et al., 2006) during pregnancy can increase the risk of obesity in offspring. Moreover, factors like breastfeeding and growth after birth play an important role in childhood development; also lifestyle, physical activity, screen time, diet and duration of sleep are important factors for a child's ponderal status (Ebbeling et al., 2002; Potter, 2006).

One of the most concerning exposures considered in recent years is traffic-related air pollution: there are studies indicating that ambient air pollution reduces birth weight, affects growth after birth and increases risk of ponderal excess (i.e. being overweight or obese during childhood) (Dadvand et al., 2013; Fleisch et al., 2015; Lakshmanan et al., 2015). Some studies showed evidence of an association between air pollution and Body Mass Index (BMI) in children of different ages (Dong et al., 2014; Jerrett M, McConnell R, C.C. Roger Chang, Wolch J, Reynolds K, Lurmann F, Gilliland F, 2010; Mao et al., 2016; Rundle et al., 2012). In 2014, Jerrett et al. proposed a conceptual framework (Jerrett et al., 2014) to clarify the possible pathways through which traffic-related air pollution may affect the risks of being obese or developing metabolic syndrome. The main pathways defined by the authors included: perceived safety (and reduced physical activity), an

increase of stress levels due to noise (which affects sleep regulation and caloric intake) and the pathway related to systemic inflammation.

BMI level is the measure most often used to analyse the risk of being overweight or obese; few studies have used waist circumference as a measure of adiposity. This measure is a better estimate of visceral fat and given that it is easily reported and understood, seems to be a better measure than BMI (National Health Services, 2009). One study demonstrated that, using both BMI levels and waist circumference, the waist measurement was the best predictor in children of being overweight later (Maffeis, Grezzani, Pietrobelli, Provera, & Tatò, 2001). In addition, information on waist and hip circumference and the waist-to-hip ratio could be used as a further measure of body fat.

Blood lipids levels are also considered related to ponderal excess. The effects of air pollution on blood lipids (total cholesterol and high-density lipoprotein cholesterol) have been studied without conclusive results. Few studies assessed the effects of air pollution on total cholesterol or on high-density lipoprotein (HDL cholesterol) in adult populations, with scarce evidence of an association (Jiang et al., 2016; Maiseyeu et al., 2015; Shanley et al., 2016; Sørensen et al., 2015; Wallwork et al., 2017). There are no studies that have analysed air pollution exposure during pregnancy, or in the first years of life, on the likelihood of having high blood lipid levels during childhood.

The aim of this study is to evaluate the effect of traffic-related air pollution on the risk of being overweight or obese among children enrolled in a birth cohort in Rome. Body mass index, waist circumference and waist-to-hip ratio were used in the analyses as measures of overweight/obese status. In addition, the relationship between exposure to traffic-related air pollution and blood lipids (total cholesterol and HDL cholesterol) was evaluated in the same prospective birth cohort.

Material and methods

Study Population

The study population consisted of mother-infant pairs enrolled in the Gene and Environment Prospective Study on Infancy in Italy (GASPII, a prospective birth cohort study which has been fully described elsewhere (D., Porta, M.P. Fantini, 2006; Porta, Forastiere, Di Lallo, & Perucci, 2007). Newborns were enrolled at birth in two obstetric hospitals in Rome from June 2003 until October 2004. The mothers were eligible if Italian, older than 18 years, and resident in the area of the Local Health Unit Rome E, total population about 500,000 inhabitants. There were 1290 mothers contacted, 55% responded; a total of 704 mothers and 719 infants (13 pair of twins and 1 triplet) were enrolled.

Data Collection

Parents were first interviewed face to face at their child's birth. Two separate questionnaires were administered to fathers and mothers in order to collect information regarding pregnancy, parent's health and lifestyles, family social conditions, demographic characteristics, previous pregnancies, and maternal emotional status during pregnancy. Information about delivery was recorded by obstetricians. Follow-up of the children was conducted at 6 months, 15 months, 4, 7 and 8 years. Measures of BMI were collected at 4 and 8 years during clinical examinations, while data on abdominal fat and blood lipids were collected only at the 8 year follow-up.

Exposure assessment

We considered six pollutants (NO_2, NOx, PM_{10}, $PM_{2.5}$, PM_{coarse} and $PM_{2.5}$ absorbance), and one traffic variable, estimated at individual residential address. Exposure values were estimated between birth and the first four years of life, reflecting all the address changes during the period, and were calculated as time-weighted average exposure. The traffic variable was estimated only at birth. In order to assess exposure at each participant's residential address, all the addresses recorded at each interview were geo-coded using TeleAtlas, the Italian road network. 99.17% of addresses were geocoded, with an accuracy of the geocoding scores greater than 80%"

The estimates of NO_2, NOx, PM_{10}, $PM_{2.5}$, PM_{coarse} and $PM_{2.5}$ absorbance concentrations were assessed using Land Use Regression models (LUR) developed within the European Study of Cohorts for Air Pollution Effects (ESCAPE) (Beelen et al., 2013; Eeftens, Beelen, et al., 2012) project. The measurements and the models are described elsewhere (Beelen et al., 2013; Cyrys et al., 2012; Eeftens, Beelen, et al., 2012; Eeftens, Tsai, et al., 2012). In brief, different fractions of particulate matter (PM_{10}, $PM_{2.5}$, PM_{coarse} and $PM_{2.5}$ absorbance) were measured at 20 sites, and nitrogen dioxide and oxides (NO_2 and NOx) at 40 sites. PM was monitored with Harvard impactors, and NO_2 and NOx with Ogawa badges. Measurements (Cyrys et al., 2012; Eeftens, Beelen, et al., 2012) were collected between January, 2010 and April, 2011, in three 2-week periods accounting for different seasons. Annual average concentrations of the pollutants were calculated for each site, adjusting for temporal variations (using measurements from the whole year taken by a centrally located background reference site). GIS predictor variables were used to model spatial variation of annual average concentrations. The variables included traffic intensity, road density, urban green, and population density (Beelen et al., 2013; Eeftens, Beelen, et al., 2012). The R^2 of the models ranged from 0.70 (PM_{coarse}) to 0.87 (NO_2). The models were validated using the leave-one-out cross-validation method, with R^2 that ranged from 0.57 (PM_{coarse}) to 0.79 ($PM_{2.5}$ absorbance). In

addition, one traffic variable (traffic load of all roads in a 100m buffer) was used to assess exposure to vehicular traffic. The variable, already included in the set of variables used to develop the ESCAPE LUR models, measured the total traffic load of all roads in a 100-meter buffer (vehicles × meters/day).

Overweight and obesity

At 4 years and 8 years of age, children underwent clinical follow-up during which measures of weight and height were recorded. Weight and height were measured in light clothing and barefoot. Height was measured standing. Anthropometric measures at 4 years of age were collected during a home visit by trained personnel following standardized procedures, while clinical follow-up at age 8 was performed by hospital personnel following standardized procedures. BMI was calculated as weight (in kilograms) divided by height squared (in meters). The age- and sex- specific BMI Z-score (standard deviations) was calculated using the World Health Organization (WHO) 2007 Growth Charts (Borghi et al., 2006; Onis, Onyango, Borghi, Siyam, & Siekmann, 2007). We decided to consider the overweight and obese children together, because of the very low prevalence of obese children at both follow-up points. Childhood overweight/obesity was defined according to the suggested WHO standards.

Waist circumference and waist-to-hip ratio

Ponderal excess in children, as in adults, can be assessed also through waist and hip circumferences. During the clinical examination of the age 8 follow-up, waist and hip circumferences were collected. The measurements were obtained standing, and using standardized procedures, to the nearest 0.1 cm. Moreover, due to the availability of both circumference measures, the waist-to-hip ratio was calculated as a supplementary measure of body fat distribution.

Total cholesterol and HDL cholesterol levels

Blood samples were taken from each child during the clinical follow-up at age eight. All samples were transferred to a central laboratory where total cholesterol and HDL cholesterol levels were analysed. Cholesterol concentrations were measured in plasma samples (Li-heparin plasma) by standard enzymatic methods (Cobas c systems, Roche Diagnostics), by manufacturer's instructions. Cholesterol esters are cleaved by the action of cholesterol esterase to yield free cholesterol and fatty acids. Cholesterol oxidase then catalyses the oxidation of cholesterol to cholest-4-en-3-one and hydrogen peroxide. In the presence of peroxidase, the hydrogen peroxide formed effects the oxidative coupling of phenol and 4-aminophenazone to form a red quinone-imine dye. The colour

intensity of the dye formed is directly proportional to the cholesterol concentration, and it is determined by measuring the increase in absorbance.

Statistical analysis

Descriptive statistics were provided for the study population, with information collected in the questionnaires at birth and at each follow-up, and for outcomes and exposures.

To study the association between air pollution and the risk of being overweight or obese, a cross-sectional and a longitudinal approach were used. Within the cross-sectional approach, a Generalized Linear Model (GLM) with a family Poisson and link log was used, for each follow-up (4 and 8 years) and the results were expressed as Relative Risks (RR). Then, within the longitudinal approach, the association between air pollution and obesity at 4 and 8 years was investigated using the Generalized Estimating Equation model (GEE) with a link log and Poisson family; the results were expressed as Relative Risks. The association between waist circumference and waist-to-hip ratio at 8 years was assessed with linear regression models, using the outcomes as continuous variables. Moreover, when exposure to vehicular traffic was considered, a Wald test was performed for each analysis in order to ascertain the presence of a trend.

Participation rate at recruitment and loss to follow-up may have produced selection biases at the three stages of this study (recruitment, 4 year follow-up and at the 8 year follow-up). To avoid biased results, we applied the inverse probability weighting (IPW), a methodology that give more weight to the information coming from subject who are more similar to those that have been lost during each step (Robins, 1997; Rotnitzky & Robins, 1997). We modelled three different selection processes separately. Logistic regression models were used to calculate weights, that have been generated by the probability of being recruited or to be not lost at follow-up points, using different covariates. The weights of being recruited and of participating in that specific follow-up have successively been multiplied and used in the corresponding analyses. This methodology has been previously applied on the same birth cohort used in this paper, and more details can be found elsewhere (Narduzzi, Golini, Porta, Stafoggia, & Forastiere, 2014; Porta et al., 2016).

The effects of the exposures were expressed for 1 unit increase in $PM_{2.5}$ absorbance, for 10μg/m^3 increase in NO_2 and $PM_{10,}$ for 5μg/m^3 increase in $PM_{2.5}$ and PM_{coarse}, and for 20μg/m^3 increase in NO_x. The effects of traffic load of all roads in a 100-meter buffer was categorised into four levels: non exposed (those who live in houses with only private access and no public roads in a 100 meters buffer), and the tertiles of the distribution of traffic load.

Separate analyses for each outcome and each exposure were performed. The associations of being exposed to air pollutants and to the traffic variable were analysed at first using crude models, then each model was adjusted for several confounders selected according to the literature and biological plausibility. The confounders used were gender (male vs female), age at follow-up point (in months), maternal educational level (university degree vs secondary school and primary school), paternal educational level (university degree vs secondary school and primary school), maternal pre-pregnancy BMI (underweight/normal weight vs overweight/obese), maternal smoking during pregnancy (yes vs no), maternal age at delivery (< 30 years vs 30-35 years and > 35 years), gestational age (< 37 week vs >= 37 week), child birth-weight (2500-3999 gr vs < 2499 gr and > 4000 gr), breastfeeding duration (never breastfed vs < 4 months, 4-6 months and > 6 months) and age at weaning (< 4 months vs 4-6 months and > 6 months). The last two confounders are different: breastfeeding duration measured how long the child was breastfed, while the variable age at weaning, was the age at which the child stopped being exclusively breastfed, and started to be fed with other kinds of food. Gender and age were not included in the analyses as potential confounders when BMI was considered, because the BMI Z-score was sex- and age- specific.

Additional analyses

Further analyses were produced using the BMI Z-score at both follow-up visits, and total cholesterol and HDL cholesterol values at 8 years, as additional outcome measures. Also in this case, cross-sectional and longitudinal approaches were used. Linear regression models were estimated for each follow-up considered (4 and 8 years), with results expressed as coefficients. The results of the longitudinal models were expressed as coefficients as well, using the GEE model with an identity link and a Gaussian family. The results of these analyses are reported in the supplementary tables.

Furthermore, we repeated all the main and additional analyses without applying the IPW methodology to the data, with the aim of checking possible bias due to nonparticipation or loss to follow-up. The results of the not weighted analyses are reported in the supplementary tables. At the same time, in order to evaluate exposure to air pollutants only during pregnancy, we decided to replicate all the analyses (with and without the IPW methodology), changing the exposure period. Although we did not have information about any changes in residential addresses of the mothers during pregnancy, we know, from Municipal Registry data, that during the study period in the city of Rome, only 7.5% of pregnant women changed their address before giving birth. For this reason, we used the birth address as a proxy of the address during pregnancy; therefore, in these analyses

we used the exposure estimate at the address at birth, as main exposure. These results are also reported in the supplementary tables.

Results

Population Characteristics

Seven hundred and nineteen children were enrolled at birth. Follow up was conducted for 581 of them (80.8%) at 4 years of age, and 499 (69.4%) at age 8. Mean age of the children at each follow-up was: 50 months (range: 39-62) at 4 years and 104 months (range: 96-123) at 8 years. Table 1 reports the characteristics of the study population at enrolment. Most mothers were 30-35 years old at delivery, and had a healthy weight before pregnancy. Almost 12.5% of them smoked during pregnancy and 4.17% suffered from gestational diabetes. High educational level (university degree) characterized 36% of the mothers and 29% of fathers. Few children were born preterm (5.84%), and 6.12% weighed less than 2500 gr at birth. Almost 11% were not breastfed and 70% were weaned within 4 months.

Table 2 reports the description of the outcomes under study. The BMI Z-score outcome was available at each follow-up considered, while waist circumference and waist-to-hip ratio values were available only for the 8 year olds, as well as total cholesterol and HDL cholesterol levels. The prevalence of overweight/obese children was 9.3% at 4 years and 36.9% at 8 years. Since the prevalence of obesity at both follow-up points was very low (1.39% and 0.83%), it was decided to consider both the conditions together,

Table 3 describes the estimates of the exposure to air pollution and the traffic variable (with mean values and standard deviations) for each follow-up. The correlation between the pollutants and the traffic variable ranged from 0.53 for $PM_{2.5}$ absorbance and NO_2, to 0.95 for $PM_{2.5}$ and PM_{10} (in the supplementary Table S2, all the correlations are reported).

The number of individuals included in each analysis is presented in the supplementary Table S1.

Statistical analysis

Table 4 reports the crude and adjusted results of the association between exposure to air pollution and the overweight/obesity outcome, from the cross-sectional and longitudinal analyses. No evidence of an association was found in the cross-sectional analyses for exposure to the pollutants considered. Similar results without evidence of a significant association were found in the analyses of traffic exposure, even though we observed a suggestion from an increase in overweight/obesity at

4 years for increasing levels of traffic load in a 100mt buffer, (RR 3rd tertile = 2.90; 95 CI% 0.88 to 9.53). No evidence of an association was found in the GEE model for any of the exposures, and no evidence of a trend was observed in the vehicular traffic analyses.

Table 5 shows the associations between pollutants and traffic variable, and the two measures of abdominal obesity considered: waist circumference and waist-to-hip ratio. We found a significant association for the second tertile of traffic load (Coeff= 2.10; 95%CI: 0.23-3.98) in the crude analysis, a result that was not confirmed in the adjusted models. No association was found for exposure to air pollution and waist-to-hip ratio. The Wald test for trend was not significant for any of these analyses.

Additional analyses

The effects estimated in the sensitivity analyses of the continuous BMI Z-score are presented in Supplementary Table S3. Evidence of an association was found for the crude analyses at age 8, for NO_x exposure, yet this result was not confirmed in the adjusted analyses. In the crude longitudinal analysis, evidence of a negative association was found for exposure to PM_{coarse} (Coeff = -0.13; 95 CI% -0.24 to -0.01), and for NO_x (Coeff = -0.09: 95 CI% -0.18 to -0.00). The only association confirmed after adjusting for confounders was for PM_{coarse} (Coeff = -0.13; 95 CI% -0.25 to -0.01). This result was not found in the analysis of the overweight/obesity; moreover, the PM_{coarse} estimate model had the worst validation (R^2 validation = 0.57), indicating that there is a possibility this result is not reliable. The results of the analyses of the traffic variable did not show any evidence of association. The effects of traffic-related air pollution on total and HDL cholesterol levels are reported in supplementary Table S4, and there was no evidence of association.

Supplementary tables S5-S8 report the results of the analyses without IPW. In general, it should be noted that the effects of both air pollutants and traffic variable are weaker compared to the results obtained with the IPW, and with similar confidence intervals. No differences were observed in the statistical significance of the results obtained.

The results of the sensitivity analyses using exposure at birth (with and without the IPW methodology) are reported in supplementary Tables S9-S18. No significant differences with the main results have been found when considering exposure at birth.

Discussion

In this study no evidence of an association was found between exposure to air pollutants and overweight/obesity in children enrolled at birth and followed to 8 years of age. The analyses of

waist circumference and waist-to-hip ratio confirmed the results of the BMI analyses and no association was found with blood lipids. Similarly, exposure to traffic showed no evidence of an association with being overweight/obese in the cross-sectional analyses or in the longitudinal approach.

The results of this study contrast the few results on this subject found in the literature. Some studies that analysed the association between air pollution and adiposity in children suggested that exposure to pollutants may contribute to an increasing risk of being overweight or obese in the first years of life. A study by Rundle et. al. found that exposure to polycyclic aromatic hydrocarbons (PAHs) during the prenatal period was associated with high (BMI) in 5 year olds. A positive association between PM_{10} and risk of being obese or overweight in children aged 2-4 years was found in a large cross-sectional study in China (Dong et al., 2014). In a recent cohort study of children born in Massachusetts, ambient $PM_{2.5}$ exposure in utero and in the first two years of life was found to be associated with the risk of being overweight or obese (Mao et al., 2016).

The results of the analyses between vehicular traffic and risk of ponderal excess, are not consistent with the results by Jerrett et al., who in 2010 found an association between high vehicular traffic volume and higher BMI levels in children aged 10-18 years (Jerrett et al., 2010. The conceptual framework proposed by Jerrett et al. in 2014 showed the possible pathways through which air pollution may affect both the risks of developing a metabolic syndrome and of being overweight/obese. Briefly, high traffic volume could influence active travel (by foot or by bike) and perceived safety, reducing physical activity and probably positively change the energy balance. Another possible pathway may operate through traffic noise that can increase stress levels, affecting sleep habits, and hence caloric intake (affecting the diet) (Sekine et al., 2002; Taheri, Lin, Austin, Young, & Mignot, 2004). Exposure to environmental pollutants might operate also through systemic inflammation, increasing the risk of being obese (Sun et al., 2009). In the same paper, Jerrett et al. using the conceptual framework discussed above, showed the effect of traffic density over the development of obesity in children aged 5-11. Results consistent with our paper were found by Grassi et al. in 2016, who investigated the association between traffic volume near children's home and school, and ponderal excess and found no association (Grassi et al., 2016). The authors found that traffic density was not associated with any significant difference in children's weight, despite literature evidence, but they explained that the results were likely due to a misclassification of the exposure assessment, which was based on parents' perception.

While there are studies that assessed the association between traffic-related air pollution and childhood BMI levels, to our knowledge, there are no studies that analysed the association between

measures of abdominal adiposity and traffic-related air pollution. Most studies that analysed the risk of being overweight or obese, in children or in adults, measured adiposity excess with BMI. This measure is easy to collect but it does not distinguish body fat from lean body mass. For this reason, several studies have used waist circumference, in addition to BMI level. Waist circumference can be used to estimate visceral fat and to predict ponderal excess, as Maffeis et al. did in 2001. Their results showed that waist circumference measured in children aged 8 years was the best predictor for ponderal excess in children aged 12 (Maffeis et al., 2001). In this study, two measures of abdominal fat at 8 years were used (i.e. waist circumference and waist-to-hip ratio), in order to consider different indicators of ponderal excess in children.

Blood lipid levels are also related to weight and obesity status. The relationship between obesity and levels of blood lipids has been assessed in several studies, both in adults and children, with overweight/obese persons showing higher levels of total cholesterol and low levels of high-density lipoprotein (HDL) cholesterol. The association between air pollution exposure and blood lipids has been studied, without consistent results. Evidence of an association between total cholesterol levels and pollutants was found in recent studies (Shanley et al., 2016; Sørensen et al., 2015). In 2016, a study by Jiang et al. showed the absence of an association between total cholesterol and $PM_{2.5}$ exposure (Jiang et al., 2016). Changing levels of HDL cholesterol in adults were not associated with air pollution exposure (Shanley et al., 2016; Wallwork et al., 2017), considering both long-term exposure to $PM_{2.5}$ (Jiang et al., 2016), and acute exposure to PM_{coarse} (Maiseyeu et al., 2015). The biological mechanisms through which air pollution could influence cholesterol levels in adults are not very clear, and more research is needed. To our knowledge, there are no studies about the effects of air pollution on cholesterol levels in children.

LUR models, developed within the ESCAPE project (Beelen et al., 2013; Eeftens, Beelen, et al., 2012), have been used to provide estimates of concentrations of different types of pollutants. These models have a limitation related to the absence of information on temporal variability. The assumption is that the spatial variability of pollutants is stable over time. This is supported by a comparison of NO_2 estimated from LUR models several years apart that showed stable results of the exposure assessment over twelve years (Cesaroni et al., 2012). The stability of exposure, together with traffic volume and the slow paced urbanisation of the city of Rome, made possible the use of the LUR 2010 models in this study, despite the fact that the GASPII cohort was enrolled in 2003-2004.

This study has limited power due to the low number of children followed from birth to age 8, as occurs in many cohort studies; indeed, both poor recruitment and attrition had an effect on the

statistical power of the analyses. Nevertheless, positive results of the effect of traffic-related air pollution exposure have been found in previous analyses using the GASPII cohort: the association between traffic-related air pollution and cognitive function has been assessed (Porta et al., 2016), as has the role of traffic-related air pollution in the first occurrence of respiratory symptoms and asthma (Ranzi et al., 2014).

One of the main strengths of this study was the prospective study design of the GASPII cohort, through which it has been possible to collect and use longitudinal measures of the exposure and outcome in the analyses. Due to the longitudinal design of the study, the use of a longitudinal model (GEE) was needed. Another strength is that the BMI Z-score was calculated taking advantage of standardized methods, based on WHO classifications (Borghi et al., 2006; Onis et al., 2007), used universally as the gold standard. In addition, using the BMI Z-score both as categorical (overweight/obese yes or no) and continuous outcomes, provided occasionto check results consistency. Despite the presence of a surveillance network to monitor the prevalence of ponderal excess in Italian children aged 8-9 years (Salute, 2014; A Spinelli, Buoncristiano, Lauria, & Pizzi, 2014; Angela Spinelli, Lamberti, Nardone, Andreozzi, & Galeone, 2010), we found only one Italian study in the literature that analysed obesity-related factors in children relative to ambient air pollution exposure (Grassi et al., 2016).

Conclusions

In conclusion, the results of this study did not show any association between vehicular traffic and being overweight/obese at 4 or 8 years of age. Despite the studies present in the literature, there is no evidence of an association between pollutants and the development of childhood obesity. The link between ambient air pollution exposures and blood lipids were not clear; neither were the effects of air pollution over BMI and waist circumference (or waist-to-hip ratio). Further studies are needed to better understand the biological mechanisms of air pollution and to clarify its role in a child's risk of becoming obese.

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Tables

Table 1. Characteristics of the children from the GASPII cohort[a].

	At birth	
	N	%[a]
Total	719	100
Maternal education		
University degree	256	35.6
Secondary school	362	50.3
Primary school	101	14.0
Paternal education		
University degree	206	28.7
Secondary school	278	38.7
Primary school	148	20.6
Maternal pre-pregnancy BMI		
Underweight/Normal	598	83.2
Overweight	84	11.7
Obese	33	4.59
Maternal smoking during pregnancy		
No	624	86.8
Yes	90	12.5
Gestational diabetes		
No	686	95.4
Yes	30	4.17
Maternal age at delivery		
< 30 years	205	28.5
30 - 35 years	310	43.1
> 35 years	204	28.4
Gestational age		
< 37 week	42	5.84
>= 37 week	672	93.5
Gender		
Male	364	50.6
Female	355	49.4
Birth weight		
< 2499 gr	44	6.12
2500 - 3999 gr	612	85.1
> 4000 gr	63	8.76
Breastfeeding duration		
Never been breastfed	80	11.1
< 4 moths	188	26.1
4 - 6 months	137	19.1
> 6 months	289	40.2
Age at weaning		
< 4 moths	503	70.0
4 - 6 months	143	19.9
> 6 months	40	5.56

[a] Parental and birth characteristics were recorded at birth, breastfeeding duration and age at weaning were recorded between birth and 15 months

[b] Because of missing values, some percentages do not add up to 100%

Table 2. Description of the outcome variables, by follow-up points: N, Means and SD

	4 year (N=581)			8 year (N=499)		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
BMI z-score	559	0.69	1.07	499	0.65	1.18
Waist Circumference	-	-	-	499	60.0	6.18
Waist-to-Hip Ratio	-	-	-	499	9.14	0.42
Total Cholesterol	-	-	-	411	162.3	25.1
HDL Cholesterol	-	-	-	411	59.2	15.2
		N	**%**		**N**	**%**
Normal weight children		505	86.9		315	63.1
Overweight/obese children		54	9.29		184	36.9

[a] Because of missing values, some percentages do not add up to 100%

Table 3. Exposure levels of air pollutants evaluated between birth and 4 years old, and traffic levels evaluated at birth, by follow-up visits (Means and SD)

		4 year (N=528)		8 year (N=477)	
		Mean	**SD**	**Mean**	**SD**
Air pollutants levels, evaluated between birth and 4 years old					
NO_2		43.3	10.1	43.4	10.2
NO_X		69.2	19.4	69.8	19.5
PM_{10}		36.8	5.51	36.9	5.48
$PM_{2.5}$		19.5	2.03	19.5	2.02
PM_{coarse}		16.7	3.82	16.7	3.84
$PM_{2.5Absorbance}$		2.70	0.56	2.7	0.56
Traffic load of roads in a 100mt buffer[a], evaluated at birth					
Not exposed	(=0; N=80)	-	-	-	-
<I tertile	(<=$24*10^4$; N=211)	143,090	54,019	145,394	54,304
I-II tertile	(<=$176*10^4$; N=211)	749,900	461,732	761,849	462,776
>III tertile	(<=$1720*10^4$; N=211)	4,935,197	3,089,275	4,954,558	3,044,056

[a] Number of vehicles × meters of road/day, at 4 year follow-up visit N=557, at 8 year follow-up visit N=497

Table 4. Association between exposure to air pollution (from birth to 4 years of life) and to vehicular traffic (evaluated at birth), and overweight/obesity. Results from generalised linear models (GLM) (at each follow-up) and generalised estimation equations (GEE) models (in the overall follow-up period).

	4 Year				8 Year				GEE			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**
NO_2 (per 10 μg/m^3)	0.91	(0.68, 1.21)	1.03	(0.79, 1.35)	0.96	(0.85, 1.08)	0.97	(0.85, 1.11)	0.95	(0.83, 1.07)	0.99	(0.86, 1.12)
NO_X (per 20 μg/m^3)	0.90	(0.68, 1.20)	1.02	(0.78, 1.34)	0.93	(0.82, 1.06)	0.96	(0.84, 1.10)	0.94	(0.82, 1.07)	0.98	(0.86, 1.12)
PM_{10} (per 10 μg/m^3)	0.98	(0.62, 1.54)	1.11	(0.70, 1.76)	0.95	(0.76, 1.19)	0.92	(0.73, 1.17)	0.96	(0.77, 1.21)	0.97	(0.77, 1.23)
$PM_{2.5}$ (per 5 μg/m^3)	1.08	(0.61, 1.89)	1.24	(0.68, 2.25)	0.97	(0.72, 1.30)	0.96	(0.70, 1.31)	1.00	(0.75, 1.34)	1.02	(0.75, 1.40)
PM_{coarse} (per 5 μg/m^3)	0.84	(0.59, 1.20)	0.96	(0.68, 1.36)	0.91	(0.77, 1.07)	0.89	(0.74, 1.06)	0.91	(0.77, 1.07)	0.91	(0.77, 1.09)
$PM_{2.5abs}$ (per 1 μg/m^3)	1.12	(0.73, 1.72)	1.28	(0.84, 1.94)	1.00	(0.81, 1.24)	1.05	(0.84, 1.30)	1.02	(0.83, 1.27)	1.10	(0.88, 1.37)
Traffic load of roads in a 100mt buffer[a]												
Not exposed	1.00		1.00		1.00		1.00		1.00		1.00	
Below 1st tertile	1.57	(0.54, 4.59)	2.45	(0.72, 8.40)	1.09	(0.70, 1.67)	0.91	(0.59, 1.41)	1.17	(0.75, 1.84)	1.08	(0.69, 1.71)
Between the 1st and the 2nd tertile	1.74	(0.61, 5.03)	2.02	(0.62, 6.65)	1.30	(0.86, 1.96)	1.15	(0.77, 1.73)	1.40	(0.90, 2.16)	1.30	(0.84, 2.00)
Beyond the 3rd tertile	1.92	(0.67, 5.50)	2.90	(0.88, 9.53)	1.06	(0.69, 1.64)	0.98	(0.63, 1.52)	1.21	(0.77, 1.90)	1.23	(0.78, 1.94)

[a] Number of vehicles × meters of road/day

RRs were adjusted for maternal and paternal education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, child birth weight, breastfeeding duration, age (in months) at weaning and inversely weighted for the probability of participation at baseline and at the two follow-ups, respectively

Table 5. Association between exposure to air pollution (from birth to 4 years of age) and to vehicular traffic (evaluated at birth), and waist circumferences and waist-to-hip ratio at 8 years, evaluated using linear regression models

	Waist Circumference (cm)				Waist-Hip Circumference Ratio (cm)			
	Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
NO_2 (per 10 µg/m^3)	0.11	(-0.45, 0.67)	0.39	(-0.20, 0.97)	0.006	(-0.03, 0.04)	0.007	(-0.03, 0.04)
NO_X (per 20 µg/m^3)	-0.17	(-0.76, 0.42)	0.17	(-0.46, 0.80)	-0.003	(-0.04, 0.04)	0.001	(-0.04, 0.04)
PM_{10} (per 10 µg/m^3)	-0.44	(-1.49, 0.60)	-0.26	(-1.36, 0.83)	-0.027	(-0.09, 0.04)	-0.024	(-0.09, 0.05)
$PM_{2.5}$ (per 5 µg/m^3)	-0.52	(-1.93, 0.91)	-0.30	(-1.79, 1.19)	-0.031	(-0.13, 0.06)	-0.026	(-0.12, 0.07)
PM_{coarse} (per 5 µg/m^3)	-0.37	(-1.11, 0.38)	-0.22	(-1.01, 0.58)	-0.002	(-0.05, 0.05)	0.000	(-0.05, 0.05)
$PM_{2.5abs}$ (per 1 µg/m^3)	-0.22	(-1.25, 0.80)	0.06	(-1.00, 1.12)	-0.027	(-0.09, 0.04)	-0.022	(-0.09, 0.05)
Traffic load of roads in a 100mt buffer[a]								
Not exposed	1.00		1.00		1.00		1.00	
Below 1st tertile	1.34	(-0.55, 3.23)	0.73	(-1.14, 2.61)	0.02	(-0.11, 0.15)	-0.01	(-0.13, 0.11)
Between the 1st and the 2nd tertile	**2.10**	**(0.23, 3.98)**	1.61	(-0.26, 3.48)	0.08	(-0.05, 0.20)	0.07	(-0.05, 0.19)
Beyond the 3rd tertile	1.51	(-0.39, 3.41)	1.45	(-0.46, 3.67)	0.04	(-0.08, 0.17)	0.03	(-0.10, 0.15)

[a] Number of vehicles × meters of road/day

Coefficients were adjusted for maternal and paternal education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, child birth weight, breastfeeding duration, age (in months) at weaning and inversely weighted for the probability of participation at baseline and at the two follow-ups, respectively

6. The relation between familial and contextual indices of socioeconomic position and overweight/obesity in children (Research paper[5])

This chapter introduces the analyses and results of the effects of families' socioeconomic position on the ponderal excess status in the GASPII birth cohort. A short introduction to the analyses and results is provided below, with specific explanations about methods and available data included.

The socioeconomic position (SEP) is generally recognized as one main cause of people's "bad health" condition; therefore, the effects it produces have always been of great interest to the research (Currie & Stabile, 2003; Spencer, 2001). Both low socioeconomic positions and situations of poverty are strictly related to a low quality of life due to the inability of accessing different kinds of goods. Socioeconomic position is a crucial health determinant for children too, who can be severely affected by their families' adverse socioeconomic position. Death in infancy as well as childhood chronic/acute illnesses are related to poverty and to low socioeconomic positions; moreover, there is evidence of a relation between the "social-economic" exposure and birth weight/weight gain in infancy (Spencer, 2001).

Researchers have studied the relation between families' socioeconomic position and children's ponderal excess mainly using parents' educational level and occupational status as measures of the SEP. Some studies make also use of not "individual" measures such as families' income or SEP indexes from the neighbourhood. Since there are multiple ways of measuring the socioeconomic position of families/individuals, different results may be possible. As Galobardes described in a glossary in 2006 (Galobardes, 2006a, 2006b), there is not one best measure to be used, because different sets of data may require different kinds of measures, which also depend on the typology of study and its outcomes.

In its last update in 2016, the Italian project "*OKkio alla Salute*" showed for the first time the distribution of overweight and obese children (aged 8-9 years old) in light of families' perceived wealth status. According to data, it is evident that the majority of children with excess body weight are from families that struggle to make ends meet, if compared to children living in families without

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"economic" problems. Furthermore, children with ponderal excess problems come from families with low educational levels for parents, that is consistent with the findings about families' wealth measurements.

6.1 Distribution of children in Rome

A part of the analyses is related to two measures of exposure calculated with data aggregation at the census block level. All the children enrolled in the GASPII project belong to the local health units (ASL) Rome E, where two major hospital centres in Rome are located.

Due to the nature of the dataset, it would be possible to use multilevel or hierarchical models in order to account for cluster data. Multilevel models can be applied for analysing data at different levels and divided in different clusters. Observations from within one single cluster are usually consistent with each other, if compared to observations from other clusters. When it happens, it is not correct to use methodologies that assume some kind of independence between data, because the results would not be correct. In this case, children and families' SEP indicators – measured at census block level – are the two possible levels of analysis.

Before starting with the analyses, here follows an overview of children's positions in the area of the ASL Rome E and within the census block. Figure 9 represents a partial map of the city of Rome. The thick black lines are the boundaries of the different ASL units and their areas, while the lines in light purple correspond to the block census in 1991. The green arrows indicate the three areas making up the ASL Rome E zone, and the small green crosses identify children's residential addresses at the time of birth. As it can be noticed, despite the fact that most children are concentrated in the central area of the ASL Rome E, that the census blocks are particularly small. This can be due to the lack of clustered data.

Consequently, another check is carried out to observe children's distribution within each census block. The results show that a few small groups of children live in the same census block, and no great difference is present between normal weight and overweight/obese children. The Intraclass Correlation Coefficient (ICC) has also been applied in order to avoid further errors. It is a statistical instrument suggesting whether it is convenient or not to use multilevel models for analysing a certain set of data. When the value of the ICC is close to zero, it means that observations within one single cluster are not that consistent with each other, if compared to observations coming from other clusters. In this case, there is no need to run multilevel models.

The Intraclass Correlation Coefficient (ICC) as indicator of the socioeconomic position is calculated with data from the 4- and the 8-year follow-up visits. The values of the ICC are always very close to zero; therefore, no analysis in this thesis makes use of the multilevel model.

Figure 9: Partial map of the city of Rome, divided by areas of ASL (black lines) and census block (purple lines)[6]

As for the analyses on air pollution exposure, a paper on this topic has been drafted, submitted to a scientific journal and at the same time included in this thesis. Appendix D comprises the Supplementary material of the paper. As mentioned before, data coming from the 4- and 8-year follow-ups are used here. Furthermore, at the end of the article, supplementary analyses on outcomes from outside the SEP topic are discussed such as the BMI Z-score and Total/HDL cholesterol levels.

[6] The three green arrows indicate the three parts of the ASL area in which children were living. All the light green crosses represent the residential addresses of the 719 children enrolled in the project (year 2003/2004).

Introduction

Overweight/obesity prevalence is increasing worldwide, becoming an important health issue and causing concern all over the world.[1,2] Overweight children are likely to develop during life metabolic diseases or non-communicable diseases, such as type 2 diabetes,[3] hypertension, cancer, and cardiovascular diseases.[4,5] The main recognised determinants of children's ponderal excess, besides genetics, are gestational diabetes, maternal BMI, maternal smoking habits, diet, physical activity, and screen time.[6–10]

Socioeconomic position (SEP) of the family may also have an important effect on the health status of children. There is a large interest in the analysis of the relationship between socioeconomic position and children's overweight/obesity. The majority of studies highlighted evidence of an association between low socioeconomic position and higher children's BMI.[11–15] This relationship can derive from unhealthy food choices, sedentary lifestyles, and lack of caregivers. These results reflect mainly the situation in developed countries, while studies conducted in developing countries show the opposite results.[16,17]

Several indicators represent the different dimensions of the socioeconomic position. Educational level and occupational status are the most common variables used as SEP's individual indicators. Educational level can represent the ability to absorb health education messages, and to access appropriate health care.[18] The occupational status is related to wealth and material living standards, but may reflect also social networks and autonomy.[18] It has been showed that a low parental educational level or occupational status may increase the risk of overweight/obesity in children.[19–23] When individual variables are not available, contextual variables are used as indicators of SEP.[11–14] These indicators represent the context in which the subjects live, and can have an independent role on health.[24] The deprivation indexes based on census information usually represent several aspects of socioeconomic position (education, occupation, family composition, housing, etc.), whereas the small area income index represents the wealth of the inhabitants of the area. In a 2008 review, it has been shown that the association between SEP measures (individual and contextual) and adiposity in children was mainly inverse, but in a few cases a positive association or an absence of association was found.[25]

This study aims to evaluate the association between different measures of socioeconomic position, contextual variables (socioeconomic indicator and income index), and individual variables (parental educational level and their occupational status), on the risk of being overweight/obese at 4 and 8 years in the Italian GASPII birth cohort.

Methods

Study Population and data collection

A cohort of newborns was enrolled within the project *Gene and Environment Prospective Study on Infancy in Italy* (*GASPII*).[26,27] The enrolment took place in two hospitals in Rome, between June 2003 and October 2004. Mothers were contacted at birth, and were enrolled if older than eighteen years old, Italian, and resident in the area of the Local Health Unit Rome E which includes about 500,000 inhabitants. At the end of this period enrolment was a total of seven hundred and four mothers and seven hundred and nineteen children, with a response rate of 55%.

Mothers and fathers were asked to complete questionnaires after delivery. Through face-to-face interviews, information concerning parent's health status, health history, lifestyle, pregnancy period, socio-demographic characteristics, social conditions and maternal emotive status, were collected. Hospital obstetricians collected all the information regarding pregnancy. Several follow-up points were scheduled at different moments of the children's life. The anthropometric measures used in this study were collected at 4 and 8 years, during specific clinical examinations.

Measures of socioeconomic position

In this study, we considered contextual and individual indexes measured at birth. We used two small area indexes that refer to census blocks of the city of Rome (average population: 480 inhabitants). The first is a composite indicator of SEP based on data from the 2001 census in the city of Rome (SEP index, online supplementary material). The index was developed using census data from the 4888 census blocks in the city with at least fifty inhabitants, that considers different characteristics of the population, and has been fully described elsewhere.[28] The distribution of this SEP index has been done in quintiles[28] and in this study we decided to categorize it in three levels: high, medium, and low (aggregating medium-high, medium, and medium-low levels in the medium category).

The second contextual index is the 1998 city-specific index based on median census block per capita income. The construction of the index has been described elsewhere.[29,30] Briefly, income data collected from the Italian Tax Register were linked to family status' data, that was taken from the population register of the city of Rome. After record linkage, the net family income per capita was calculated aggregating the values obtained at the census block level and calculating the blocks' median value. Its distribution in this study was divided into quintiles: the first defined as high, the last as low, and all the rest as medium level.

For individual indexes, we considered maternal and paternal educational level (classified as: university degree, secondary and primary school), and occupational status of the parents (classified as: working vs. not working). Students and housewives were included in the "not working" category.

Anthropometric measurements

Anthropometric measurements i.e. weight, and height were collected during clinical examinations at 4 and 8 years. Children in light clothing and barefoot were weighed, and height was measured standing. BMI is calculated as weight (kilograms) divided by height squared (metre). Age- and sex-specific BMI Z-score (defined as the number of SD by which a child differs from the mean BMI of children with the same age and sex), were calculated using the World Health Organization (WHO) 2007 Growth Charts reference.[31,32] We used WHO standards to define obesity status.

We also used waist and hip circumference data collected at 8 years as indicators of the child's ponderal excess. Waist and hip circumference measurements, collected from the upright position used standardised methods (to the nearest 0.1 cm). We calculated the waist-to-hip ratio as supplementary measure of the body fat distribution in children.

Statistical analysis

Descriptive statistics of population characteristics were produced for all the children that completed both follow-ups. A cross-sectional and longitudinal approach assessed the association of contextual and individual SEP measures with children's excess weight. Generalized Linear Models (family Poisson, link log) were used to assess the association in the cross-sectional approach, while Generalized Estimating Equation (GEE) models (family Poisson, link log), were used in the longitudinal approach. Results are expressed as relative risk.

Each SEP measure was analysed separately for all outcome. We adjusted the models for confounders selected according to the literature. The confounders used were: age at follow-up point, maternal pre-pregnancy BMI, child birth weight, screen time, hours of physical activity per week, hours of sleep per day, number of siblings, and diet. Diet was measured using the Kidmed index, a tool that evaluates the adequacy of Mediterranean children's dietary patterns.[33] Gender and age were not included in the analyses as potential confounders when BMI was considered as an outcome because the BMI Z-score was sex- and age- specific. The analyses using the waist circumference and the waist-to-hip ratio measures as outcomes collected at 8 years old were computed with the two abdominal measures as continuous.

Poor recruitment (45.4%) and loss of subjects at follow-up (19.2% and 30.6% at 4 and 8 years) could produce selection bias. We tried to take this bias into account using an Inverse Probability Weighting (IPW) approach.[34] The IPW is a methodology that gives more weight to the enrolled children which information are similar to those of the children not enrolled during the study. More details on this methodology that have already been applied to the GASPII cohort, can be found elsewhere[35,36], while information about the variables used in this IPW calculation can be found in the online supplementary material.

Additional analyses

For each follow-up at 4 and 8 years, we produced additional analyses. The aim of these sensitivity analyses was to assess if the association between SEP and overweight/obesity changed when using alternatively or as a series of combinations the income index and the individual measurements of SEP as confounders. Furthermore, we compared the analyses to models without IPW, to evaluate the presence of selection bias at enrolment and at follow-up.

Results

Seven hundred and nineteen children were enrolled in the GASPII cohort. Among them, 80.8% and 69.4% underwent the follow-up at 4 and 8 years (Table 1) respectively. The mean age (in months) was fifty months at 4 years (range: 39 - 62), and one hundred and four months at 8 years (range: 96 – 123), half of the children were males (data not shown). The main characteristics of the cohort are in Table 1.

Measures of SEP considered are in Table 2. The percentages of all contextual and individual variables remained stable between one follow-up to the other, suggesting that there was no difference among children retained in the study in the two follow-up points.

The mean value of BMI Z-score was 0.69 (SD:1.07) at 4 years and 0.65 (SD:1.18) at 8 years. Mean waist circumference of children aged 8 was 60 cm (SD:6.18), and waist-to-hip ratio 0.91 (SD:0.04). The prevalence of overweight/obese children was of 9.29% at 4 years and 36.9% at 8 years. We did not consider the obesity condition alone because of a low prevalence at both follow-ups (1.39% and 0.83% at 4 and 8 years, respectively).

Table 3 presents the results of the crude and adjusted analyses for the association between individual and contextual exposures and the outcomes considered. In the adjusted analysis, children with a low SEP index level had a higher risk of being overweight/obese at 4 years (RR:4.00; 95%CI: 1.22-13.1). Similar results were found for children aged 8, where children having medium

and low SEP index levels had a higher risk of being overweight/obese (RRMedium:1.54; 95%CI: 0.99-2.41; RRLow:1.80; 95%CI: 1.09, 2.96). Longitudinal analysis confirmed these results (RRMedium:1.54; 95%CI: 1.00,2.40; RRLow:1.81; 95%CI: 1.10,2.98). Evidence of association between income level and ponderal excess in children was found in the adjusted analysis at 4 years (RR4years:3.72; 95%CI: 1.17-11.8), as in the longitudinal analysis using the GEE model.

In the analyses with individual variables the results showed no evidence of association between individual SEP measures and ponderal excess in children, except for maternal occupational status: the risk of being overweight or obese, having an unoccupied mother increased at 4 years (RR:1.95, 95%CI: 1.05-3.65). Only the crude analysis at 4 years suggested an effect of a paternal low educational level.

The effects of the exposures on the measures of abdominal fat are reported in Table 4. Results for the SEP index confirmed previous findings: children having a medium or a low SEP index have a higher risk of larger waist circumference (CoeffMedium:1.82; 95%CI: 0.28-3.36; CoeffLow:3.19; 95%CI: 1.21-5.17). Evidence of association between a low-level income and waist circumference was only in the crude analyses. The analyses for the waist-to-hip ratio showed no association. When we considered the individual variables as exposures, no evidence of association was found.

The results of the additional analyses of SEP on childhood overweight/obesity, are reported in Table S1 and Table S2. The results of these analyses uphold our previous findings: no evidence of association was found for children aged 4, while most of the models for children aged 8 confirmed the presence of the association between the SEP contextual indexes levels and being overweight/obese. Differences are observed depending on the combination of income and individual variables included/excluded within the models. In Table S3 and S4 we report results obtained without applying IPW. They do not differ from IPW-based findings, except for slightly lower RR and narrower CI's.

Discussion

We evaluated the association between indicators of SEP and children's overweight/obesity. Contextual and individual indicators of the socioeconomic position gave different results. We see evidence of associations between exposure to contextual socioeconomic indicators and overweight/obesity in children at 4 and 8 years. These results are confirmed in the longitudinal analyses. Our results showed an increased risk of being overweight/obese for children aged 4 without a working mother (adjusted analysis). In addition, the low educational level of the father is weakly associated to the ponderal status of children aged 4 (crude analysis).

In previous literature similar results relating to contextual indicators has been concluded. One study conducted by Hardy et al. (2017) found that the risk of overweight/obesity and increasing waist-to-height ratio in subjects aged 4-17 was sensibly higher for these living in low socioeconomic status (SES) families.[13] Results showing that the risk of overweight/obesity decreased for children living in families with high SEP levels has also been found in studies conducted in the UK,[20] North Korea,[12] and Massachusetts (USA).[11]

Grassi et al. (2016) analysed the association between individual socioeconomic factors and children of overweight or obese status. The authors found that low parental educational level as well as low-level parental employment, are determinants of the risk of their children being overweight/obese.[19] An association between parental educational level and unhealthy weight in children aged 6 has also been found in a Swedish and a German study.[21,22] In a separate study authors found that children over 6 years of age have a higher risk of being overweight or obese if their parents had low occupational status, while for children aged 3-5 years there was no evidence of this association.[23] A meta-analysis investigating whether low maternal education is associated with overweight/obesity among European children, used 11 European birth cohorts among which the GASPII cohort. Overall results showed evident inequalities due to low maternal educational level in European children, but the results were inconsistent for our cohort.[37]

In Italy a national surveillance network, established in 2008, aims to control and monitor the prevalence of obesity in Italian children aged 8-9.[38] Results of the 2016 surveillance shows that children with parents of low education have a higher prevalence of obesity, as well as these children which families struggle to make ends meet. To our knowledge there are very few studies that used both contextual and individual socioeconomic position exposures showing that both types of exposure can associated with obesity in children.[14,15]

As Galobardes et al. (2004) assessed each socioeconomic indicator and measured SEP levels in different ways and found, differing results when using two or more indicators can be expected.[18] The area measures of SEP levels differ from the individual indicators of SEP because they not only represent the family/parent position but also the entire context in which the subject is living. The SEP Index used does not account for other contextual factors (such as schools, gym or parks nearby the residential address) which may have an effect for the outcomes considered. The absence of associations between children's overweight/obesity and SEP individual exposures, legitimise our presumption that in our cohort the child's living context have a stronger impact on their ponderal status compared to individual exposures. We propose that highly educated parents prefer to live in areas where the accessibility and quality of public resources (schools, parks, pedestrian areas and

playgrounds) is better compared to deprived areas. Therefore, it could be that parents' occupational status and their educational level may not have a strong role in our analyses to the same extent as the context where the children live.

This study has some limitations that prevented us from fully understanding the influence of the context in which children live. We do not have information about schools, or other kind of children's meeting points, which may contribute to the mechanism at study. This mechanism could relate the context in which children are living, and their ponderal status. As with most of the cohort studies, the GASPII cohort also suffers from poor recruitment. This is a limitation of the study because a few hundred children were enrolled and followed-up with, causing limited power in the analyses. Moreover, the participation rate was higher for mothers with a high level of education compared to low educated mothers.[27] This could be related to the absence of a significant effect of maternal educational status on ponderal excess in children. We tried to address this problem using the IPW, accounting for the educational level of all parents that did not participated in the study.

The prospective study design of the GASPII project is one of the main strengths of this study. We performed longitudinal analyses thanks to the repeated collection of the same information (outcomes and confounders) during the various follow-ups. In this way, we had the possibility to perform analyses within a cross-sectional and a longitudinal approach. Another point of strength of this study is related to the way we calculated, standardized and classified the BMI Z-score of the children, that is, the WHO recommendations[31,32]. This method of classifications makes the results comparable with other studies using the same classification. Moreover, we used a broad range of variables measuring different aspects of SEP levels, in comparison to most of the studies found in literature.

Conclusion

The present study analysed the association between ponderal excess condition in children aged 4 and 8 years, and the exposure to different indicators of socioeconomic position. The results suggest that the contextual variables are those that mainly influenced the development of overweight/obesity in children, while individual variables seem to not affect the status of ponderal excess in our cohort. The results of our research are quite consistent with studies found in literature for the association between contextual SEP measures and ponderal excess in children. Further researches are needed to understand and justify the different effects of contextual and individual indicators of SEP. A good understanding of this phenomenon could lead to preventative measures

use in practice to halt the rising prevalence of childhood overweight/obesity, with various social interventions and strategies.

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Tables

Table 1. Characteristics of the children from the GASPII cohort at the 4 and 8 years follow-up calls

	4 years		8 years	
	N	%[a]	N	%[a]
Total	581	100	499	100
Birth weight				
< 2499 gr	35	6.02	34	6.81
2500-3999 gr	497	85.5	422	84.6
>4000 gr	49	8.43	43	8.62
Number of siblings				
Zero	176	30.3	104	20.8
One	331	57.0	272	54.5
More than one	73	12.6	79	15.8
Screen hours per day (4 year)				
< 1 hours	191	32.9	-	-
>= 1 hours	389	67.0	-	-
Screen hours per day (8 year)				
< 2 hours	-	-	57	11.4
>= 2 hours	-	-	442	88.6
Physical activity (8 year)				
<= 2 hours	-	-	172	34.5
2 - 4 hours	-	-	170	34.1
>= 4 hours	-	-	103	20.6
Sleep hours per day				
<= 9 hours	186	32.0	346	69.3
> 9 hours	393	67.6	153	30.7
Adeguacy to Mediterranean dietary patterns				
Optimal Mediterranean diet	92	15.8	145	29.1
Improvement needed	319	54.9	306	61.3
Very low diet quality	21	3.61	47	9.42
Maternal pre-pregnancy BMI				
Underweight/Normal	488	84.0	414	83.0
Overweight	67	11.5	61	12.2
Obese	25	4.30	23	4.61

[a] Because of missing values, some percentages do not add up to 100%

Table 2. Description of the contextual and individual indices of SEP, measured at the moment of birth, for respondents at 4 and 8 years

	4 years (N=581)		8 years (N=499)	
Contextual exposures	**N**	**%[a]**	**N**	**%[a]**
SEP Index				
High	92	15.8	78	15.6
Medium	375	64.5	325	65.1
Low	99	17.0	83	16.6
Income				
High	94	16.2	76	15.2
Medium	331	57.0	286	57.3
Low	152	26.2	134	26.9
Individual exposures				
Maternal education				
University degree	217	37.3	184	36.9
Secondary school	292	50.3	248	49.7
Primary school	72	12.4	67	13.4
Paternal education				
University degree	183	31.5	152	30.5
Secondary school	234	40.3	200	40.1
Primary school	123	21.2	111	22.2
Maternal occupational status				
Employed	438	75.4	387	77.6
Not working	124	21.3	99	19.8
Paternal occupational status				
Employed	506	87.1	435	87.2
Not working	14	2.41	10	2.00

[a] Because of missing values, some percentages do not add up to 100%

Table 3. Association between contextual and individual variables of the SEP evaluated at birth, and overweight/obesity. Result from GLM models (4 and 8 year follow-ups) and longitudinal models

	4 Years				8 Years				GEE			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
	RR	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**
Contextual Variable												
SEP Index												
High (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Medium	2.16	(0.79, 5.93)	2.64	(0.88, 7.96)	1.37	(0.93, 2.03)	1.54	(0.99, 2.41)	**1.54**	**(1.04, 2.27)**	**1.54**	**(1.00, 2.40)**
Low	**3.57**	**(1.23, 10.4)**	**4.00**	**(1.22, 13.1)**	**1.70**	**(1.10, 2.62)**	**1.80**	**(1.09, 2.96)**	**2.04**	**(1.32, 3.15)**	**1.81**	**(1.10, 2.98)**
Income												
High (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Medium	2.29	(0.71, 7.40)	1.66	(0.52, 5.23)	1.22	(0.84, 1.77)	1.31	(0.86, 1.99)	1.37	(0.95, 1.99)	1.34	(0.89, 2.01)
Low	**4.83**	**(1.50, 15.6)**	**3.72**	**(1.17, 11.8)**	1.33	(0.89, 1.98)	1.48	(0.94, 2.31)	**1.81**	**(1.22, 2.69)**	**1.77**	**(1.14, 2.75)**
Individual Variable												
Maternal education												
University degree (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Secondary school	0.96	(0.54, 1.70)	1.00	(0.53, 1.92)	1.13	(0.88, 1.46)	1.07	(0.81, 1.41)	1.11	(0.86, 1.42)	1.06	(0.80, 1.40)
Primary school	1.54	(0.75, 3.17)	1.16	(0.46, 2.91)	0.96	(0.65, 1.42)	0.87	(0.52, 1.46)	1.14	(0.77, 1.69)	0.90	(0.50, 1.63)
Paternal education												
University degree (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Secondary school	1.81	(0.88, 3.70)	1.59	(0.71, 3.56)	0.90	(0.68, 1.19)	0.88	(0.65, 1.19)	1.05	(0.79, 1.40)	0.97	(0.71, 1.33)
Primary school	**2.81**	**(1.35, 5.85)**	2.22	(0.94, 5.27)	1.15	(0.85, 1.54)	1.09	(0.77, 1.53)	**1.43**	**(1.06, 1.94)**	1.20	(0.83, 1.74)
Maternal occupational status												
Working (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Not working	1.66	(0.95, 2.90)	**1.95**	**(1.05, 3.65)**	1.26	(0.97, 1.63)	1.03	(0.74, 1.43)	**1.32**	**(1.02, 1.72)**	1.14	(0.81, 1.60)
Paternal occupational status												
Working (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Not working	0.94	(0.14, 6.12)	1.21	(0.18, 8.11)	0.85	(0.33, 2.17)	0.77	(0.28, 2.11)	0.78	(0.28, 2.20)	1.20	(0.43, 3.33)

Confounders: Screen hours, pre-pregnancy BMI, hours of sport (8 year), kidmed test (diet), birth weight, sleep hours, number of siblings and inversely weighted for the probability of participation at baseline and at the two follow-ups, respectively

Table 4. Association between contextual and individual variables of the SEP evaluated at birth, and Waist circumference and Waist-to-hip ratio at 8 years follow-up. Result from regression models

	Waist circumference				Waist-to-hip ratio (*10)			
	Crude		Adjusted		Crude		Adjusted	
	Coeff	IC (95%)	Coeff	IC (95%)	Coeff	IC (95%)	Coeff	IC (95%)
Contextual Variable								
SEP Index								
High (Ref.)	1.00		1.00		1.00		1.00	
Medium	1.01	(-0.54, 2.56)	**1.82**	**(0.28, 3.36)**	-0.05	(-0.15, 0.06)	-0.06	(-0.16, 0.05)
Low	**2.72**	**(0.79, 4.65)**	**3.19**	**(1.21, 5.17)**	-0.05	(-0.18, 0.08)	-0.08	(-0.21, 0.05)
Income								
High (Ref.)	1.00		1.00		1.00		1.00	
Medium	0.40	(-1.19, 1.99)	0.78	(-0.80, 2.36)	-0.04	(-0.15, 0.07)	-0.06	(-0.17, 0.05)
Low	1.57	(-0.19, 3.34)	**1.79**	**(0.00, 3.60)**	-0.03	(-0.14, 0.10)	-0.09	(-0.22, 0.03)
Individual Variable								
Maternal education								
University degree (Ref.)	1.00		1.00		1.00		1.00	
Secondary school	0.01	(-1.18, 1.21)	-0.07	(-1.32, 1.17)	-0.07	(-0.15, 0.01)	-0.08	(-0.17, 0.01)
Primary school	**1.79**	**(0.07, 3.51)**	0.48	(-1.59, 2.56)	-0.04	(-0.15, 0.08)	-0.03	(-0.17, 0.11)
Paternal education								
University degree (Ref.)	1.00		1.00		1.00		1.00	
Secondary school	-0.61	(-1.91, 0.70)	-0.78	(-2.09, 0.559	0.00	(-0.09, 0.09)	-0.03	(-0.12, 0.06)
Primary school	1.30	(-0.21, 2.81)	0.77	(-0.85, 2.40)	0.00	(-0.11, 0.10)	0.00	(-0.11, 0.11)
Maternal occupational status								
Working (Ref.)	1.00		1.00		1.00		1.00	
Not working	0.56	(-0.82, 1.93)	-0.53	(-2.04, 0.98)	0.00	(-0.09, 0.09)	0.04	(-0.07, 0.14)
Paternal occupational status								
Working (Ref.)	1.00		1.00		1.00		1.00	
Not working	2.78	(-0.95, 6.51)	4.38	(0.18, 8.599	0.10	(-0.16, 0.35)	0.17	(-0.12, 0.46)

Confounders: Screen hours, pre-pregnancy BMI, hours of sport (8 year), kidmed test (diet), birth weight, sleep hours, number of siblings, age and sex and inversely weighted for the probability of participation at baseline and at the two follow-ups, respectively

6.1.1 Addendum to the second research paper

In order to being in line with the analyses of the thesis discussed until now, in this additional section of the SEP article, the results of the analyses using as measures of ponderal excess the BMI Z-score and the Total and HDL cholesterol, are presented. The models and analyses performed in this addendum are the same methodologies used in the analyses presented within the article, according to the nature of the outcome. All the subsequent analyses are performed using the IPW methodology. The results of the same analyses performed without the IPW, are reported in the Appendix E.

In Table 20 the results of the analyses performed using as outcome the BMI Z-score (continuous variable), are presented. As it can be notice in general this analysis confirms what has been found in the previous analysis using the categorical outcome overweight/obese (yes vs. no). Children living in families with a low socioeconomic position, have a higher risk of a higher BMI Z-score at 4 and at 8 years ($Coeff_{4years}$ = 0.38; CI 95% 0.02, 0.74 ; $Coeff_{8years}$ = 0.63; CI 95% 0.23, 1.02). At the 8 year follow-up also the children living in families with a medium socioeconomic position have a higher risk (compared to these children with a high SEP Index level) of increasing BMI Z-score (Coeff = 0.36; CI 95% 0.05, 0.66). The results of the two follow-up analyses are also confirmed by the results of the longitudinal analysis, elaborated with the GEE model ($Coeff_{Medium\ Level}$ = 0.31; CI 95% 0.06, 0.55 ; $Coeff_{Low\ level}$ = 0.48; CI 95% 0.14, 0.82).

Table 20: Association between contextual and individual variables of the SEP Index evaluated at birth, and overweight/obesity. Result from linear regression models (4 and 8 years follow-up) and longitudinal models

	4 Years				8 Years				Longitudinal model			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
	Coeff	IC (95%)	Coeff	IC (95%)	Coeff	IC (95%)	Coeff	IC (95%)	Coeff	IC (95%)	Coeff	IC (95%)
Contextual Variable												
SEP Index												
High (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Medium	0.21	(-0.04, 0.47)	0.26	(-0.03, 0.54)	0.26	(-0.04, 0.55)	**0.36**	**(0.05, 0.66)**	**0.23**	**(0.03, 0.44)**	**0.31**	**(0.06, 0.55)**
Low	**0.38**	**(0.06, 0.69)**	**0.38**	**(0.02, 0.74)**	**0.56**	**(0.19, 0.93)**	**0.63**	**(0.23, 1.02)**	**0.49**	**(0.21, 0.76)**	**0.48**	**(0.14, 0.82)**
Income												
High (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Medium	0.17	(-0.08, 0.43)	0.13	(-0.16, 0.42)	0.02	(-0.12, 0.49)	0.23	(-0.09, 0.54)	0.19	(-0.02, 0.40)	**0.24**	**(0.02, 0.47)**
Low	**0.37**	**(0.08, 0.66)**	**0.33**	**(0.00, 0.66)**	0.31	(-0.02, 0.65)	**0.38**	**(0.02, 0.74)**	**0.35**	**(0.09, 0.60)**	**0.39**	**(0.09, 0.69)**
Individual Variable												
Maternal education												
University degree (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Secondary school	-0.06	(-0.26, 0.14)	-0.01	(-0.24, 0.22)	-0.01	(-0.24, 0.22)	-0.05	(-0.30, 0.20)	-0.01	(-0.18, 0.16)	-0.04	(-0.23, 0.15)
Primary school	0.05	(-0.23, 0.33)	0.03	(-0.32, 0.38)	0.16	(-0.18, 0.49)	-0.09	(-0.51, 0.32)	0.13	(-0.15, 0.42)	-0.11	(-0.55, 0.33)
Paternal education												
University degree (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Secondary school	0.03	(-0.19, 0.25)	0.07	(-0.18, 0.33)	-0.10	(-0.35, 0.15)	-0.10	(-0.38, 0.16)	-0.02	(-0.21, 0.18)	-0.04	(-0.26, 0.19)
Primary school	0.24	(-0.01, 0.50)	0.15	(-0.15, 0.45)	0.19	(-0.10, 0.48)	0.19	(-0.14, 0.52)	0.25	(-0.00, 0.49)	0.17	(-0.11, 0.44)
Maternal occupational sta												
Working (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Not working	-0.03	(-0.25, 0.19)	0.03	(-0.23, 0.29)	0.11	(-0.16, 0.37)	-0.06	(-0.36, 0.24)	0.04	(-0.18, 0.27)	-0.08	(-0.38, 0.23)
Paternal occupational stat												
Working (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Not working	0.37	(-0.23, 0.97)	0.25	(-0.44, 0.94)	0.23	(0.49, 0.96)	0.23	(-0.62, 1.08)	0.27	(-0.28, 0.82)	0.39	(-0.60, 1.38)

Coefficients were adjusted for screen hours, pre-pregnancy BMI, hours of sport (8 year), kidmed test (diet), birth weight, sleep hours, number of siblings and inversely weighted for the probability of participation at baseline and at the two follow-up, respectively

Also the results obtained with the Income index reflect the findings of the previous analyses for children aged 4 years, which have an increase in the risk of higher BMI Z-score, if they live in a family with a low income level (Coeff = 0.33; CI 95% 0.00, 0.66). A difference has been found for children aged 8, when exposed to a low Income level: in the previous analysis the result was not significant, while in this case they have a higher risk (Coeff = 0.38; CI 95% 0.02, 0.74) of having a higher BMI Z-score. Again, the results of the GEE models reflect the situation found in the previous analysis, and in the cross-sectional analyses at 4 and 8 year follow-ups. On the other side, the only result found considering the individual exposures in the analyses integrated in the article, is no longer significant. The occupational status of the mother does not have an effect on the risk of being overweight/obese at both 4 and 8 year old.

The results of the analyses exploring the association between the contextual and individual variables, measuring the socioeconomic position of the families, and the Total and HDL cholesterol levels are reported in the subsequent Table 21. It is immediately clear that no evidence of association has been found between each different exposure and the two blood lipids measures. Probably these two additional measures of the excess of weights do not catch in the right way the phenomenon at study, especially if compared to the results of the categorical variable (overweight/obese yes vs. no), of the BMI Z-score and of the abdominal fat measures (waist circumference and waist-to-hip ratio).

In Appendix E are reported the results of these two set of analyses presented in this supplementary part (without applying the IPW methodology). In the Table E1 the results of the analyses of the BMI Z-score levels are reported, while in Table E2 there are the results of the analyses for the two blood lipids levels. Briefly, it seems that the results do not changed when the analyses are performed without the IPW methodology. For both BMI Z-score and blood lipids levels outcomes the results are similar, with a slightly change of the coefficients and of the confidence intervals. The same situation has been observed in the main analyses integrated in the article, where the results of the analyses with and without the IPW methodology are basically equal. Probably this situation is due to the absence of selection biases at recruitment as at both follow-up points at 4 and at 8 years.

Table 21: Association between contextual and individual variables of the SEP Index evaluated at birth, and Total and HDL Cholesterol at 8 years, evaluated with regression models

	Total cholesterol				HDL			
	Crude		Adjusted		Crude		Adjusted	
	Coeff	IC (95%)	Coeff	IC (95%)	Coeff	IC (95%)	Coeff	IC (95%)
Contextual Variable								
SEP Index								
High (Ref.)	1.00		1.00		1.00		1.00	
Medium	-0.68	(-7.64, 6.28)	-1.83	(-9.66, 6.00)	2.04	(-2.19, 6.26)	2.85	(-1.99, 7.66)
Low	2.59	(-6.12, 11.3)	0.90	(-9.25, 11.0)	2.21	(-3.06, 7.50)	2.69	(-3.54, 8.93)
Income								
High (Ref.)	1.00		1.00		1.00		1.00	
Medium	-2.40	(-9.54, 4.75)	-2.90	(-10.8, 5.03)	1.41	(-2.90, 5.72)	2.86	(-2.01, 7.73)
Low	-4.07	(-11.9, 3.84)	-8.01	(-16.9, 0.97)	-1.31	(-6.08, 3.46)	-1.18	(-6.70, 4.33)
Individual Variable								
Maternal education								
University degree (Ref.)	1.00		1.00		1.00		1.00	
Secondary school	-2.15	(-7.48, 3.18)	-2.61	(-8.70, 3.49)	-0.71	(-3.93, 2.51)	0.45	(-3.29, 4.19)
Primary school	1.58	(-6.05, 9.22)	-4.62	(-14.7, 5.41)	-1.83	(-6.45, 2.79)	-2.05	(-8.22, 4.11)
Paternal education								
University degree (Ref.)	1.00		1.00		1.00		1.00	
Secondary school	-2.00	(-7.89, 3.88)	-2.49	(-9.27, 4.29)	0.06	(-3.55, 3.66)	-0.16	(-4.33, 4.01)
Primary school	-2.07	(-8.86, 4.71)	-2.20	(-10.5, 6.08)	-1.94	(-6.10, 2.21)	0.51	(-4.60, 5.60)
Maternal occupational status								
Working (Ref.)	1.00		1.00		1.00		1.00	
Not working	5.19	(-1.01, 11.4)	4.56	(-2.79, 11.99	-1.79	(-5.54, 1.96)	-2.90	(-7.40, 1.59)
Paternal occupational status								
Working (Ref.)	1.00		1.00		1.00		1.00	
Not working	7.49	(-10.7, 25.6)	1.45	(-23.8, 26.7)	-5.93	(-17.1, 5.24)	-5.43	(-21.1, 10.2)

Coefficients were adjusted for screen hours, pre-pregnancy BMI, hours of sport (8 year), kidmed test (diet), birth weight, sleep hours, number of siblings, age and sex and inversely weighted for the probability of participation at baseline and at the follow-up

7. Discussion

The rising prevalence of overweight/obese people worldwide has attracted the interests and concerns of both the whole population and researchers from different fields of study. Several studies give us an idea of the magnitude and consequences of obesity all over the world, with more and more people today in a ponderal excess status. The World Health Organization (WHO) also acknowledges the yearly increase of the percentages of individuals with an excess of body fat.

The status of ponderal excess may generate a number of health and social problems, which can produce either synchronic or diachronic results on the subject such as poor self-esteem, eating disorders, psychosocial and psychological issues, etc. In addition, some health conditions such as asthma, hypertension, chronic inflammation, diabetes and cardiovascular diseases in general may arise at a certain point during one's life, moreover if they have been overweight/obese during childhood. However, it is not easy either to control or to treat or even to prevent this unhealthy condition, that is undoubtedly one main determinant of future bad health conditions among the population. Overweight and obesity have been studied for a long time now, with the aim of capturing their crucial determinants. In the last decades, a particular interest has arisen on the infant ponderal excess status. In fact, pregnancy and children's early postnatal years are fundamental for their development, in which several factors may play an important role.

It is worth noting that in Italy there are no studies addressing the overweight/obesity issue in children with data extracted from a prospective birth cohort. In fact, there are a few studies assessing the prevalence of overweight and obese children in Italian cities, while there is another one showing the differences in overweight/obese prevalence in Northern and Southern Italy: the latter region seems to have a higher number of children in a ponderal excess status (Claudio Maffeis et al., 2006). Thanks to the project "*OKkio alla Salute*", funded by the Italian Ministry of Health, it has been possible to monitoring through time the prevalence of ponderal excess in children aged 8-9 years. The first wave was completed in 2008/2009, the last one in 2016. Eventually, the project underlines a deep gap between Northern and Southern Italy, and urges us to intervene actively to prevent the spread of this

condition. Apparently, the results from this project are in line with the main findings from the literature that is, healthy diets, healthy lifestyles and proper living environments are crucial to reduce the risk of ponderal excess in children. This thesis tries to fill in the existing gaps with data from a birth cohort in Rome, providing information about possible determinants of overweight/obesity and studying the effects of environmental exposure on children's ponderal excess.

As mentioned before, the main findings on overweight/obesity determinants here reflect somehow the evidence from the literature. The results can be interpreted along two different analysis, both performed for this thesis:

1. Analysis of the possible determinants of overweight/obesity status, according to the outcome measurements in this thesis;
2. Analysis of the potential developments of these determinants through the changing ponderal status, only based on the categorical measurements of the body fat.

Firstly, our findings suggest that maternal pre-pregnancy BMI is one of the most important determinants of overweight/obesity among children, regardless of their age (findings are from three follow-ups when children were 15 months old, 4 years old and 8 years old). The results are indeed consistent with the literature's: an increase in mothers' weight during pregnancy, may be a trigger factor for their children to become overweight/obese. As a matter of fact, they demonstrate that excessive adiposity in children derives from parents' obesity. BMIs of both mothers and fathers dramatically influence their children's future body size; nevertheless, mothers are those to play a fundamental role in their children's health status (Linabery et al., 2013).

It is evident that in their first months the determinants of children's ponderal excess are influenced by maternal body weight and by genetics. Children's eating habits start playing a negative role during the firsts years of life and can lead to overweight/obesity when they are 4. Furthermore, when children are 8 years old, the composition of the family is equally determinant: our data suggest that children with two or more siblings have got a lower risk of ponderal excess.

Secondly, all the other determinants included in the present research can be possible causes of infant ponderal excess. The small amount of children in our cohort can be one reason why the gestational age, maternal smoking habits during pregnancy, the screen time and the physical activity seem not the be determinants of the children's excessive ponderal status (something that we will discuss later in the paragraph on the limitations of this study). It is well known that maternal health conditions, lifestyles and habits before and during pregnancy have an impact on children's health and later on during their lives. Our study shows that maternal ponderal status before pregnancy is the main determinant of children's overweight/obesity status, regardless of children's age and independently from other variables.

When coming to the waist circumference, maternal pre-pregnancy BMI seems to be the main determinant of the abdomen to grow fat in 8-year-old children. Moreover, the time of weaning also seems a central factor in children's ponderal excess, being in contrast with the recommendations by the WHO to wait until children are 6 months old to wean them off breast milk. The moment when the so called complementary feeding is added to children's diet is delicate and may kick-start a trend of malnutrition. There is no way to further verify the factors behind such a contrasting result, mainly due to the scarceness of available data from the GASPII cohort. As said before, it is not in line with either the literature or the recommendations by the WHO. Nonetheless, it is a significant result of our analyses.

The results discussed above are not reinforced by other outcomes included in the research such as the waist-to-hip ratio measure and the blood lipids level (both Total and HDL Cholesterol). It seems that there is no other variable to be alone a determinant of these other outcomes.

On the analysis of the possible determinants of the changing ponderal status, we observe that the results change according to the trajectories adopted in the study. Among all possible trajectories we have decided to analyse those who follow here:

1. 15-month-old not overweight/obese children, who become overweight/obese at age 4;
2. 4-year-old not overweight/obese children, who become overweight/obese at age 8;
3. 4-year-old overweight/obese children, whose overweight/obesity status does not change at age 8.

The results confirm the role of children's eating habits on their changing ponderal status. For example, bad quality or inappropriate amount of food are factors associated with this condition. In addition, parents' educational level also influences children's changes between ages 15 months and 4 years, as frequently reported in the literature.

Again, the results from the analysis of the ponderal status which changes when children are 4 and 8 years old are consistent with what we said before. First, having two or more siblings produces a protective effect on children' changing ponderal status. Furthermore, it emerged that both maternal pre-pregnancy BMI and a late weaning (after their sixth month of age) are determinants of becoming overweight/obese between ages 4 and 8. This case also shows that maternal lifestyles, family compositions and diet habits are the main triggers of children's ponderal excess.

Thirdly, the analysis concentrates on the not-changing ponderal status of overweight/obese children at ages 4 and 8. We discovered that the only reason to explain such a permanent condition lies in the late weaning, regardless of a number of variables such as physical activity, maternal pre-pregnancy BMI and the screen or sleeping times.

The findings above are of particular interest because they confirm the existence of an association between eating habits, maternal behaviour, "genetics" and children's overweight/obesity status. Nothing new emerges from within our analyses, if compared to the findings from the literature, but we further support the need of some specific action to prevent the epidemic spread among children. Educating children to healthy habits may be the main preventive action. Two systematic reviews (E. C. Brown et al., 2016; Cauchi, Glonti, Petticrew, & Knai, 2016) have agreed that school teachers are important actors in reducing the risk of children's ponderal excess, since they spend most time at school where dedicated interventions should be implemented. To ensure better levels of BMI, schools should limit the consumption of sugar sweetened beverages (SSB) and snacks high in fat, sugar or salt (HFSS). Menus should be modified to reduce fat concentration at lunch time. Fruit and fresh juices should be easily available in order to increase fruit intake (T. Brown & Summerbell, 2009; Lavelle, MacKay, & Pell, 2012). At the same time, parental role is very important. Some studies demonstrate that their co-involvement contributes to the overall effectiveness of the school interventions (Van Der Kruk, Kortekaas, Lucas, & Jager-Wittenaar, 2013). Since mothers are usually more involved in their children's eating habits, they should be more aware of what kind of diet their children follow, to limit the risk of having future obesogenic

offspring. Furthermore, the relation between the number of siblings and the protective effects on children's weight status is a brand-new result which needs deeper investigation, in order to evaluate whether or not the composition of the family can have some impact on children's ponderal excess.

In addition to the analyses of the possible determinants of children's excessive ponderal status in the GASPII birth cohort, we have also considered two studies which focus on the role that the environment plays in children's life and analyse the situation from a more general point of view.

No association is found between children's ponderal excess and their multiple exposures to traffic-related air pollution, also regardless of the different outcomes considered. Nonetheless, exposure to environmental pollution knowingly affects people's health. During the last ten years, research on the effects of air pollution leading to a potential onset of children's overweight/obesity status has become more and more important and therefore debated.

As mentioned before, there is no evidence of an association between the exposure to air pollution and the outcomes in the study. This is consistent with the results obtained by Grassi et al. (2016), even though their methods for measuring the vehicular traffic all around children's houses and schools is definitely not objective. In fact, their measurements are based on parents' perceptions, and do not rely on real traffic estimates. On the contrary, the estimates for this thesis are extracted from a European project collecting measurements of different kinds of pollutants concentrated in different areas in Rome. A LUR model is then used, with monitors placed all around the city to model the concentrations of pollutants in Rome. As stated somewhere before in this text, the estimates of pollutants do not account for the variable of time, and they are assumed to refer to a stable variable of space. Nevertheless, comparative studies have been conducted on one specific pollutant (NO_2) among the six considered and no difference appears through time.

To our knowledge, no study has ever assessed the effects of air pollution on abdominal measurements and blood lipids levels, which may become then two additional measures of ponderal excess in children. Generally speaking, ponderal excess status is always assessed through children's BMI, which is categorized according to the WHO standards. Since no association has been detected between exposure to air pollution and overweight/obesity indicators, we can affirm that our results are not conflicting. In addition, the longitudinal

analyses have also denied any association between traffic-related air pollution and the likelihood of becoming overweight/obese. Anyway, all the analyses in this thesis suffer from the lack of a consistent number of children through time, a number which has always been scarce since the beginning and has decreased through the various follow-ups. Therefore, this one may be the reason why no significant results have emerged.

Ultimately, this thesis wants to evaluate the effect of the family socioeconomic position (SEP) on and children's risk of becoming overweight/obese, making use of the individual and the contextual measures. To our knowledge, a few other studies have tried to assess the association between SEP and overweight/obesity in children focusing on both contextual and individual measures of socioeconomic position (Ogden, Carroll, Fryar, & Flegal, 2015; Schüle, von Kries, Fromme, & Bolte, 2016). Apart from them, all studies usually make use of either the individual measures, such as parents' educational level and parents' occupational status, or the contextual ones, such as income index, level of accessibility to good and services, composite indexes, etc. In our research parents' educational and occupational statuses, and two composite measures, namely the SEP Index and the Income Index, are used according to the census blocks in Rome. Individual and contextual measurements are fixed values through time and they refer to data collected at children's birth.

The Italian study by Grassi et al. (2016) evidences that parents' educational level and employment status are negatively associated with the risk for children to become overweight/obese. Furthermore, children living in families that struggle to make ends meet are potential subjects of overweight/obesity problems, as it is reported in the last wave of the project funded by the Italian Ministry of Health "*OKkio alla Salute*".

Our results show that the contexts and the areas where children used to live during their first 8 years after birth have a big impact on their ponderal status, more than parents' educational level or occupational statuses. Children living in families with a low SEP Index have a higher risk of becoming overweight/obese at both ages 4 and 8 (and similar results emerge for 4-year-old children living in families with a low Income level). Among all individual exposures, an association is present between mothers' occupational status and 4-year-old children's overweight/obesity status, since the likelihood for them to become overweight/obese is higher when their mothers are not occupied. Furthermore, in our crude analyses, another association is found between 4-year-old children's ponderal excess status

and fathers with a low educational level (i.e., primary school education), which potentially constitutes also a determinant for children not overweight/obese at 15 months of age to become overweight/obese at 4 years. Moreover, the longitudinal analyses and the use of the abdominal fat measurements as an outcome also confirm our main findings, which is not true for the blood lipids levels.

Contextual and individual indicators of the socioeconomic position are used separately in different analyses and different results emerge. Since small area indicators of SEP levels not only represent a certain family's socioeconomic position, but also account for the whole context where children live, they ultimately differ from individual factors such as parents' education and occupation. Since there seems not to be any association between overweight/obesity and individual exposures, we are quite convinced that the contexts and areas where children live play a stronger role here, if compared to parents-related individual factors. This surely needs to be further analysed. Furthermore, since families' socioeconomic position is measured with both individual and contextual indicators referring to lifestyles and eating habits, it is obvious that these aspects have also to be considered. More research on the different effects of individual and contextual measures of the socioeconomic position is much needed. Eventually, if we understand all the reasons (including socioeconomic reasons) behind the onset of overweight/obesity status in children, we believe that a number of social strategies could be activated to face this rising trend.

7.1 Limitations, strengths and further developments

This study has some limitations that need to be discussed. Basically, they are related to the structure and the nature of the data.

As previously explained in Chapter 3, the GASPII project follows through time a cohort of children whose mothers gave them birth in two hospitals in Rome E local health units, in Rome (Italy). Important limitations here are thus represented by the restricted area considered and the religious nature of the hospitals selected. In fact, the GASPII birth cohort is not representative of all the births which took place in the municipality of Rome in 2003/2004. Nevertheless, the cohort's internal validity ensures the data are reliable for conducting our analyses.

Unfortunately, despite a fair number of mothers contacted during the period of enrolment, only 54% of them have decided to enter the study. This is another limitation of the GASPII cohort, which ultimately has been a small birth cohort since the beginning. We maintain that higher percentages of participation in the project would have been possible, if only the personnel involved in the project had been better trained and the study better promoted. In fact, mothers became aware of the project only at the moment of delivery. If they had got familiar with it before such a delicate moment (for example, during prenatal courses or at medical ambulatories/clinics), they might have been more sensitive to the nature and objectives of the study. At the same time, the percentages of children who have dropped out of the study through the different follow-ups represent another important weakness. Abandonments are very difficult to avoid, since mothers can get bored or may have less time to commit to the study. Eventually, the ultimate power of our analyses is limited by the abovementioned situations.

One problem from losing subjects for the study is that results can be biased from the fact that dropping-out subjects may be different from the ones who do not. This is the reason why a statistical methodology called Inverse Probability Weighting (IPW) is used here, based on the assumption that subjects who refuse to take part in or drop out of the study have got similar characteristics as the subjects who instead are involved in the study. If all subjects own these basic characteristics, the inclusion probability (non-missingness) can be used to calculate weights. Weights will be higher for the subjects involved who are similar to the drop-out ones, in order to account for this lack of information. Since the information about enrolled and not enrolled subjects was enough at the time of enrolment, we have always been confident about the calculation methods in our analyses. Overall, the results obtained are quite similar regardless of whether the IPW methods were applied or not. Therefore, we believe that no selection bias has ever occurred in our cohort.

For what concerns the missing values of the main outcome, we have tried to understand first why this information was not available, also if percentages were not so high. As explained in Chapter 3 paragraph 3.3, the overweight/obesity variable is calculated considering three other variables, that are weight, height and age in months. When one of the abovementioned is missing, data for the categorical outcome will be missing too. For example, in the case of 15-month-old children, length measurements were difficult to take. Moreover, when it comes to age 4 follow-up, missing data on the very date of the visit did not allow us to calculate children's age in months, this latter because of the personnel's

inefficiency. Therefore, in both cases, problems with missing data do not occur because of real measurements of the variable. Moreover, if looking at the pattern of the missing data, no statistical difference appears between subjects with missing data and those with all necessary data. Said that, we can assume that the likelihood of obtaining "missing values" does not depend on the unobserved value itself.

Another limitation is represented by the unavailability of other addresses than children's residential ones, since they actually spend most time at nursery schools, schools and grandparents' houses, especially when they are 4 and 8 years old. In fact, if all this information had been available, we could have used it to reconstruct both children's daily habits outside their houses and their potential exposures to pollutants. Furthermore, mothers' unknown residential address during pregnancy should also be viewed as an important piece of missing information, since we could have known their exposure to air pollution. Since we already knew that only 7.5% of pregnant women in Rome had changed their home address during childbearing, we can assume that few changes of residential address also occurred in our cohort.

Other potential limitations to this study are children's enrolment period in the GASPII cohort (2003/2004) and the different times when data on air pollution and contextual measurements of SEP were collected. Data on air pollution were collected from January 2010 to April 2011, but we assume that air pollution levels in Rome did not change in the lapse of time between 2003/2004 and 2010/2011, because of an already demonstrated uniformity in the air pollution exposures (Giulia Cesaroni et al., 2012), a slow-paced urbanization in Rome and the city's uniform traffic volume. This is the reason why the estimates about the abovementioned variables are used in this study. Data from the 2001 census and from the 1998 Italian Tax Register are extracted to calculate respectively the contextual measurements for the SEP Index and for the Income Index. Since there are no SEP or Income indexes from data close to the period of enrolment of the GASPII cohort, we have taken for granted their validity and uniformity through time and have applied them to the period of enrolment.

Despite of all the limitations presented here, there are also some important strengths to consider. As for the limitations, they are related to the nature of the data and to the approaches used.

One first strength comes from the use of different kinds of measures that are usually considered indicators of the populations' ponderal status. As we already know, the main

measure for children's ponderal status is the BMI, thanks to its easy computation methods and intuitive cut-offs' evaluation. The waist circumference and the waist-to-hip ratio are other measures of abdominal fat that are used here to assess ponderal excess in children. Nonetheless, it is correct to remember that, when they are used on children, they are more susceptible of measurement errors than the BMI is. In spite of that, it is true that the BMI does not measure directly the body adiposity, even though it is undoubtedly useful to calculate the condition of a person. On the contrary, abdominal circumferences are more precise measures of localized fat. Then, we have the blood lipids levels, which are also related to the ponderal excess status in the population. Nevertheless, we are not aware today of the existence of previous studies using this information as additional measure of body fat composition. Furthermore, total cholesterol and HDL cholesterol are two other measures used in this research, both related to the onset of the metabolic syndrome and of overweight/obesity in children/adults. As a matter of fact, BMI and waist circumference are the two measures giving here similar results in almost every analysis, while waist-to-hip ratio and blood lipids levels are not often consistent with the exposures considered.

As fully described in Chapter 3, paragraph 3.3, WHO guidelines and standards are used in this thesis for an exact calculation of the BMI, according to the age and sex of children. We then decided to consider the WHO standard growth curve among all different types of classifications, since it is mostly used in research and is constantly updated. The WHO and the adult classifications refer to different periods of one's lifetime. The former classifies children from their first months of age until they are 18 years old, the latter from age 18 on. Furthermore, the WHO gives its users free access to a program for calculating children's BMI Z-score in a simple and clear way.

Finally, another strength is represented by the data used for the analyses which come from a longitudinal and prospective project. This means that we can more easily identify which exact exposure is the one leading to the onset of a specific disease, following its timing and the sequence of events without incurring in any biased situation. In addition, this is the first Italian study to be conducted over a population of newborns, enrolled at delivery and followed through time. Longitudinal studies are complex, they need a lot of time to be completed but at the same time they allow researchers to collect information that can be the same over time.

Future research can build on this thesis to further develop our knowledge about possible determinants of children's overweight/obesity. For example, all the analyses could be repeated with a prospective birth cohort created by the Department of Epidemiology of the Lazio Regional Health Service - Lazio Region, which follows the same guidelines of the GASPII project. At present it is still an ongoing project, with data of children coming from five different cities in Italy: Rome, Turin, Florence, Trieste and Viareggio. At the moment of enrolment, the cohort counted some 3,338 individuals, and relevant anthropometric measurements were collected at each single wave (measurements from their first months of life were more detailed). The children involved in the project are now 4 years old and the last wave will be completed within a few months. A repetition of the analyses could deliver important results accounting also for the different places of birth, collecting diverse information on air pollution and socioeconomic positions. Furthermore, the analyses may be more reliable thanks to the large amount of children enrolled.

Traffic related air pollution data are also coming from the Department of Epidemiology of the Lazio Regional Health Service - Lazio Region. As described in Chapter 5, the estimates are part of a European project called European Study of Cohorts for Air Pollution Effects (ESCAPE) (Beelen et al., 2013; Eeftens, Beelen, et al., 2012). At the time being, the Department of Epidemiology is collecting traffic-related air pollution data through satellite observations. Apparently, these data are more reliable and can cover larger areas of interest. In addition, data estimates will definitely be more precise, something allowing new potential analyses to be more significant thanks to more reliable data on pollution. Furthermore, since these data are collected day by day, further analyses of time series on the exposure to air pollution can be easily conducted, and potential differences over years can be highlighted.

The SEP indexes and the database on air pollution included in this thesis were drafted and created from scratch by the Department of Epidemiology of the Lazio Region. Today, researchers working at the Department are building a new deprivation index, which is based on the 2011 census data and takes into account censuses' block levels, as the other two indexes do. It is likely that it will be used as exposure in socioeconomic analyses. Moreover, this new deprivation index could be then applied on children's data from the GASPII birth cohort, and this will be interesting for two main reasons. Firstly, the results from different analyses can be compared, keeping in mind that different indexes are created using similar data and methodologies. Secondly, since the deprivation index is composed of data from the

census of 2011, which is the same year when the children from the GASPII cohort were turning eight (i.e., the last follow-up of the project), it would then be very interesting to discover any potential association with the outcome of our study.

7.2 Conclusion

The aim of this study is twofold: first, to improve our knowledge on the main determinants of children's overweight/obesity status; second, to investigate any possible association between children's ponderal excess and the environment where they live. The interest in children's ponderal status comes from our awareness that it may be an important determinant for the onset of a wide range of diseases during childhood and later in life. We have used the GASPII prospective birth cohort where children were followed from their birth until they were 8 years old, and different measures of the ponderal excess status have been used to focus on its different aspects.

To sum up, for the GASPII cohort's children at ages 15 months, 4 years and 8 years, our findings are consistent with the existent literature's. First of all, maternal BMI plays a crucial role and it is confirmed by our analyses, causing serious risks for the children to become overweight/obese. Second of all, results also confirm that dietary habits in general are very important determinants of overweight/obesity, including the moment of weaning. One of the most interesting findings in this thesis concerns children's siblings: it seems that having two or more siblings is central in preventing the onset of ponderal excess in 8-year-old children. These results underline the importance of promoting healthy lifestyles for mothers and children: interventions targeting mothers (and fathers) are very much needed for them to learn how to deal with their children's ponderal excess (and also potentially with theirs).

While results on the main determinants give an overview of the main factors associated with the overweight/obesity status in children, it cannot be said the same for those on traffic-related air pollution, that are important to investigate for the association between exposures to air pollution and the health status of the population. There can be different reasons why our analyses on traffic-related air pollution data do not give any particular insight on the topic of the research, and further studies are needed for confirmations or objections to the relevant results of this thesis. Furthermore, great interest comes from the analysis of families' socioeconomic position. The findings suggest the importance of the contexts and the

areas where children live, whereas there is no evidence of the association between individual exposures and children's ponderal status.

A lot has been said in the literature about the relationship between the risk of being overweight/obese during childhood and its possible determinants. This study sets the basis for further research which can improve our knowledge of the main determinants of childhood overweight/obesity in Italy through prospective cohort studies. On the other side, in spite of the fact that the environmental exposures used here have already been studied all over the world, the results on traffic-related air pollution and socioeconomic positions provided by this thesis will definitely contribute to the relevant debates which need more and more clarifications.

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Appendix A

Table A.1: Descriptive statistics of the baseline characteristics, analysed for the additional outcomes

	Waist circumference			Waist-to-hip ratio			Total Cholestrol			HDL Cholesterol		
	Mean	**SD**	**Freq.**	**Mean**	**SD**	**Freq.**	**Mean**	**SD**	**Freq.**	**Mean**	**SD**	**Freq.**
Total	60,0	6,183	499	0,91	0,042	499	162,3	25,07	412	59,2	15,16	412
Baseline characteristics												
Maternal age at birth												
< 30 years	60,0	6,451	127	0,92	0,041	127	163,6	25,59	103	60,5	19,76	103
30-35 years	60,1	5,883	215	0,91	0,041	215	162,7	25,69	177	58,6	13,77	177
> 35 years	60,0	6,399	157	0,91	0,043	157	160,8	23,90	132	59,1	12,67	132
Maternal BMI pre-pregnancy												
Underweight/Normal weight	59,6	5,809	414	0,91	0,042	414	161,5	24,75	342	59,5	15,81	342
Overweight	63,2	7,628	61	0,91	0,041	61	164,2	26,37	49	56,9	10,61	49
Obese	60,3	6,343	23	0,92	0,031	23	170,4	26,07	20	60,6	13,57	20
Birth weight												
< 2499 gr	59,7	6,906	34	0,92	0,035	34	166,2	31,22	27	61,4	13,58	27
2500-3999 gr	59,8	6,119	422	0,91	0,043	422	162,7	24,77	350	58,9	15,62	350
>4000 gr	62,7	5,694	43	0,92	0,037	43	155,6	22,27	35	60,3	11,34	35
Gestational age												
<37 week	59,8	6,338	29	0,92	0,034	29	162,1	31,53	23	59,9	14,15	23
>=37 week	60,1	6,182	468	0,91	0,042	468	162,4	24,69	388	59,2	15,25	388
Maternal smoking habits during pregnancy												
No	59,8	5,986	439	0,91	0,042	439	162,4	25,66	365	59,5	15,45	365
Yes	62,1	7,340	56	0,91	0,042	56	162,7	20,13	44	57,1	13,05	44
Maternal educational status												
University degree	59,8	5,318	184	0,92	0,039	184	163,2	23,74	150	60,0	18,72	150
Secondary school	59,8	6,174	248	0,91	0,044	248	160,9	25,84	205	59,1	12,80	205
Primary school	61,5	8,047	67	0,91	0,037	67	165,3	25,70	57	57,7	12,40	57
Paternal educational status												
University degree	60,0	5,617	152	0,91	0,043	152	164,0	26,70	125	59,8	19,38	125
Secondary school	59,4	5,914	200	0,91	0,042	200	161,6	25,51	164	59,9	13,50	164
Primary school	61,3	7,011	111	0,91	0,039	111	161,1	21,80	92	57,7	11,99	92

Table A.2: Descriptive statistics of the six months characteristics, analysed for the additional outcomes

	Waist circumference			Waist-to-hip ratio			Total Cholestrol			HDL Cholesterol		
	Mean	**SD**	**Freq.**	**Mean**	**SD**	**Freq.**	**Mean**	**SD**	**Freq.**	**Mean**	**SD**	**Freq.**
Total	60,0	6,183	499	0,91	0,042	499	162,3	25,07	412	59,2	15,16	412
Six months characteristics												
Breastfeeding duration (in months)												
Never been breastfed	59,4	5,764	60	0,92	0,044	60	165,6	23,32	46	57,3	11,25	46
Until 4 months	59,5	5,936	109	0,91	0,041	109	167,4	25,84	87	59,4	13,98	87
Between 4 and 6 months	60,2	6,143	95	0,92	0,041	95	161,6	22,83	82	58,4	13,39	82
Beyond 6 months	60,4	6,436	233	0,91	0,041	233	159,3	25,60	195	59,8	17,12	195
Weaning (in months)												
Until 4 months	60,0	6,008	348	0,92	0,039	348	162,0	23,88	284	58,7	16,09	284
Between 4 and 6 months	59,7	6,279	113	0,91	0,046	113	161,7	27,45	93	60,5	12,66	93
Beyond 6 months	62,4	7,973	30	0,91	0,055	30	165,6	29,02	27	58,9	12,37	27
Post-partum depression												
No	60,2	6,345	416	0,92	0,042	416	161,6	25,79	343	59,4	15,57	343
Yes	59,3	5,269	79	0,91	0,039	79	164,5	20,51	65	57,9	13,13	65

Table A.3: Descriptive statistics of the seven and eight years characteristics, analysed for the additional outcomes

	Waist circumference			Waist-to-hip ratio			Total Cholestrol			HDL Cholesterol		
	Mean	**SD**	**Freq.**	**Mean**	**SD**	**Freq.**	**Mean**	**SD**	**Freq.**	**Mean**	**SD**	**Freq.**
Total	60,0	6,183	499	0,91	0,042	499	162,3	25,07	412	59,2	15,16	412
Seven years characteristics												
Presence of grandparents												
No	59,5	6,532	175	0,91	0,041	175	161,2	25,22	153	59,5	18,22	153
Yes	60,1	5,853	283	0,91	0,043	283	162,9	25,44	229	58,7	13,38	229
Number of siblings												
No one	59,5	6,045	104	0,91	0,040	104	160,4	23,33	84	60,0	13,63	84
One	60,1	6,115	272	0,92	0,041	272	162,5	25,65	229	58,5	12,99	229
Two or more	59,7	6,338	79	0,91	0,049	79	163,7	27,20	67	59,2	23,69	67
Child eating habits												
Main meal	59,4	5,541	283	0,92	0,041	283	161,5	25,33	239	59,8	16,71	239
Also between meal	60,6	6,918	175	0,91	0,044	175	163,5	25,39	143	57,6	13,13	143
Eight years characteristics												
Screen time (per day)												
<= 7 hours	59,7	5,868	443	0,91	0,042	443	162,6	24,96	372	59,4	15,35	372
> 7 hours	62,5	7,908	56	0,91	0,040	56	160,0	26,28	40	57,5	13,31	40
Diet												
Optimal Mediterranean diet	60,2	6,604	145	0,92	0,042	145	160,7	23,23	123	61,3	19,18	123
Improvement needed	60,0	6,002	306	0,91	0,042	306	163,5	26,43	249	57,9	12,57	249
Very low diet quality	59,8	6,173	47	0,92	0,037	47	159,8	21,56	39	59,9	14,90	39
Physical activity (per week)												
<=2 h	59,5	6,427	172	0,91	0,042	172	162,7	23,98	145	58,4	13,79	145
2-4 h	60,4	6,260	170	0,91	0,042	170	163,4	27,75	139	60,2	18,22	139
>= 4 h	60,0	4,987	103	0,92	0,041	103	159,6	24,39	85	60,4	13,65	85
Sleeping habits (hours per day)												
<= 9 h	60,4	6,529	346	0,92	0,040	346	161,9	24,50	284	58,3	12,89	284
> 9 h	59,2	5,240	153	0,91	0,044	153	163,4	26,35	128	61,3	19,17	128

Appendix B

Table B.1: Analysis of the possible determinants of being overweight/obese at 15 months

	15 months	
	OR	**IC 95%**
Maternal pre-pregnancy BMI		
Underweight/Normal weight (Ref.)	1.00	
Overweight	0.49	(0.06, 3.83)
Obese	**4.68**	**(1.16, 18.9)**
Presence of grandparents		
No (Ref.)	1.00	
Yes	2.89	(0.92, 9.11)
Gestational age		
Continous	1.34	(0.92, 1.94)
Weaning (in months)		
Until 4 months (Ref.)	1.00	
Between 4 and 6 months	0.26	(0.03, 2.06)
Beyond 6 months	3.06	(0.79, 2.06)

Table B.2: Analysis of the possible determinants of being overweight/obese at 4 years

	4 years	
	OR	**IC 95%**
Weaning (in months)		
Until 4 months (Ref.)	1.00	
Between 4 and 6 months	0.62	(0.23, 1.70)
Beyond 6 months	2.20	(0.73, 6.58)
Maternal pre-pregnancy BMI		
Underweight/Normal weight (Ref.)	1.00	
Overweight	1.47	(0.59, 3.67)
Obese	**2.98**	**(1.00, 9.12)**
Screen time		
< 1 hours (Ref.)	1.00	
>= 1 hours	2.37	(0.99, 5.60)
Eating habits		
Main meal (Ref.)	1.00	
Also between main meal	**2.02**	**(1.03, 4.00)**

Table B.3: Analysis of the possible determinants of being overweight/obese at 8 years

	8 years	
	OR	**IC 95%**
Number of siblings		
No one (Ref.)	1.00	
One	1.18	(0.70, 1.99)
Two or more	**0.47**	**(0.22, 0.99)**
Presence of grandparents		
No (Ref.)	1.00	
Yes	1.40	(0.89, 2.20)
Physical activity		
Continous	1.08	(0.96, 1.22)
Weaning (in months)		
Until 4 months (Ref.)	1.00	
Between 4 and 6 months	1.18	(0.68, 2.05)
Beyond 6 months	**2.51**	**(1.02, 6.17)**
Maternal pre-pregnancy BMI		
Underweight/Normal weight (Ref.)	1.00	
Overweight	**2.71**	**(1.37, 5.37)**
Obese	1.26	(0.38, 4.11)
Screen time		
< 2 hours (Ref.)	1.00	
>= 2 hours	1.64	(0.78, 3.45)

Table B.4: Analysis of the possible determinants of increasing waist circumference at 8 years

	8 years - Waist Circumference	
	Coeff	**IC 95%**
Maternal pre-pregnancy BMI		
Underweight/Normal weight (Ref.)	1.00	
Overweight	**4.40**	**(2.53, 6.27)**
Obese	0.02	(-3.20, 3.23)
Maternal smoking habits		
No (Ref.)	1.00	
Yer	1.76	(-0.18, 3.70)
Sleeping time (hours)		
Continous	-0.69	(-1.50, 0.12)
Physical activity		
Continous	0.31	(-0.02, 0.63)
Presence of grandparents		
No (Rif.)	1.00	
Yes	0.95	(-0.25, 2.15)
Gestational age		
Continous	0.26	(-0.09, 0.61)
Weaning (in months)		
Until 4 months (Ref.)	1.00	
Between 4 and 6 months	-0.78	(-2.27, 0.72)
Beyond 6 months	**2.50**	**(0.14, 4.85)**
Screen time		
< 2 hours (Ref.)	1.00	
>= 2 hours	1.37	(-0.50, 3.24)

Table B.5: Analysis of the possible determinants of increasing waist-to-hip ratio at 8 years

	8 years - Waist-to-hip Ratio	
	Coeff	**IC 95%**
Eating habits		
Main meal (Ref.)	1.00	
Also between main meal	-0.10	(-0.19, 0.01)
Maternal education		
University degree (Ref.)	1.00	
Secondary school	-0.08	(-0.17, 0.01)
Primary school	0.02	(-0.13, 0.18)
Diet		
Continous	0.01	(-0.03, 0.01)
Gestational age		
Continous	-0.02	(-0.05, 0.01)
Screen time		
< 2 hours (Ref.)	1.00	
>= 2 hours	-0.09	(-0.23, 0.04)

Table B.6: Analysis of the possible determinants of increasing total cholesterol levels at 8 years

	8 years- Total Cholesterol	
	Coeff	**IC 95%**
Breastfeeding duration		
Never been breastfed (Ref.)	1.00	
Until 4 months	1.11	(-9.38, 11.6)
Between 4 and 6 months	-3.38	(-13.8, 7.07)
Beyond 6 months	-8.40	(-17.8, 0.92)

Table B.7: Analysis of the possible determinants of increasing HDL cholesterol levels at 8 years

		8 years - Cholesterol HDL	
		Coeff	**IC 95%**
Screen time			
	< 2 hours (Ref.)	1.00	
	>= 2 hours	-4.96	(-10.9, 0.94)
Maternal smoking habits			
	No (Ref.)	1.00	
	Yer	-4.59	(-10.8, 1.58)
Diet			
	Continous	0.56	(-0.25, 1.38)

Table B.8: Longitudinal backward stepwise analysis of normal weight children at 15 months, switching to overweight/obesity at 4 years

		15 months to 4 years	
		OR	**IC 95%**
Eating habits			
	Main meal (Ref.)	1,00	
	Also between main meal	**2,36**	**(1.06, 5.28)**
Paternal education			
	University degree (Ref.)	1,00	
	Secondary school	1,65	(0.54, 5.09)
	Primary school	**4,16**	**(1.21, 14.3)**
Maternal education			
	University degree (Ref.)	1,00	
	Secondary school	0,46	(0.17, 1.23)
	Primary school	0,96	(0.29, 3.26)
Screen time			
	< 1 hours (Ref.)	1,00	
	>= 1 hours	0,96	(0.29, 3.26)

Table B.9: Longitudinal backward stepwise analysis of normal weight children at 4 years, switching to overweight/obesity at 8years

	4 - 8 years	
	OR	**IC 95%**
Number of siblings		
No one (Ref.)	1,00	
One	1,24	(0.70, 2.21)
Two or more	**0,30**	**(0.12, 0.77)**
Maternal pre-pregnancy BMI		
Underweight/Normal weight (Ref.)	1,00	
Overweight	**2,23**	**(1.05, 4.74)**
Obese	0,77	(0.15, 3.91)
Weaning (in months)		
Until 4 months (Ref.)	1,00	
Between 4 and 6 months	1,53	(0.85, 2.73)
Beyond 6 months	**3,30**	**(1.09, 9.98)**
Physical activity		
Continous	1,11	(0.97, 1.28)

Table B.10: Longitudinal backward stepwise analysis of overweight/obesity in children at 4 and 8 years

	4 - 8 years	
	OR	**IC 95%**
Weaning (in months)		
Until 4 months (Ref.)	1,00	
Between 4 and 6 months	0,41	(0.09, 1.87)
Beyond 6 months	**6,98**	**(1.92, 25.4)**
Maternal pre-pregnancy BMI		
Underweight/Normal weight (Ref.)	1,00	
Overweight	1,93	(0.46, 8.06)
Obese	3,79	(0.83, 17.4)
Sleeping time (hours)		
Continous	0,54	(0.28, 1.02)
Physical activity		
Continous	1,23	(0.98, 1.55)

Appendix C

Supplementary material of the "*Traffic-related air pollution and childhood obesity in an Italian birth cohort"* research paper.

Supplementary Tables

Table C.1: Number of children from the GASPII cohort with available information on each outcome and exposure considered.

	4 year		8 year	
	N	**%**	**N**	**%**
Total	581	100	499	100
BMI				
Pollutant	528	90.9	477	95.6
Traffic variable	557	95.9	497	99.6
Waist and Hip circumference				
Pollutant	-		477	95.6
Traffic variable	-		497	99.6
Total and HDL cholesterol				
Pollutant	-		390	78.2
Traffic variable	-		410	82.2

Table C.2: Correlation between air pollutants and the traffic variable.

	NO_2	NO_X	PM_{10}	$PM_{2.5}$	$PM_{2.5}$ abs	PM coarse	Traffic load
NO_2	1						
NO_X	0.755	1					
PM_{10}	0.639	0.701	1				
$PM_{2.5}$	0.687	0.733	0.946	1			
$PM_{2.5}$ abs	0.529	0.612	0.727	0.768	1		
PM coarse	0.768	0.768	0.943	0.923	0.704	1	
Traffic load	0.603	0.706	0.624	0.687	0.639	0.619	1

Table C.3: Association between exposure to air pollution (from birth to 4 years of life) and to vehicular traffic (evaluated at birth), and BMI Z-score. Result from regression models (at each follow-up) and generalised estimation equations (GEE) models (in the overall follow-up period).

	4 Year				8 Year				GEE			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
NO_2 (per 10 μg/m^3)	-0.06	(-0.15, 0.04)	-0.04	(-0.14, 0.06)	-0.08	(-0.18, 0.03)	-0.04	(-0.15, 0.08)	-0.07	(-0.16, 0.01)	-0.05	(-0.14, 0.04)
NO_X (per 20 μg/m^3)	-0.07	(-0.17, 0.03)	-0.04	(-0.15, 0.06)	**-0.11**	**(-0.23, -0.00)**	-0.08	(-0.21, 0.04)	**-0.09**	**(-0.18, -0.00)**	-0.07	(-0.17, 0.03)
PM_{10} (per 10 μg/m^3)	-0.09	(-0.26, 0.08)	-0.08	(-0.26, 0.10)	-0.14	(-0.34, 0.06)	-0.12	(-0.33, 0.09)	-0.12	(-0.28, 0.03)	-0.12	(-0.29, 0.05)
$PM_{2.5}$ (per 5 μg/m^3)	-0.10	(-0.33, 0.13)	-0.08	(-0.33, 0.17)	-0.17	(-0.44, 0.10)	-0.15	(-0.44, 0.14)	-0.15	(-0.36, 0.07)	-0.14	(-0.37, 0.09)
PM_{coarse} (per 5 μg/m^3)	-0.12	(-0.24, 0.01)	-0.11	(-0.24, 0.03)	-0.13	(-0.27, 0.01)	-0.12	(-0.28, 0.03)	**-0.13**	**(-0.24, -0.01)**	**-0.13**	**(-0.25, -0.01)**
$PM_{2.5abs}$ (per 1 μg/m^3)	-0.03	(-0.20, 0.14)	0.00	(-0.19, 0.18)	-0.06	(-0.25, 0.14)	-0.02	(-0.23, 0.19)	-0.06	(-0.22, 0.10)	-0.02	(-0.19, 0.14)
Traffic load of roads in a 100mt buffer[a]												
Not exposed	1.00		1.00		1.00		1.00		1.00		1.00	
Below 1st tertile	-0.01	(-0.32, 0.30)	0.01	(-0.35, 0.34)	0.14	(-0.22, 0.50)	0.06	(-0.31, 0.42)	0.09	(-0.20, 0.38)	0.07	(-0.23, 0.37)
Between the 1st and the 2nd tertile	0.07	(-0.24, 0.38)	0.02	(-0.32, 0.35)	0.29	(-0.07, 0.64)	0.24	(-0.13, 0.60)	0.19	(-0.09, 0.48)	0.17	(-0.13, 0.46)
Beyond the 3rd tertile	0.08	(-0.23, 0.40)	0.11	(-0.22, 0.45)	0.06	(-0.31, 0.42)	0.03	(-0.34, 0.41)	0.10	(-0.19, 0.39)	0.12	(-0.18, 0.42)

[a] Number of vehicles × meters of road/day

Coefficients were adjusted for maternal and paternal education, mother's pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, mother's age at delivery, gestational age, child birth weight, breastfeeding duration, age (in months) at weaning and inversely weighted for the probability of participation at baseline and at the two follow-ups, respectively

Table C.4: Association between exposure to air pollution (from birth to 4 years of life) and to vehicular traffic (evaluated at birth), and Total and HDL Cholesterol at 8 years, evaluated with regression models.

	Total Cholesterol				HDL Cholesterol			
	Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
NO_2 (per 10 $\mu g/m^3$)	0.09	(-2.48, 2.65)	-0.39	(-3.25, 2.46)	-0.85	(-2.36, 0.66)	-1.44	(-3.20, 0.33)
NO_X (per 20 $\mu g/m^3$)	-0.35	(-2.91, 2.21)	-1.52	(-4.42, 1.39)	0.36	(-1.16, 1.90)	-0.01	(-1.82, 1.80)
PM_{10} (per 10 $\mu g/m^3$)	-0.87	(-5.45, 3.71)	-1.99	(-7.03, 3.04)	-0.29	((-3.05, 2.47)	-1.03	(-4.19, 2.13)
$PM_{2.5}$ (per 5 $\mu g/m^3$)	-1.33	(-7.59, 4.94)	-2.63	(-9.60, 4.32)	-0.57	(-4.33, 3.19)	-1.71	(-6.07, 2.64)
PM_{coarse} (per 5 $\mu g/m^3$)	-0.80	(-4.11, 2.50)	-2.03	(-5.77, 1.72)	-0.07	(-2.05, 1.91)	-0.73	(-3.08, 1.62)
$PM_{2.5abs}$ (per 1 $\mu g/m^3$)	-2.65	(-7.04, 1.74)	-2.79	(-7.59, 2.01)	-0.07	(-2.73, 2.58)	-0.57	(-3.59, 2.46)
Traffic load of roads in a 100mt buffer[a]								
Not exposed	1.00		1.00		1.00		1.00	
Below 1st tertile	-9.11	(-17.6, 0.63)	-9.61	(-18.5, 0.74)	-1.92	(-7.04, 3.21)	-1.01	(-6.58, 4.55)
Between the 1st and the 2nd tertile	-9.60	(-17.9, 1.24)	-11.4	(-20.1, 2.58)	1.42	(-3.63, 6.48)	2.83	(-2.68, 8.33)
Beyond the 3rd tertile	-7.71	(-16.1, 0.72)	-9.41	(-18.3, 0.47)	-2.23	(-7.32, 2.86)	-2.70	(-8.30, 2.90)

[a] Number of vehicles × meters of road/day

Coefficients were adjusted for maternal and paternal education, mother's pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, mother's age at delivery, gestational age, child birth weight, breastfeeding duration and inversely weighted for the probability of participation at baseline and at the two follow-ups, respectively

Analyses without IPW

Table C.5: Association between exposure to air pollution (from birth to 4 years of life) and to vehicular traffic (evaluated at birth), and subsequent overweight/obesity. Result from generalised linear model (GLM) models (at each follow-up) and generalised estimation equations (GEE) models (in the overall follow-up period).

	4 Year				8 Year				GEE			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**
NO_2 (per 10 μg/m^3)	0.92	(0.69, 1.22)	1.04	(0.80,1.35)	0.95	(0.84, 1.07)	0.97	(0.85, 1.11)	0.95	(0.83, 1.07)	0.99	(0.86, 1.12)
NO_X (per 20 μg/m^3)	0.90	(0.68, 1.20)	1.02	(0.78, 1.33)	0.92	(0.81, 1.05)	0.95	(0.83, 1.09)	0.93	(0.81, 1.06)	0.97	(0.85, 1.11)
PM_{10} (per 10 μg/m^3)	0.66	(0.62, 1.52)	1.09	(0.69, 1.72)	0.95	(0.77, 1.18)	0.92	(0.72, 1.16)	0.95	(0.76, 1.20)	0.96	(0.76, 1.22)
$PM_{2.5}$ (per 5 μg/m^3)	1.06	(0.60, 1.87)	1.21	(0.67, 2.18)	0.96	(0.72, 1.29)	0.95	(0.70, 1.30)	0.98	(0.73, 1.32)	1.01	(0.74, 1.38)
PM_{coarse} (per 5 μg/m^3)	0.84	(0.58, 1.20)	0.96	(0.68, 1.35)	0.91	(0.77, 1.07)	0.89	(0.74, 1.06)	0.90	(0.76, 1.06)	0.91	(0.76, 1.09)
$PM_{2.5abs}$ (per 1 μg/m^3)	1.10	(0.71, 1.68)	1.24	(0.82, 1.87)	1.00	(0.81, 1.24)	1.04	(0.84, 1.30)	1.02	(0.82, 1.26)	1.08	(0.87, 1.35)
Traffic load of roads in a 100mt buffer[a]												
Not exposed	1.00		1.00		1.00		1.00		1.00		1.00	
Below 1st tertile	1.45	(0.50, 4.20)	2.21	(0.66, 7.45)	1.07	(0.70, 1.66)	0.91	(0.60, 1.40)	1.12	(0.72, 1.76)	1.05	(0.67, 1.64)
Between the 1st and the 2nd tertile	1.58	(0.55, 4.53)	1.83	(0.56, 5.94)	1.27	(0.84, 1.92)	1.14	(0.76, 1.71)	1.33	(0.86, 2.05)	1.25	(0.81, 1.91)
Beyond the 3rd tertile	1.75	(0.62, 4.98)	2.58	(0.80, 8.35)	1.04	(0.67, 1.61)	0.97	(0.63, 1.49)	1.14	(0.73, 1.79)	1.16	(0.74, 1.82)

[a] Number of vehicles × meters of road/day

RRs were adjusted for parental education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, birth weight, breastfeeding duration (in months), age (in months) at weaning

Table C.6: Association between exposure to air pollution (from birth to 4 years of life) and to vehicular traffic (evaluated at birth), and Waist circumferences and Waist-to-hip ratio at 8 years, evaluated using linear regression models.

	Waist Circumference (cm)				Waist-Hip Circumference Ratio (cm)			
	Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
NO_2 (per 10 $\mu g/m^3$)	0.08	(-0.48, 0.63)	0.33	(-0.25, 0.91)	0.01	(-0.03, 0.05)	0.01	(-0.03, 0.05)
NO_X (per 20 $\mu g/m^3$)	-0.19	(-0.77, 0.38)	0.10	(-0.51, 0.72)	0.00	(-0.04, 0.04)	0.00	(-0.04, 0.04)
PM_{10} (per 10 $\mu g/m^3$)	-0.46	(-1.49, 0.57)	-0.34	(-1.41, 0.73)	-0.02	(-0.09, 0.05)	-0.02	(-0.09, 0.05)
$PM_{2.5}$ (per 5 $\mu g/m^3$)	-0.54	(-1.93, 0.85)	-0.40	(-1.86, 1.05)	-0.02	(-0.12, 0.07)	-0.02	(-0.12, 0.07)
PM_{coarse} (per 5 $\mu g/m^3$)	-0.38	(-1.11, 0.35)	-0.28	(-1.06, 0.50)	0.00	(-0.05, 0.05)	0.00	(-0.05, 0.05)
$PM_{2.5abs}$ (per 1 $\mu g/m^3$)	-0.23	(-1.23, 0.77)	-0.01	(-1.04, 1.03)	-0.02	(-0.08, 0.05)	-0.02	(-0.09, 0.05)
Traffic load of roads in a 100mt buffer[a]								
Not exposed	1.00		1.00		1.00		1.00	
Below 1st tertile	1.25	(-0.64, 3.14)	0.66	(-1.20, 2.53)	0.02	(-0.11, 0.14)	-0.01	(-0.13, 0.11)
Between the 1st and the 2nd tertile	**1.97**	**(0.10, 3.83)**	1.49	(-0.37, 3.36)	0.08	(-0.05, 0.20)	0.07	(-0.06, 0.19)
Beyond the 3rd tertile	1.39	(-0.50, 3.28)	1.28	(-0.62, 3.18)	0.04	(-0.08, 0.17)	0.03	(-0.09, 0.15)

[a] Number of vehicles × meters of road/day

Coefficients were adjusted for parental education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, birth weight, breastfeeding duration (in months), age (in months) at weaning

Table C.7: Association between exposure to air pollution (from birth to 4 years of life) and to vehicular traffic (evaluated at birth), and BMI Z-score. Result from regression models (at each follow-up) and generalised estimation equations (GEE) models (in the overall follow-up period).

	4 Year				8 Year				GEE			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
NO_2 (per 10 μg/m^3)	-0.05	(-0.14, 0.04)	-0.04	(-0.14, 0.06)	-0.08	(-0.19, 0.02)	-0.05	(-0.16, 0.06)	-0.07	(-0.16, 0.01)	-0.05	(-0.14, 0.04)
NO_X (per 20 μg/m^3)	-0.07	(-0.16, 0.03)	-0.04	(-0.14, 0.07)	**-0.12**	**(-0.23, -0.01)**	-0.10	(-0.22, 0.02)	**-0.10**	**(-0.18, -0.01)**	-0.07	(-0.17, 0.02)
PM_{10} (per 10 μg/m^3)	-0.08	(-0.25, 0.08)	-0.07	(-0.25, 0.11)	-0.15	(-0.34, 0.05)	-0.14	(-0.35, 0.07)	-0.13	(-0.29, 0.03)	-0.12	(-0.29, 0.04)
$PM_{2.5}$ (per 5 μg/m^3)	-0.09	(-0.32, 0.14)	-0.07	(-0.32, 0.17)	-0.19	(-0.45, 0.08)	-0.18	(-0.47, 0.10)	-0.15	(-0.36, 0.06)	-0.14	(-0.37, 0.08)
PM_{coarse} (per 5 μg/m^3)	-0.11	(-0.23, 0.01)	-0.10	(-0.24, 0.03)	-0.14	(-0.28, 0.00)	-0.13	(-0.27, 0.02)	**-0.13**	**(-0.25, -0.02)**	**-0.13**	**(-0.25, -0.01)**
$PM_{2.5abs}$ (per 1 μg/m^3)	-0.02	(-0.19, 0.14)	0.00	(-0.18, 0.17)	-0.07	(-0.26, 0.12)	-0.04	(-0.25, 0.16)	-0.06	(-0.22, 0.10)	-0.03	(-0.20, 0.13)
Traffic load of roads in a 100mt buffer[a]												
Not exposed	1.00		1.00		1.00		1.00		1.00		1.00	
Below 1st tertile	-0.02	(-0.35, 0.29)	-0.01	(-0.34, 0.32)	0.13	(-0.23, 0.50)	0.05	(-0.32, 0.41)	0.07	(-0.22, 0.36)	0.05	(-0.24, 0.34)
Between the 1st and the 2nd tertile	0.05	(-0.26, 0.36)	0.00	(-0.33, 0.33)	0.27	(-0.09, 0.63)	0.22	(-0.15, 0.58)	0.17	(-0.12, 0.45)	0.14	(-0.15, 0.43)
Beyond the 3rd tertile	0.07	(-0.24, 0.38)	0.10	(-0.23, 0.43)	0.03	(-0.33, 0.39)	0.00	(-0.37, 0.37)	0.07	(-0.22, 0.36)	0.09	(-0.21, 0.39)

[a] Number of vehicles × meters of road/day

Coefficients were adjusted for parental education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, birth weight, breastfeeding duration (in months), age (in months) at weaning

Table C.8: Association between exposure to air pollution (from birth to 4 years of life) and to vehicular traffic (evaluated at birth), and Total and HDL Cholesterol at 8 years, evaluated with regression models.

	Total Cholesterol				HDL Cholesterol			
	Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
NO_2 (per 10 $\mu g/m^3$)	0.15	(-2.37, 2.67)	-0.21	(-3.00, 2.57)	-0.75	(-2.26, 0.75)	-1.28	(-3.02, 0.47)
NO_X (per 20 $\mu g/m^3$)	-0.22	(-2.73, 2.29)	-1.23	(-4.05, 1.59)	0.45	(-1.06, 1.97)	0.12	(-1.66, 1.91)
PM_{10} (per 10 $\mu g/m^3$)	-0.74	(-5.22, 3.74)	-1.70	(-6.69, 3.18)	-0.16	(-2.89, 2.57)	-0.84	(-.394, 2.26)
$PM_{2.5}$ (per 5 $\mu g/m^3$)	-1.00	(-7.12, 5.12)	-2.07	(-8.80, 4.65)	-0.28	(-3.99, 3.43)	-1.34	(-5.59, 2.92)
PM_{coarse} (per 5 $\mu g/m^3$)	-0.74	(-3.99, 2.51)	-1.80	(-5.44, 1.84)	0.01	(-1.96, 1.99)	-0.61	(-2.92, 1.70)
$PM_{2.5abs}$ (per 1 $\mu g/m^3$)	-2.31	(-6.59, 1.98)	-2.26	(-6.90, 2.39)	0.19	(-2.42, 2.81)	-0.25	(-3.21, 2.71)
Traffic load of roads in a 100mt buffer[a]								
Not exposed	1.00		1.00		1.00		1.00	
Below 1st tertile	-8.90	(-17.4, 0.79)	-9.62	(-18.4, 0.79)	-1.88	(-7.04, 3.29)	-0.90	(-6.51, 4.70)
Between the 1st and the 2nd tertile	-9.29	(-17.6, 0.95)	-11.11	(-19.8, 2.39)	1.60	(-3.49, 6.70)	3.10	(-2.42, 8.63)
Beyond the 3rd tertile	-7.13	(-15.5, 1.24)	-8.85	(-17.6, 0.03)	-1.97	(-7.08, 3.14)	-2.32	(-7.91, 3.27)

[a] Number of vehicles × meters of road/day

Coefficients were adjusted for parental education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, birth weight, breastfeeding duration (in months), age (in months) at weaning

Analyses with air pollutants exposure measured at birth (with and without IPW methodology)

Table C.9: Number of children from the GASPII cohort with available information on each outcome and air pollutant evaluated at birth.

	4 year		8 year	
	N	**%**	**N**	**%**
Total	581	100	499	100
BMI				
Pollutant	557	95.9	497	99.6
Traffic variable	557	95.9	497	99.6
Waist and Hip circumference				
Pollutant	-		497	99.6
Traffic variable	-		497	99.6
Total and HDL cholesterol				
Pollutant	-		410	82.2
Traffic variable	-		410	82.2

Table C.10: Exposure levels of air pollutants evaluated at birth, by follow-up visits (Means and SD).

	4 year (N=557)		8 year (N=497)	
	Mean	**SD**	**Mean**	**SD**
Air pollutants levels				
NO_2	44.6	10.0	44.9	10.1
NO_X	70.2	20.6	71.0	20.8
PM_{10}	36.9	5.65	37.0	5.69
$PM_{2.5}$	19.5	2.09	19.5	2.11
PM_{coarse}	2.72	0.59	2.7	0.60
$PM_{2.5Absorbance}$	16.8	3.90	16.9	3.95

Analyses with the IPW methodology.

Table C.11: Association between exposure to air pollution at birth, and subsequent overweight/obesity. Result from generalised linear model (GLM) models (at each follow-up) and generalised estimation equations (GEE) models (in the overall follow-up period).

	4 Year				8 Year				GEE			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**
NO_2 (per 10 $\mu g/m^3$)	0.87	(0.65, 1.18)	0.97	(0.72, 1.30)	0.96	(0.85, 1.08)	0.98	(0.78, 1.22)	0.95	(0.83, 1.08)	0.99	(0.86, 1.13)
NO_X (per 20 $\mu g/m^3$)	0.91	(0.70, 1.17)	0.97	(0.75, 1.26)	0.95	(0.85, 1.07)	0.97	(0.85, 1.10)	0.96	(0.85, 1.08)	0.99	(0.87, 1.12)
PM_{10} (per 10 $\mu g/m^3$)	0.92	(0.58, 1.44)	1.06	(0.67, 1.66)	0.98	(0.80, 1.21)	1.01	(0.75, 1.36)	0.98	(0.80, 1.21)	1.02	(0.81, 1.27)
$PM_{2.5}$ (per 5 $\mu g/m^3$)	1.04	(0.61, 1.77)	1.22	(0.70, 2.12)	0.99	(0.75, 1.31)	1.07	(0.88, 1.31)	1.03	(0.78, 1.35)	1.09	(0.81, 1.45)
PM_{coarse} (per 5 $\mu g/m^3$)	0.84	(0.61, 1.16)	0.96	(0.69, 1.35)	0.93	(0.80, 1.08)	0.97	/0.85, 1.10)	0.93	(0.80, 1.08)	0.94	(0.80, 1.12)
$PM_{2.5abs}$ (per 1 $\mu g/m^3$)	1.07	(0.73, 1.57)	1.20	(0.81, 1.76)	1.02	(0.83, 1.24)	0.91	(0.77, 1.08)	1.03	(0.85, 1.26)	1.12	(0.92, 1.37)

RRs were adjusted for parental education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, birth weight, breastfeeding duration (in months), age (in months) at weaning and inversely weighted for the probability of participation at baseline and at the two follow-ups, respectively

Table C.12: Association between exposure to air pollution at birth, and Waist circumferences and Waist-to-hip ratio at 8 years, evaluated using linear regression models.

	Waist Circumference (cm)				Waist-Hip Circumference Ratio (cm)			
	Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
NO_2 (per 10 $\mu g/m^3$)	0.09	(-0.45, 0.64)	0.45	(-0.13, 1.02)	0.010	(-0.03, 0.05)	0.009	(-0.03, 0.05)
NO_X (per 20 $\mu g/m^3$)	-0.05	(-0.58, 0.48)	0.23	(-0.30, 0.79)	-0.001	(-0.04, 0.04)	0.002	(-0.03, 0.04)
PM_{10} (per 10 $\mu g/m^3$)	-0.03	(-1.22, 0.72)	0.09	(-0.93, 1.11)	-0.025	(-0.09, 0.04)	-0.019	(-0.09, 0.05)
$PM_{2.5}$ (per 5 $\mu g/m^3$)	-0.22	(-1.54, 1.10)	0.16	(-1.23, 1.54)	-0.027	(-0.12, 0.06)	-0.014	(-0.10, 0.08)
PM_{coarse} (per 5 $\mu g/m^3$)	-0.29	(-0.99, 0.41)	-0.02	(-0.77, 0.73)	-0.005	(-0.05, 0.04)	0.000	(-0.05, 0.05)
$PM_{2.5abs}$ (per 1 $\mu g/m^3$)	0.04	(-0.89, 0.98)	0.40	(-0.56, 1.35)	-0.018	(-0.08, 0.04)	-0.011	(-0.07, 0.05)

Coefficients were adjusted for parental education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, birth weight, breastfeeding duration (in months), age (in months) at weaning and inversely weighted for the probability of participation at baseline and at the two follow-ups, respectively

Table C.13: Association between exposure to air pollution evaluated at birth, and BMI Z-score. Result from regression models (at each follow-up) and generalised estimation equations (GEE) models (in the overall follow-up period).

	4 Year				8 Year				GEE			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
NO_2 (per 10 $\mu g/m^3$)	-0.03	(-0.12, 0.06)	0.00	(-0.11, 0.09)	-0.08	(-0.19, 0.20)	-0.03	(-0.14, 0.08)	-0.05	(-0.14, 0.03)	-0.02	(-0.11, 0.07)
NO_X (per 20 $\mu g/m^3$)	-0.03	(-0.11, 0.16)	0.00	(-0.09, 0.09)	-0.09	(-0.19, 0.02)	-0.05	(-0.16, 0.06)	-0.05	(-0.13, 0.03)	-0.02	(-0.11, 0.07)
PM_{10} (per 10 $\mu g/m^3$)	-0.03	(-0.19, 0.13)	0.00	(-0.18, 0.17)	-0.09	(-0.28, 0.09)	-0.05	(-0.25, 0.15)	-0.05	(-0.20, 0.09)	-0.02	(-0.18, 0.13)
$PM_{2.5}$ (per 5 $\mu g/m^3$)	-0.01	(-0.23, 0.21)	0.02	(-0.22, 0.26)	-0.11	(-0.37, 0.14)	-0.06	(-0.33, 0.21)	-0.05	(-0.25, 0.16)	-0.01	(-0.22, 0.21)
PM_{coarse} (per 5 $\mu g/m^3$)	-0.07	(-0.19, 0.04)	-0.06	(-0.18, 0.07)	-0.11	(-0.24, 0.02)	-0.08	(-0.23, 0.06)	-0.08	(-0.19, 0.02)	-0.07	(-0.18, 0.05)
$PM_{2.5abs}$ (per 1 $\mu g/m^3$)	-0.01	(-0.16, 0.14)	0.01	(-0.16, 0.18)	-0.01	(-0.19, 0.17)	0.04	(-0.15, 0.23)	-0.02	(-0.16, 0.13)	0.02	(-0.13, 0.17)

Coefficients were adjusted for parental education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, birth weight, breastfeeding duration (in months), age (in months) at weaning and inversely weighted for the probability of participation at baseline and at the two follow-ups, respectively

Table C.14: Association between exposure to air pollution evaluated at birth, and Total and HDL Cholesterol at 8 years, evaluated with regression models.

	Total Cholesterol				HDL Cholesterol			
	Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
NO_2 (per 10 $\mu g/m^3$)	-0.32	(-2.80, 2.16)	-0.86	(-3.65, 1.93)	0.14	(-1.33, 1.60)	-0.33	(-2.06, 1.40)
NO_X (per 20 $\mu g/m^3$)	-0.52	(-2.85, 1.80)	-1.52	(-4.13, 1.10)	0.46	(-0.94, 1.85)	-0.05	(-1.70, 1.59)
PM_{10} (per 10 $\mu g/m^3$)	-1.30	(-5.58, 2.99)	-2.35	(-7.07, 2.37)	-0.01	(-2.58, 2.57)	-0.78	(-3.75, 2.18)
$PM_{2.5}$ (per 5 $\mu g/m^3$)	-2.32	(-8.77, 3.50)	-3.90	(-10.3, 2.54)	0.32	(-3.17, 3.80)	-0.82	(-4.85, 3.21)
PM_{coarse} (per 5 $\mu g/m^3$)	-1.24	(-4.35, 1.88)	-2.44	(-5.99, 1.11)	0.22	(-1.65, 2.09)	-0.47	(-2.70, 1.75)
$PM_{2.5abs}$ (per 1 $\mu g/m^3$)	-2.12	(-6.12, 1.88)	-1.77	(-6.10, 2.56)	0.75	(-1.67, 3.17)	0.39	(-2.33, 3.11)

Coefficients were adjusted for parental education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, birth weight, breastfeeding duration (in months), age (in months) at weaning and inversely weighted for the probability of participation at baseline and at the two follow-ups, respectively

Analyses without the IPW methodology.

Table C.15: Association between exposure to air pollution at birth, and subsequent overweight/obesity. Result from generalised linear model (GLM) models (at each follow-up) and generalised estimation equations (GEE) models (in the overall follow-up period).

	4 Year				8 Year				GEE			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**
NO_2 (per 10 μg/m^3)	0.87	(0.65, 1.18)	0.97	(0.72, 1.30)	0.95	(0.84, 1.07)	0.98	(0.97, 1.12)	0.94	(0.82, 1.07)	0.98	(0.86, 1.13)
NO_X (per 20 μg/m^3)	0.91	(0.70, 1.17)	0.97	(0.75, 1.26)	0.94	(0.84, 1.06)	0.96	(0.85, 1.10)	0.95	(0.84, 1.07)	0.97	(0.86, 1.11)
PM_{10} (per 10 μg/m^3)	0.92	(0.58, 1.44)	1.06	(0.67, 1.66)	0.97	(0.79, 1.19)	0.97	(0.76, 1.21)	0.97	(0.78, 1.20)	1.00	(0.80, 1.25)
$PM_{2.5}$ (per 5 μg/m^3)	1.04	(0.61, 1.77)	1.22	(0.70, 2.12)	0.98	(0.74, 1.30)	1.00	(0.74, 1.34)	1.00	(0.76, 1.32)	1.06	(0.79, 1.42)
PM_{coarse} (per 5 μg/m^3)	0.84	(0.61, 1.16)	0.96	(0.69, 1.35)	0.92	(0.79, 1.08)	0.09	(0.77, 1.08)	0.91	(0.78, 1.07)	0.93	(0.79, 1.11)
$PM_{2.5abs}$ (per 1 μg/m^3)	1.07	(0.73, 1.57)	1.20	(0.81, 1.76)	1.01	(0.83, 1.23)	1.07	(0.88, 1.30)	1.02	(0.84, 1.25)	1.10	(0.91, 1.34)

RRs were adjusted for parental education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, birth weight, breastfeeding duration (in months), age (in months) at weaning

Table C.16: Association between exposure to air pollution at birth, and Waist circumferences and Waist-to-hip ratio at 8 years, evaluated using linear regression models.

	Waist Circumference (cm)				Waist-Hip Circumference Ratio (cm)			
	Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
NO_2 (per 10 $\mu g/m^3$)	0.06	(-0.48, 0.60)	0.39	(-0.18, 0.95)	0.01	(-0.02, 0.05)	0.01	(-0.03, 0.05)
NO_X (per 20 $\mu g/m^3$)	-0.07	(-0.60, 0.45)	0.16	(-0.33, 0.72)	0.00	(-0.03, 0.04)	0.00	(-0.03, 0.04)
PM_{10} (per 10 $\mu g/m^3$)	-0.27	(-1.23, 0.68)	0.00	(-1.00, 0.99)	-0.19	(-0.08, 0.05)	-0.01	(-0.08, 0.05)
$PM_{2.5}$ (per 5 $\mu g/m^3$)	-0.03	(-1.55, 1.04)	0.04	(-1.31, 1.39)	-0.02	(-0.11, 0.07)	-0.01	(-0.09, 0.08)
PM_{coarse} (per 5 $\mu g/m^3$)	-0.32	(-1.01, 0.37)	-0.09	(-0.83, 0.64)	0.00	(-0.05, 0.05)	0.00	(-0.05, 0.05)
$PM_{2.5abs}$ (per 1 $\mu g/m^3$)	0.03	(-0.89, 0.95)	0.32	(-0.61, 1.26)	-0.01	(-0.07, 0.05)	-0.01	(-0.06, 0.05)

Coefficients were adjusted for parental education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, birth weight, breastfeeding duration (in months), age (in months) at weaning

Table C.17: Association between exposure to air pollution evaluated at birth, and BMI Z-score. Result from regression models (at each follow-up) and generalised estimation equations (GEE) models (in the overall follow-up period).

	4 Year				8 Year				GEE			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
NO_2 (per 10 μg/m^3)	-0.03	(-0.12, 0.06)	0.00	(-0.10, 0.09)	-0.09	(-0.19, 0.01)	-0.04	(-0.15, 0.07)	-0.06	(-0.15, 0.02)	-0.02	(-0.11, 0.06)
NO_X (per 20 μg/m^3)	-0.02	(-0.11, 0.06)	0.00	(-0.09, 0.10)	-0.09	(-0.19, 0.01)	-0.06	(-0.17, 0.04)	-0.06	(-0.13, 0.02)	-0.03	(-0.11, 0.06)
PM_{10} (per 10 μg/m^3)	-0.02	(-0.18, 0.13)	0.00	(-0.17, 0.16)	-0.11	(-0.29, 0.08)	-0.07	(-0.26, 0.13)	-0.06	(-0.21, 0.08)	-0.04	(-0.19, 0.12)
$PM_{2.5}$ (per 5 μg/m^3)	0.00	(-0.22, 0.21)	0.03	(-0.20, 0.25)	-0.13	(-0.38, 0.12)	-0.09	(-0.36, 0.17)	-0.06	(-0.26, 0.14)	-0.02	(-0.23, 0.18)
PM_{coarse} (per 5 μg/m^3)	-0.07	(-0.18, 0.04)	-0.06	(-0.18, 0.07)	-0.12	(-0.26, 0.01)	-0.10	(-0.24, 0.05)	-0.09	(-0.20, 0.01)	-0.08	(-0.19, 0.04)
$PM_{2.5abs}$ (per 1 μg/m^3)	-0.01	(-0.16, 0.14)	0.01	(-0.15, 0.17)	-0.02	(-0.20, 0.15)	0.02	(-0.16, 0.20)	-0.03	(-0.17, 0.12)	0.01	(-0.13, 0.15)

Coefficients were adjusted for parental education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, birth weight, breastfeeding duration (in months), age (in months) at weaning

Table C.18: Association between exposure to air pollution evaluated at birth, and Total and HDL Cholesterol at 8 years, evaluated with regression models.

	Total Cholesterol				HDL Cholesterol			
	Crude		Adjusted		Crude		Adjusted	
Variable (increment)	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
NO_2 (per 10 $\mu g/m^3$)	-0.26	(-2.71, 2.18)	-0.73	(-3.45, 2.00)	0.21	(-1.25, 1.68)	-0.23	(-1.95, 1.49)
NO_X (per 20 $\mu g/m^3$)	-0.42	(-2.70, 1.86)	-1.33	(-3.87, 1.23)	0.50	(-0.89, 1.89)	0.02	(-1.60, 1.64)
PM_{10} (per 10 $\mu g/m^3$)	-1.11	(-5.30, 3.10)	-2.03	(-6.62, 2.56)	0.11	(-2.44, 2.67)	-0.61	(-3.52, 2.30)
$PM_{2.5}$ (per 5 $\mu g/m^3$)	-1.91	(-7.60, 3.77)	-3.29	(-9.53, 2.95)	0.54	(-2.91, 3.99)	-0.55	(-4.50, 3.40)
PM_{coarse} (per 5 $\mu g/m^3$)	-1.12	(-4.18, 1.95)	-2.20	(-5.65, 1.26)	0.30	(-1.57, 2.16)	-0.38	(-2.56, 1.81)
$PM_{2.5abs}$ (per 1 $\mu g/m^3$)	-1.89	(-5.80, 2.02)	-1.47	(-5.67, 2.74)	0.95	(-1.44, 3.33)	0.60	(-2.07, 3.27)

Coefficients were adjusted for parental education, maternal pre-pregnancy BMI, maternal smoking during pregnancy, gestational diabetes, maternal age at delivery, gestational age, birth weight, breastfeeding duration (in months), age (in months) at weaning

Appendix D

Supplementary material of the "*The relation between familial and contextual indices of socioeconomic position and overweight/obesity in children"* research paper.

Supplementary

Brief description of the construction of the SEP Index

The main variables considered to create the indicator were: education (% of subjects with a university degree and % of subjects with less than a primary school degree), occupation (unemployment rate, youth unemployment rate, % of high qualified professionals, % of blue collars, % of temporary workers), housing (% of rented homes, % of owned homes, high and low household density i.e. number of persons/number of rooms, % of houses without telephone, % of owned parking lots), family condition (% of one-person families, % of families with five or more family members, % of single parents families), and % of migrant population. A factor analysis with varimax rotation has been performed on the standardized variables considered for each census block. The first factor represented education, occupation, and household density; the second migration, the third family composition, and the fourth housing tenure. The first four factors obtained from the analysis were summed, and the value obtained was considered as an overall measure of the SEP in each census block considered.

Inverse Probability Weighting (IPW) Methodology used to avoid the bias due to selection processes

First selection process (at enrolment)

The variable refusal/participation has been created, based on the number of women contacted at the enrolment. It assumes value 0 if the woman decided to do not participate, and 1 if she accepted. A logistic regression model has been performed and with a backward elimination strategy, with a pr < 0.20, the subsequent variables were selected: number of previous pregnancy and maternal educational level. The first set of weights were calculated as the inverse of the predicted probabilities of the considered logistic regression model. We controlled for extreme values performing a second logistic regression (same outcome and only the maternal educational level as covariate), and the set of penalized weights was calculated as the inverse of the ration between the probabilities of the first and of the second predictive model (with just one covariate).

Second selection process (at the 4 years follow-up)

The outcome variable created in this case is related to the finalization of the follow-up at 4 years and to the presence of the BMI measurement. It assumes value 0/1 according to the absence/presence of the relative information. A logistic regression model has been performed and with a backward elimination strategy (pr < 0.20), the subsequent variables were selected: maternal age at delivery and maternal educational level. Weights were calculated as the inverse of the predicted probabilities of the considered logistic regression model. Extreme values were again controlled performing a second logistic regression (using only the maternal age at delivery as covariate), and the set of penalized weights was calculated as the inverse of the ration between the probabilities of the first and the second predictive models. The obtained weights were multiplied to the weights obtained in the first selection process, to account for the enrolment and the loss to follow-up selection processes in the analyses.

Third selection process (at the 8 years follow-up)

The outcome variable has been created according to the finalization of the follow-up at 8 years and to the presence of the BMI measurement (it assumes value 0/1). The first logistic regression model has been performed and with a backward elimination strategy (pr < 0.20), the same variables of the 4 years follow-up were selected (maternal age at delivery and maternal educational level). After calculating the weights as the inverse of the predicted probabilities, the extreme values were again

controlled performing a second logistic regression (using only the maternal age at delivery as covariate). The obtained predicted probabilities were divided for the results obtained with the complete model, to calculate the set of penalized weights. Multiplying the obtained weights with the weights obtained in the first selection process, we obtained a set of weights accounting for both enrolment and loss to follow-up selection processes within the analyses.

Supplementary Tables

Table D.1: Association between SEP Index evaluated at birth, and overweight/obesity. Models adjusted for combinations of income and the other individual variables. Results from GLM models at 4 year follow-up.

		SEP Index				
	N	**High**	**Medium**		**Low**	
		Ref	**RR**	**IC (95 %)**	**RR**	**IC (95 %)**
Model 0	411	1.00	2.64	(0.88, 7.96)	**4.00**	**(1.22, 13.1)**
Model 1	410	1.00	2.03	(0.65, 6.33)	2.12	(0.56, 8.08)
Model 2	411	1.00	2.78	(0.95, 8.12)	**4.42**	**(1.35, 14.5)**
Model 3	383	1.00	2.16	(0.70, 6.79)	3.42	(0.97, 12.1)
Model 4	410	1.00	2.12	(0.70, 6.45)	2.30	(0.61, 8.62)
Model 5	382	1.00	1.76	(0.53, 5.79)	1.92	(0.48, 7.71)
Model 6	383	1.00	2.30	(0.77, 6.86)	**4.00**	**(1.18, 13.6)**
Model 7	382	1.00	1.81	(0.55, 5.90)	2.08	(0.51, 8.42)
Model 8	398	1.00	3.56	(0.92, 13.7)	**5.07**	**(1.23, 20.9)**
Model 9	371	1.00	2.53	(0.83, 7.72)	3.97	(1.19, 13.2)
Model 10	397	1.00	2.99	(0.90, 9.96)	2.53	(0.63, 10.2)
Model 11	370	1.00	1.94	(0.60, 6.22)	2.09	(0.53, 8.20)
Model 12	362	1.00	3.52	(0.92, 13.5)	**5.11**	**(1.23, 21.2)**
Model 13	361	1.00	3.02	(0.90, 10.1)	2.66	(0.64, 10.9)
Model 14	360	1.00	3.12	(0.81, 12.0)	**4.45**	**(1.01. 19.6)**
Model 15	359	1.00	2.77	(0.80, 9.57)	2.77	(0.52, 10.4)

Model 0 adjusted for: Screen hours, pre-pregnancy BMI, hours of sport, kidmed test (diet), birth weight, sleep hours, and number of siblings

Model 1 adjusted for: Model 0 + Income

Model 2 adjusted for: Model 0 + Maternal education

Model 3 adjusted for: Model 0 + Paternal education

Model 4 adjusted for: Model 1 + Maternal education

Model 5 adjusted for: Model 1 + Paternal education

Model 6 adjusted for: Model 4 + Paternal education

Model 7 adjusted for: Model 2 + Paternal education

Model 8 adjusted for: Model 0 + Maternal occupational status

Model 9 adjusted for: Model 0 + Paternal occupational status

Model 10 adjusted for: Model 1 + Maternal occupational status

Model 11 adjusted for: Model 1 + Paternal occupational status

Model 12 adjusted for: Model 7 + Paternal occupational status

Model 13 adjusted for: Model 9 + Paternal occupational status

Model 14 at 4 years adjusted for: Model 2 + Paternal education + Maternal occupational status + Paternal occupational status

Model 15 at 4 years adjusted for: Model 6 + Maternal occupational status + Paternal occupational status

Table D.2: Association between SEP Index evaluated at birth, and overweight/obesity. Models adjusted for combinations of income and the other individual variables. Results from GLM models at 8 year follow-up.

		SEP Index				
	N	**High**	**Medium**		**Low**	
		Ref	**RR**	**IC (95 %)**	**RR**	**IC (95 %)**
Model 0	395	1.00	1.54	(0.98, 2.41)	**1.80**	**(1.10, 2.96)**
Model 1	395	1.00	1.48	(0.88, 2.46)	1.72	(0.94, 3.14)
Model 2	395	1.00	1.55	(0.99, 2.48)	**1.88**	**(1.12, 3.18)**
Model 3	369	1.00	**1.63**	**(1.02, 2.60)**	**1.94**	**(1.15, 3.27)**
Model 4	395	1.00	1.49	(0.89, 2.51)	1.78	(0.96, 3.30)
Model 5	369	1.00	1.43	(0.85, 2.40)	1.65	(0.89, 3.04)
Model 6	369	1.00	**1.61**	**(1.01, 2.58)**	**1.96**	**(1.15, 3.35)**
Model 7	369	1.00	1.41	(0.84, 2.38)	1.68	(0.91, 3.11)
Model 8	386	1.00	**1.62**	**(1.02, 2.57)**	**1.92**	**(1.15, 3.21)**
Model 9	356	1.00	1.50	(0.95, 2.38)	**1.76**	**(1.05, 2.96)**
Model 10	386	1.00	1.58	(0.93, 2.67)	**1.91**	**(1.04, 3.52)**
Model 11	356	1.00	1.41	(0.82. 2.41)	1.63	(0.87, 3.08)
Model 12	349	1.00	1.59	(0.99, 2.57)	**1.87**	**(1.09, 3.21)**
Model 13	349	1.00	1.52	(0.87, 2.66)	1.80	(0.94, 3.44)
Model 14	347	1.00	**1.76**	**(1.08, 2.87)**	**1.99**	**(1.14, 3.47)**
Model 15	347	1.00	1.57	(0.91, 2.70)	**1.73**	**(0.92, 3.28)**

Model 0 adjusted for: Screen hours, pre-pregnancy BMI, hours of sport, kidmed test (diet), birth weight, sleep hours, and number of siblings

Model 1 adjusted for: Model 0 + Income

Model 2 adjusted for: Model 0 + Maternal education

Model 3 adjusted for: Model 0 + Paternal education

Model 4 adjusted for: Model 1 + Maternal education

Model 5 adjusted for: Model 1 + Paternal education

Model 6 adjusted for: Model 4 + Paternal education

Model 7 adjusted for: Model 2 + Paternal education

Model 8 adjusted for: Model 0 + Maternal occupational status

Model 9 adjusted for: Model 0 + Paternal occupational status

Model 10 adjusted for: Model 1 + Maternal occupational status

Model 11 adjusted for: Model 1 + Paternal occupational status

Model 12 adjusted for: Model 7 + Paternal occupational status

Model 13 adjusted for: Model 9 + Paternal occupational status

Model 14 adjusted for: Model 2 + Paternal education + Maternal occupational status + Paternal occupational status

Model 15 adjusted for: Model 6 + Maternal occupational status + Paternal occupational status

Analyses without using the IPW methodology

Table D.3: Association between contextual and individual variables of the SEP evaluated at birth, and overweight/obesity. Results from GLM models (4 and 8 year follow-ups) and longitudinal models.

	4 Years				8 Years				Longitudinal			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
	RR	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**	**RR**	**IC (95%)**
Contextual Variable												
SEP Index												
High (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Medium	2.18	(0.79, 5.97)	2.63	(0.87, 7.94)	1.38	(0.93, 2.05)	**1.56**	**(1.00, 2.44)**	**1.10**	**(1.00, 1.21)**	**1.55**	**(1.00, 2.40)**
Low	**3.59**	**(1.24, 10.4)**	**3.98**	**(1.22, 13.0)**	**1.70**	**(1.10, 2.63)**	**1.82**	**(1.10, 3.00)**	**1.21**	**(1.07, 1.37)**	**1.81**	**(1.10, 2.98)**
Income												
High (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Medium	2.39	(0.74, 7.72)	1.71	(0.54, 5.42)	1.21	(0.83, 1.76)	1.30	(0.86, 1.98)	1.37	(0.95, 1.99)	1.34	(0.89, 2.01)
Low	**5.15**	**(1.60, 16.6)**	**3.90**	**(1.23, 12.4)**	1.33	(0.89, 1.98)	1.49	(0.95, 2.34)	**1.81**	**(1.22, 2.69)**	**1.77**	**(1.14, 2.75)**
Individual Variable												
Maternal education												
University degree (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Secondary school	0.98	(0.55, 1.72)	1.02	(0.54, 1.96)	1.14	(0.88, 1.46)	1.07	(0.81, 1.42)	1.11	(0.86, 1.42)	1.06	(0.79,1.40)
Primary school	1.62	(0.79, 3.31)	1.21	(0.48, 3.02)	0.94	(0.64, 1.40)	0.87	(0.52, 1.47)	1.14	0.77, 1.69)	0.90	(0.50, 1.63)
Paternal education												
University degree (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Secondary school	1.83	(0.89, 3.74)	1.60	(0.72, 3.57)	0.89	(0.67, 1.19)	0.88	(0.64, 1.19)	1.05	(0.79, 1.40)	0.97	(0.71, 1.33)
Primary school	**2.80**	**(1.35, 5.82)**	2.21	(0.94, 5.22)	1.15	(0.86, 1.55)	1.09	(0.78, 1.54)	**1.43**	**(1.06, 1.94)**	1.20	(0.83, 1.74)
Maternal occupational status												
Working (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Not working	1.67	(0.96, 2.91)	**1.96**	**(1.05, 3.64)**	1.26	(0.97, 1.63)	1.03	(0.74, 1.44)	**1.32**	**(1.02, 1.72)**	1.14	(0.81, 1.60)
Paternal occupational status												
Working (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Not working	0.82	(0.12, 5.44)	1.04	(0.15, 7.36)	0.82	(0.32, 2.12)	0.73	(0.25, 2.07)	0.78	(0.28, 2.20)	1.20	(0.43, 3.33)

Confounders: Screen hours, pre-pregnancy BMI, hours of sport (8 year), kidmed test (diet), birth weight, sleep hours, number of siblings

Table D.4: Association between contextual and individual variables of the SEP evaluated at birth, and Waist circumference and Waist-to-hip ratio at 8 year follow-ups. Results from regression models.

	Waist circumference				Waist-to-hip ratio (*10)			
	Crude		Adjusted		Crude		Adjusted	
	Coeff	IC (95%)	Coeff	IC (95%)	Coeff	IC (95%)	Coeff	IC (95%)
Contextual Variable								
SEP Index								
High (Ref.)	1.00		1.00		1.00		1.00	
Medium	1.07	(-0.46, 2.60)	**1.87**	**(0.35, 3.39)**	-0.05	(-0.15, 0.05)	-0.06	(-0.16, 0.04)
Low	**2.71**	**(0.79, 4.62)**	**3.21**	**(1.24, 5.17)**	-0.06	(-0.18, 0.07)	-0.08	(-0.22, 0.05)
Income								
High (Ref.)	1.00		1.00		1.00		1.00	
Medium	0.42	(-1.14, 1.99)	0.81	(-0.75, 2.36)	-0.04	(-0.15, 0.06)	-0.06	(-0.16, 0.05)
Low	1.63	(-0.11, 3.37)	**1.87**	**(0.08, 3.66)**	-0.02	(-0.14, 0.10)	-0.09	(-0.21, 0.03)
Individual Variable								
Maternal education								
University degree (Ref.)	1.00		1.00		1.00		1.00	
Secondary school	0.01	(-1.17, 1.19)	-0.06	(-1.29, 1.17)	-0.07	(-0.15, 0.01)	-0.08	(-0.16, 0.01)
Primary school	**1.73**	**(0.00, 3.46)**	0.57	(-1.52, 2.66)	-0.04	(-0.15, 0.08)	-0.02	(-0.17, 0.12)
Paternal education								
University degree (Ref.)	1.00		1.00		1.00		1.00	
Secondary school	-0.60	(-1.89, 0.70)	-0.75	(-2.06, 0.56)	-0.01	(-0.10, 0.08)	-0.04	(-0.13, 0.05)
Primary school	1.27	(-0.22, 2.77)	0.81	(-0.80, 2.43)	0.00	(-0.10, 0.10)	0.00	(-0.11, 0.11)
Maternal occupational status								
Working (Ref.)	1.00		1.00		1.00		1.00	
Not working	0.52	(-0.85, 1.88)	-0.55	(-2.05, 0.94)	0.00	(-0.09, 0.09)	0.04	(-0.06, 0.14)
Paternal occupational status								
Working (Ref.)	1.00		1.00		1.00		1.00	
Not working	2.46	(-1.33, 6.26)	3.90	(-0.36, 8.17)	0.11	(-0.15, 0.37)	0.18	(-0.12, 0.48)

Confounders: Screen hours, pre-pregnancy BMI, hours of sport (8 year), kidmed test (diet), birth weight, sleep hours, number of siblings, age and sex

Appendix E

Table E.1: Association between contextual and individual variables of the SEP evaluated at birth, and overweight/obesity. Result from linear regression models (4 and 8 years follow-up) and longitudinal models.

	4 Years				8 Years				Longitudinal			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
	Coeff	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**	**Coeff**	**IC (95%)**
Contextual Variable												
SEP Index												
High (Rif.)	1.00		1.00		1.00		1.00		1.00		1.00	
Medium	0.22	(-0.03, 0.47)	0.27	(-0.01, 0.55)	0.26	(-0.03, 0.55)	**0.36**	**(0.06, 0.67)**	**0.24**	**(0.04, 0.44)**	**0.33**	**(0.09, 0.56)**
Low	**0.38**	**(0.07, 0.69)**	**0.39**	**(0.04, 0.75)**	**0.55**	**(0.19, 0.92)**	**0.63**	**(0.24, 1.02)**	**0.48**	**(0.21, 0.75)**	**0.50**	**(0.17, 0.82)**
Income												
High (Rif.)	1.00		1.00		1.00		1.00		1.00		1.00	
Medium	0.19	(-0.06, 0.44)	0.15	(-0.13, 0.43)	0.18	(-0.12, 0.48)	0.22	(-0.09, 0.53)	0.19	(-0.12, 0.40)	**0.25**	**(0.03, 0.47)**
Low	**0.38**	**(-0.09, 0.66)**	**0.34**	**(0.02, 0.67)**	0.31	(-0.02, 0.64)	**0.39**	**(0.03, 0.74)**	**0.35**	**(0.11, 0.60)**	**0.40**	**(0.10, 0.69)**
Individual Variable												
Maternal education												
University degree (Rif.)	1.00		1.00		1.00		1.00		1.00		1.00	
Secondary school	-0.06	(-0.25, 0.14)	-0.01	(-0.23, 0.22)	-0.01	(-0.23, 0.22)	-0.04	(-0.28, 0.21)	-0.01	(-0.18, 0.17)	-0.04	(-0.23, 0.15)
Primary school	0.05	(-0.24, 0.34)	0.01	(-0.34, 0.37)	0.14	(-0.19, 0.47)	-0.09	(-0.51, 0.33)	0.13	(-0.16, 0.42)	-0.11	(-0.56, 0.33)
Paternal education												
University degree (Rif.)	1.00		1.00		1.00		1.00		1.00		1.00	
Secondary school	0.05	(-0.17, 0.26)	0.09	(-0.16, 0.34)	-0.10	(-0.35, 0.15)	-0.10	(-0.37, 0.16)	-0.01	(-0.20, 0.18)	-0.15	(-0.24, 0.21)
Primary school	0.24	(-0.01, 0.50)	0.16	(-0.14, 0.46)	0.18	(-0.10, 0.47)	0.20	(-0.13, 0.52)	0.24	(-0.01, 0.48)	0.17	(-0.10, 0.44)
Maternal occupational status												
Working (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Not working	-0.03	(-0.25, 0.19)	0.02	(-0.24, 0.28)	0.11	(-0.16, 0.37)	-0.06	(-0.36, 0.24)	0.04	(-0.18, 0.26)	-0.07	(0.37, 0.22)
Paternal occupational status												
Working (Ref.)	1.00		1.00		1.00		1.00		1.00		1.00	
Not working	0.35	(-0.27, 0.96)	0.21	(-0.50, 0.93)	0.19	(-0.54, 0.93)	0.18	(-0.69, 1.04)	0.23	(-0.28, 0.74)	0.27	(-0.65, 1.19)

Coefficients were adjusted for screen hours, pre-pregnancy BMI, hours of sport (8 year), kidmed test (diet), birth weight, sleep hours, number of siblings

Table E.2: Association between contextual and individual variables of the SEP evaluated at birth, and Total and HDL Cholesterol at 8 years, evaluated with regression models.

	Total cholesterol				HDL			
	Crude		Adjusted		Crude		Adjusted	
	Coeff	IC (95%)	Coeff	IC (95%)	Coeff	IC (95%)	Coeff	IC (95%)
Contextual Variable								
SEP Index								
High (Rif.)	1.00		1.00		1.00		1.00	
Medium	-0.55	(-7.42, 6.31)	-1.67	(-9.37, 6.04)	2.16	(-2.04, 6.37)	3.01	(-1.78, 7.81)
Low	2.41	(-6.23, 11.1)	0.68	(-9.39, 10.8)	2.09	(-3.21, 7.39)	2.73	(-3.54, 9.01)
Income								
High (Rif.)	1.00		1.00		1.00		1.00	
Medium	-2.46	(-9.49, 4.57)	-3.04	(-10.8, 4.74)	1.67	(-2.61, 5.96)	3.09	(-1.76, 7.92)
Low	-4.26	(-12.1, 3.56)	-8.00	(-16.9, 0.87)	-1.36	(-6.12, 3.40)	-1.17	(-6.69, 4.34)
Individual Variable								
Maternal education								
University degree (Rif.)	1.00		1.00		1.00		1.00	
Secondary school	-2.38	(-7.64, 2.87)	-2.80	(-8.08, 3.21)	-0.95	(-4.16, 2.60)	0.24	(-3.49, 3.98)
Primary school	0.89	(-6.78, 8.55)	-5.51	(-15.5, 4.56)	-2.25	(-6.92, 2.43)	-2.52	(-8.79, 3.74)
Paternal education								
University degree (Rif.)	1.00		1.00		1.00		1.00	
Secondary school	-1.85	(-7.67, 3.97)	-2.16	(-8.86, 4.54)	0.08	(-3.51, 3.68)	-0.09	(-4.27, 4.08)
Primary school	-2.40	(-9.13, 4.33)	-2.50	(-10.7, 5.72)	-2.11	(-6.27, 2.06)	0.26	(-4.86, 5.38)
Maternal occupational status								
Working (Ref.)	1.00		1.00		1.00		1.00	
Not working	5.08	(-1.08, 11.2)	4.32	(-2.94, 11.6)	-1.96	(-5.72, 1.80)	-3.26	(-7.75, 1.23)
Paternal occupational status								
Working (Ref.)	1.00		1.00		1.00		1.00	
Not working	7.85	(-10.7, 26.6)	2.67	(-23.2, 28.6)	-5.81	(-17.4, 5.83)	-5.26	(-21.5, 11.0)

Coefficients were adjusted for screen hours, pre-pregnancy BMI, hours of sport (8 year), kidmed test (diet), birth weight, sleep hours, number of siblings, age and sex