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The association of childhood obesity with asthma and rhinitis symptoms in 6-8 years old children living in the Coimbra district, Portugal: the role of environmental, family and socioeconomic factors

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"But I don't want to go among mad people," Alice remarked.

"Oh, you can't help that," said the Cat: "we're all mad here. I'm mad. You're mad."

"How do you know I'm mad?" said Alice.

"You must be," said the Cat, "or you wouldn't have come here."

Lewis Carroll, "Alice's Adventures in Wonderland"

Abstract

Introduction: The increase in the prevalence of obesity, asthma, and rhinitis in childhood suggests a link between them. Socio-demographic and early life risk factors, sedentary lifestyle, diet and tobacco exposure, among other factors, could be responsible for the increase in the number of obese asthmatics. There are two main phenotypes of obese asthmatics described so far and one includes children. The existence of obesity-related asthma and rhinitis means that obese children with asthma or rhinitis are not only different from healthy children, but also from normal-weight children with these diseases. Little is known about the effects of the risk factors on the different asthma phenotypes.

Objectives: To investigate how common environmental, family and socioeconomic risk factors for obesity, asthma and rhinitis modulate the association between these diseases and to study whether birth weight (*BW*) values differ between overweight children with asthma/rhinitis and children with asthma/rhinitis and normal weight.

Methods: This cross-sectional study was done in a sample of 1043 children 6-8 years old from the Coimbra district. Data on asthma *(A*), rhinitis *(R)* and environmental and family factors were obtained using the *ISAAC* (The International Study of Asthma and Allergies in Childhood) questionnaires. Obesity indicators were calculated: Body Mass Index (*BMI*); *BMI* z-score based on the World Health Organization's (*WHO*) methodology; Waist to Height Ratio (*WHtR*) and the body fat percentage *(%BF*). Obesity (*OB*) and overweight (*O*) were defined using the *WHO* cut-off points. The cut-off point of WHtR=0.5 was used to define abdominal obesity *(AOB).* %BF values were categorized as normal, overfat (*OF*) and high fat (*HF*) using age and gender-specific percentiles. The risk factors studied were: *BW*; breastfeeding (*BFD*) ever, total *(TBFD)* and exclusive *(EBFD);* tobacco exposure in early life and in childhood; dietary patterns; vigorous physical activity (*VPA*); television (*TV*) watching; heavy truck traffic (*HTT*); degree of urbanization of the residential area and socioeconomic status (*SES*). Chi ^{2} tests were applied to calculate the prevalences of studied diseases. Logistic regressions were used to study the association between *OB*, *A*, and *R* with risk factors. Student's T-test and one-way ANOVA means comparisons were applied to compare means. Logistic regressions were used to study the association of *OB* with *A/R* and the role of risk factors in these associations. One-way ANOVA was performed to compare means of BW between: 1. children with (+) *A*, wheeze (*W*) or *R (A+/W+/R+)* and *O+/OF+;* 2. children *A+/W+/R+* but without (-) *O* or *OF (O-/OF-);* 3. *O+/OF+* but *A-/W-/R-* and 4. children *A-/W-/R-* and *O-/OF-*.

Results: Of all studied children, 23.3% were *O*, 10.8% *OB*. Factors related to a significant increase in *OB* risk were: high *BW*; being a girl; saturated fat diet; lower *SES*; never having been *BFD* or *EBFD*; anyone smoking at home; current maternal smoking (*MS*); *MS*>10cigarettes (cig.) /day and watching *TV*≥3h/day. Factors significantly increasing the risk of *AOB* were: female gender; lower *SES*; urban areas of residence (*UR*); *MS*>10cig/day and child watching *TV*≥3h/day. Factors increasing the risk of having a *HBF* were:

being a boy; lower *SES; UR*; current *MS; MS*>10cig/day and watching *TV*≥3h/day. The prevalence of *A* ever was 10.4%, *R* ever 22.8%. Factors increasing the risk of *A* symptoms were: family history of *A*; higher *SES*; high *BW*; never *BFD*; shorter periods of *TBFD* and *EBFD*; *MS*>10cig/day; *MS* during pregnancy and during the 1st year of the child's life; ≥2people smoking in the household and the child never or occasionally practicing *VPA*. Factors increasing the risk of *R* symptoms were: family history of *R*; high *BW*; not being *BFD* or being *TBFD* and *EBFD* for shorter periods; *MS* during pregnancy and during the 1st year of the child's life; watching *TV*≥3h/day and *HTT*. We found that being *OB* or *O* increased the risk for all *A* and *R* symptoms, with a significant result for *W* 12m (OR=1.79; p=0.01). *OB* had a stronger effect on *A* symptoms for girls than for boys. *AOB* did not show any significant association with *A* or *R*. *HBF* was the strongest predictor of *A* and *R*, significantly increasing the risk of exercise-induced *A* (OR=2.06; p=0.02) and *R* ever (OR=1.57; p=0.02). *HBF* showed a stronger impact on *A* in girls and on *R* in boys. Phenotypes (*BW* comparison): Mean *BW* was the highest for the *A+O+* (3.442kg) and the lowest for *A-O-* (diff. =0.258kg; p= 0.001). The difference was also statistically significant between the group *A-O+* and *A+O+* (diff.=0.160kg; p=0.04). *W+O+* had the highest mean of *BW* (3.357kg), significantly higher than *W-O-* (diff.=0.166kg; p<0.001). Body fat: the highest mean *BW* was observed for *A+OF+* (3.397kg), significantly higher than *A-OF-* (diff.=0.206kg; p<0.01). The difference was borderline significant between *A+OF+* and *A-OF+* (diff. =0.140kg; p=0.07). The highest BW mean was observed for *W+OF+* 3.323kg and the lowest for *W+OF-* (3.196kg) with a difference of 0.127kg (p=0.01). Patterns observed in the case of *A* and *W* were not reproduced for *R*, although children with *R+OB+/OF+* were also born with the highest mean *BW*.

Conclusion: We showed that childhood obesity and especially high body fat levels increase the risk of asthma and rhinitis, which seemed to be independent of common risk factors. Obesity showed a stronger effect on asthma for girls than for boys. Results suggest that the overweight/obese asthmatics might already be born with a predisposition to this phenotype, which might indicate its prenatal origin. High level of asthma heterogeneity highlights the need for individualized, phenotype- or patient-specific prevention, intervention, and treatment strategies.

Key words: childhood obesity, asthma, rhinitis, environmental factors, socioeconomic status, birth weight

Resumo

Introdução: O aumento da prevalência da obesidade, asma e rinite na infância, sugere uma ligação entre eles. Os fatores sócio-demográficos, de início da vida, o sedentarismo, a dieta e a exposição ao fumo de tabaco, entre outros, podem ter aumentando o número de asmáticos obesos. Existem dois principais fenótipos de asmáticos obesos descritos e um deles inclui crianças. A existência de asma e rinite relacionada com a obesidade, significa que crianças com este fenotipo não só são diferentes das crianças saudáveis, mas também das crianças com asma e rinite e peso normal.

Objetivos: Investigar como os fatores ambientais, socioeconómicos e familiares que são comuns para a obesidade, asma e rinite modelam a associação entre estas doenças e estudar se os valores do peso ao nascimento diferem entre crianças com fenotipos diferentes de asma e rinite.

Métodos: Este estudo transversal foi realizado numa amostra de 1043 crianças entre 6-8 anos do distrito de Coimbra. Os dados sobre asma *(A*), rinite (*R*) e os fatores ambientais e socioeconómicos foram obtidos utilizando os questionários do ISAAC (The International Study of Asthma and Allergies in Childhood). Indicadores de adiposidade usados: Índice de Massa Corporal (*IMC*); *IMC* z-score estandardizado para o sexo e a idade (Organização Mundial de Saúde-*OMS*); a relação cintura estatura (do inglês *Waist to Height Ratio - WHtR*) e a % de gordura corporal (ing.*% of Body Fat - %BF*). A obesidade (*OB*) e exesso de peso (ing.*Overweight – O*) foram definidos aplicando os pontos de corte da *OMS*. A obesidade abdominal (*AOB*) foi definida como *WHTR*>0.5. O exesso de gordura (ing.*Overfat – OF*) e gordura elevada (ing.*High Fat – HF*) foram classificados utilizando os percentis específicos para a idade e sexo. Os fatores de risco estudados foram: peso ao nascimento (ing.*Birth Weight – BW*); aleitamento materno (ing.*Breast feeding – BFD*) e períodos de aleitamento total (ing.*Total breast feeding –TBFD*) e exclusivo (ing.*Exclusive breast feeding – EBFD*); dieta; atividade física vigorosa (ing.*vigorous physical activity -VPA*); tempo de ver televisão (*TV*); tráfego de camiões na área de residência; grau de urbanização da área residencial e nível socioeconómico (ing. *Socioeconomic Status - SES*). O teste Chi^2 foi aplicado para calcular as prevalências de doenças. Foi usada a Regressão Logística para estudar a associação entre *OB, A* e *R* com fatores de risco, e também para estudar o papel destes fatores na associação da *OB* com a *A* e *R*. Foram aplicados o Teste t de Student e one-way ANOVA para comparação de médias. Foram usadas regressões logísticas para estudar a associação da *OB* com *A* e *R* e o papel dos fatores de risco nessas associações. Foram usados os testes One-way ANOVA e ANCOVA para comparar as médias de BW entre crianças 1. com (+) *A*, pieira (ing.*Wheeze - W*) ou *R (A+/W+/R+)* e tambem com *O* ou *OF (O+/OF+)*; 2. as crianças *A+/ W+/R+* mas sem (-) *O* ou *OF* (*O-/OF-);* 3. Crianças *O+/OF+*, mas *A-/W-/R-* e 3.crianças *A-/W-/R-* e *O-/OF-*.

Resultados: 23.3% das crianças estavam com *O* e 10.8% com *OB*. Os fatores que aumentaram o risco de *OB* foram: elevado *BW*; sexo feminino; dieta rica em gordura saturada; menor *SES*; nunca *BFD* e *EBFD*; ter alguém a fumar em casa; a mãe fumar (ing.*Maternal smoking - MS*) atualmente; *MS*>10cigarros (cig.)/dia e

ver *TV*≥3h/dia. Os fatores que aumentaram o risco de *AOB* foram: sexo feminino; menor *SES*; as áreas de residência urbanas (*UR*); *MS*>10cig./dia e ver *TV*≥3h/dia. Os fatores que aumentaram o risco de *HF* foram: sexo masculino; menor *SES*; as *UR*; *MS* atualmente; a *MS*>10cig./dia e ver *TV*≥3h/dia. A prevalência de *A* foi de 10.4%, e de *R* de 22.8%. Os fatores que aumentaram o risco de *A* foram: história familiar de *A*; maior *SES*; alto *BW*; nunca *BFD*; períodos mais curtos de *TBFD* e *EBFD*; *MS* atual; *MS*>10cig./dia; *MS* durante a gravidez e durante o 1 º ano de vida da criança; ≥2pessoas fumar em casa e a criança nunca ou ocasionalmente praticar *VPA*. A aumentarem o risco de R foram: história familiar de *R*; *BW* elevado; nunca *BFD* ou um período mais curto de *TBFD* e *EBFD*; *MS* durante a gravidez e durante o 1º ano de vida da criança; ver *TV*≥3h/dia e tráfego frequente de camiões na área de residência. Mostrou-se que *OB* ou *O* aumentaram o risco de todos os sintomas de *A* e *R*, com um resultado significativo para *W* nos últimos 12 meses (12m) (OR = 1.79, p = 0.01). A *OB* tinha um efeito mais forte sobre a *A* para as meninas do que para meninos. *AOB* não mostrou associação significativa com a asma, nem rinite. O indicador mais forte de *A* e *R* foi *HF* e aumentou o risco de *A* de esforço (OR = 2.06, p = 0.02) e *R* (OR= 1.57, p = 0.02). *HBF* mostrou um forte impacto sobre a *A* em meninas e sobre a *R* em meninos. A média *BW* foi maior para *A*+*O*+ (3.442kg) e menor para *A*+*O*- (diferença de 0.258kg, p =0.001). A diferença (dif.) também foi significativa entre *A*-*O*+ e *A*+*O*+ (dif.=0.160kg, p=0.04). *W*+*O*+ teve a maior média de *BW* (3.357kg), maior do que o *W*+*O*- (dif.=0.166kg, p<0.001). Gordura corporal: a maior média do *BW* foi observada para *A*+*OF* + (3.397kg), maior do que a do *A*-*OF*- (dif.=0.206kg, p=0.005). A maior média do *BW* foi observada para *W*+*OF*+ 3.323kg e a menor para *W*+*OF*- (3.196kg), com a diferença de 0.127kg (p=0.01). Os padrões observados no caso de *A* e *W* não foram reproduzidos para *R*, embora as crianças com *R* e valores altos de adiposidade também tenham nascido com a maior média *BW* de todos os grupos.

Conclusão: Mostramos que a obesidade infantil e especialmente a a percentagem de gordura corporal elevada aumenta o risco de asma e rinite, que foi independente dos fatores de risco comuns. A obesidade está associada ao maior risco de asma nas meninas e de rinite nos meninos. Os resultados de comparação ao nascimento sugerem que os asmáticos com exesso de peso ou obesidade já nascem com predisposição para este fenótipo de asma, o que indica a sua origem pré-natal. O alto nível de heterogeneidade de asma destaca a necessidade de aplicação de estratégias de prevenção, de intervenção e de tratamento individualizadas, específicas para o fenótipo do paciente.

Palavras-chave: obesidade infantil, asma, rinite, fatores ambientais, nível socioeconómico, peso ao nascimento

Acknowledgments

If your actions inspire others to dream more, learn more, do more and become more, you are a leader. (John Quincy Adams)

Six years ago I was only dreaming of becoming a PhD student in University of Coimbra, in the charming country that is Portugal, with the people with the biggest hearts. I remember how happy I was when Prof. Cristina Padez replied my email, accepting me as her student, and giving me hope. Later on, she convinced me "not gave up so soon" and told me "You need to fight for what you want". And I did. I fought, and I won. And I will keep fighting, because these four years of the PhD, with all the successes and difficulties it served me, convinced me I want to be a scientist, and do my best, and a little bit more, to achieve it. I would like to thank Prof. Cristina Padez for all these years of showing me what the life of a scientist is like, sharing her experience and expertise, for all the support and supervision, for the critics and encouragement.

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Mix a little foolishness with your serious plans. It is lovely to be silly at the right moment. (Horace)

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Why, sometimes I've believed as many as six impossible things before breakfast. (Lewis Carroll)

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Success consists of going from failure to failure without loss of enthusiasm. (Winston Churchill)

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A friend is someone who gives you total freedom to be yourself-and especially to feel, or not feel. Whatever you happen to be feeling at any moment is fine with them. That's what real love amounts to - letting a person be what he really is. (Jim Morrison)

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O lar é onde o coração do homem cria raízes. (Henrik Ibsen)

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Nudge, nudge, wink, wink. Know what I mean? (Monty Python)

I know you do, Moj Narzeczony.

Kochasz ty dom, rodzinny dom, / Co wpośród burz, w zwątpienia dnie, / Gdy w duszę ci uderzy grom,/ Wspomnieniem swym ocala cię? (Maria Konopnicka)

Najtrudniej mi przychodzi podziękować rodzinie, bo słowa tego ogromu wdzięczności nie uniosą. Mam rodzinę idealną. Wyniosłam z domu opór i wytrwałość w dążeniu do celu. Nauczyliście mnie szacunku do pracy i tego, że nie ważne co się w życiu robi, trzeba to robić najlepiej jak się potrafi. Mamusiu, tatusiu, nigdy niczego bym nie osiągnęła, gdybyście we mnie nie wierzyli, i gdybym nie wiedziała, że mogę polegnąć i ponieść najbardziej gorzkie porażki a potem wrócić do miejsca, gdzie jestem najważniejsza na świecie, i przypomnieć sobie co naprawdę jest w życiu ważne. Izabela, wiem, że zawsze mogłam na Ciebie liczyć i, że byłaś dumna ze mnie na każdym kroku, tak jak ja jestem dumna z Ciebie i z tego jakim jesteś człowiekiem. Jesteś uzupełnieniem wszystkich moich braków i dziękuje za to, że mimo, że często byłaś daleko, byłaś zawsze obok, kiedy najbardziej tego potrzebowałam. Dziękuję Babci Zosi, Dziadziusiowi Marianowi, Babci Olesi i Dziadziusiowi Heniusiowi. Nie tylko jesteście moja najukochańsza rodzina, ale najbliższymi przyjaciółmi, którzy zawsze stoją za mną murem, wierzą we wszystko co robię, wysłuchują moich smutków i radości, wiedza o mnie wszystko i którym zawdzięczam, to kim jestem.

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Dziekuje!

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1. General Introduction

1.1. Diseases of affluence

As reported by the World Health Organization (WHO) the average world life expectancy at birth increased from 48 years in 1955 to 65 years in 1995 and is expected to reach 73 years in 2025. Additionally, the WHO prognosis states that by the year 2025 no country will have a life expectancy of lower than 50 years (WHO, 1998, 2011).

In 1990 in Portugal, the average life expectancy was 74 years; it went up to 77 years in the year 2000. More recently, in 2011 it was reported to be as high as 80 years (WHO, 2011).

Another important observable indicator of the development of medical, health care and living conditions is provided by the rates in child mortality trends under the age of 5. In the developed world, the under 5 mortality rate (U5MR) per 1000 births was estimated as 15 in the year 1990, dropped down to 10 a decade later in 2000, and decreased further to 7 deaths per 1000 births in 2011. In Portugal, the rates are even lower: starting from the same level of 15 deaths under 5 years old per 1000 births in 1990, it dropped down to 7 in the year 2000 and further decreased to only 3 deaths in 2012 (You, New, & Wardlaw, 2012).

Compared to developing countries, where people's access to health care, economic situation and standard of living are lower, the U5MR is much higher and a source of great concern. In 1990, as many as 97 children per 1000 births died before the age of 5. Despite decreasing rates, the number of deaths is still high, with 80 deaths reported in 2000, decreasing to 57 deaths in 2011 (You et al., 2012). To summarize, the death rate of children under the age of 5 is ten times higher in the developing as compared to the developed world.

Nevertheless, as evolutionary medicine teaches us, advances also come with trade-offs. While in the developed world, infectious diseases and parasites have started to lose the battle against modern medicine armed with new antibiotics, anti-inflammatory drugs, prevention, interventions and other measures, another group of diseases has unexpectedly hit with more power. These are so called diseases of affluence, as they are observed to gain higher prevalence in wealthier and more developed populations. These diseases, also known as the "Western diseases," are associated with improving life conditions, economic development of societies, and changing lifestyles. Most examples of these are furnished by non-communicable diseases (NCDs), since these diseases are not transmittable (infectious) between individuals (in other ways than through hereditary, genetic predisposition). A few examples of such diseases are obesity, asthma, some allergies, type-2 diabetes, coronary heart disease, and cancer (Ezzati et al., 2005).

Obesity, asthma and rhinitis are diseases that have been increasing in recent decades and are described widely in the epidemiological literature. They are mentioned as most likely caused by the westernization of the world, but also obesity has been found to increase the risk of asthma and rhinitis (Van Cleave, Gortmaker, & Perrin, 2010). The large and pathologically specific group of obese patients with asthma has attracted the attention of scientists and medical doctors worldwide.

1.2. Obesity

Overweight and obesity are defined by the WHO as excess fat accumulation that presents a risk to health (WHO, 2013a). Obesity has become an acute focal point of research, as it is a strong risk factor for various diseases, including cardiovascular disease, diabetes, asthma, orthopaedic diseases, and some forms of cancers, not to mention the stigma and low self-esteem that obese people suffer (Guh et al., 2009). Looking at the aetiology of obesity in a very simplistic way, we can say that these conditions appear when the energy consumed by the individual exceeds its expenditure by the organism. By now we know that several factors underlie this health problem (Galvez, Pearl, & Yen, 2010; Gluckman, Hanson, Zimmet, & Forrester, 2011; Prentice, Hennig, & Fulford, 2008; Wang & Lim, 2012a).

The tendency to store additional consumed energy in the form of fat is a strong evolutionary adaptation. Up until the last several decades, for hundreds of thousands of years, most humans were exposed to alternating periods of nutritional abundance and scarcity. Not only a cultural capacity to store the excess of food for rough times, but also and more importantly the physiological capacity to store extra energy in the form of fat tissue were crucial survival strategies (Prentice et al., 2008; Speakman, 2007). Recent developments in technology, transportation and food preservation, and the rapid urbanization and westernization of world civilizations has led to common, easy and cheap access to large quantities of food. Evolution remained far behind these social and cultural developments, and our bodies are still programmed to store whatever excess we consume for times of deprivation, which now rarely occur, at least in developed countries (Speakman, 2007). In industrialized countries, almost simultaneously with increasingly easy access to highly caloric foods, people developed a highly sedentary lifestyle. We have limited our walking due to widespread ownership of cars and easy access to public transport. Due to technological innovations, more and more work tasks are performed from behind a desk. TV, computers, or consoles fill our leisure hours. With the Internet arriving at virtually every household in developed and developing countries, many aspects of our life have been transferred to the computer. This has caused a dangerous decrease in the expenditure of energy (Bingham et al., 2013; Machado-Rodrigues et al., 2012; Stamatakis et al., 2013). In consequence, not only do we consume significantly larger amounts of calories

but we use less and less in our daily activity, which results in rising epidemics of weight problems and obesity (Jacobs, 2006; Peters, Wyatt, Donahoo, & Hill, 2002).

There are many other factors involved, such as early life factors including birth weight and breastfeeding, second-hand exposure to tobacco, and many other behavioural, familial and environmental factors that we will explain in more detail in further chapters.

We are now aware that adipose tissue is not merely for storage of spare energy consumed but not used. Adipose tissue is a physiologically complex and highly active metabolic and endocrine organ, secreting various hormones (adipokines), regulating the appetite in the central nervous system, as well as regulating insulin, fatty acid levels and gender hormones precursors (Guerre-Millo, 2004; Proietto, Galic, Oakhill, & Steinberg, 2010). Though maintaining the right level of this tissue is crucial for the healthy functioning of our bodies, excess amounts of it are associated with various life-threatening conditions, such as type-2 diabetes, cardiovascular diseases, high blood pressure, some types of cancer, obstructive sleep apnoea, and asthma (Guh et al., 2009; Hursting, 2014; Liu, Kieckhefer, & Gau, 2013; Park, Falconer, Viner, & Kinra, 2012; Rice et al., 2012). Therefore, the increasing rapidly prevalence of obesity and weight problems, especially in developed countries, has alarmed health professionals and led to a series of studies of this public health problem. According to the WHO, in 2008, over 1.4 billion adults over 20 years of age were overweight, among them approximately 200 million men and 300 million women who were obese (WHO, 2013a).

Childhood obesity rates are just as alarming. In 2010, the number of overweight children under the age of five was estimated to be over 42 million, of whom 35 million were living in developing countries (WHO, 2014). The highest rates of obesity are observed in the Americas and eastern Mediterranean regions; the lowest, in the south-east Asian, western Pacific, and African regions (Wang & Lim, 2012b).

We now know that obese children are at higher risk of becoming obese adults, and developing serious comorbidities such as type 2 diabetes, arterial hypertension, dyslipidaemia, cardiovascular diseases, stroke, gallbladder disease, osteoarthritis, sleep apnoea, asthma, and certain cancers such as colorectal, breast, endometrial, renal, oesophageal, gallbladder, melanoma, multiple myeloma, leukaemia, lymphoma and prostate cancer (Biro & Wien, 2010; Shehzad, Khan, & Sup Lee, 2012). Moreover, there are psychological issues affecting these children: in particular, lower self-esteem (Strauss, 2000) and a higher predisposition to bullying (Griffiths, Wolke, Page, & Horwood, 2006).

On balance, the obesity epidemic has now become a heavy burden not only on those carrying the extra weight and their relatives, but also for public health systems and health policy

(Kiess et al., 2013). Reaching to the roots of the problems and preventing rather than simply treating has once again become a priority for professional specialists in dealing with the problem of obesity, and the importance of studies and interventions in this field needs to be constantly underlined.

1.3. Asthma and rhinitis

Similarly, an increase in the prevalence of another group of diseases, namely asthma and allergies (Masoli, M., Fabian, D., Holt, S., & Beasley, 2004; Pawankar, Canonica, Holgate & Lockey, 2011), has been observed in recent decades. This rapid increase, with clearly observable social and demographic patterns, again suggests changes in lifestyle to be the putative culprit (von Hertzen & Haahtela, 2004).

Asthma is a chronic inflammatory disorder of the respiratory system characterized by a decline in pulmonary function that is correlated with age and the duration and severity of the disease. Since more than 300 million individuals suffer from this disease and its prevalence is increasing, its importance to studies in this field has also increased. It is often reported in children but affects all age groups (Vale-Pereira et al., 2011). According to the guidelines of the Global Initiative for Asthma (GINA), asthma is defined as follows:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. Chronic inflammation is associated with hyper responsiveness of the airways, leading to recurrent episodes of wheezing, breathlessness, tightness in the chest, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung, often reversible either spontaneously or with treatment.(Bateman et al., 2008)

A high level of morbidity and mortality characterizes this most common chronic disease of childhood. The onset of asthma begins mostly before the age of 10 and is a serious health problem with a decrease in quality of life (Asher et al., 1995).Asthma is a chronic respiratory dysfunction and treatments for it have focused on eliminating or diminishing the symptoms. Besides causing everyday discomfort and stress, asthma and allergies are also a financial burden for families and public health systems. With this in mind, the focus of the response has been put on investigating atopic diseases, determining their risk factors, and efforts to design prevention programs, control the development of asthma, or minimize its consequences.

Epidemiologists, after close and detailed analyses of the asthmatic spectrum, pointed out the necessity of distinguishing not only different asthma phenotypes (different observable

characteristics of the same disease) but also endotypes (different pathophysiological origins of the same disease) (Agache, Akdis, Jutel, & Virchow, 2012; Lötvall et al., 2011). This complexity under the same disease label complicates the study of this pathology and the drawing of uniform conclusions.

Asthma has a very strong genetic component, and new genes contributing to its development and severity continue to be found (Bønnelykke et al., 2013; Melén et al., 2011; Ober & Yao, 2011). Nevertheless, environmental, behavioural, and socioeconomic risk factors significantly modulate the development and course of the disease (Asher et al., 2010; Salam, Li, Langholz, & Gilliland, 2004).

As reported by the WHO, asthma deaths are most frequent in lower and lower-middle income countries. Studies also show that the prevalence of the disease increases together with the increase in westernization and urbanization processes in societies (Douwes, 2002; Ezzati et al., 2005; Hasan, Gofin, & Bar-Yishay, 2009; Nicolaou, Siddique, & Custovic, 2005). Although prevalence differs among different countries, levels seem to be equalizing due to the increasing incidence of the disease in developing countries and its simultaneous reaching a plateau in developed ones (Pawankar, Canonica, Holgate & Lockey, 2011).

Rhinitis is a respiratory condition characterized by irritation and excessive mucus secretion of the nasal mucosa associated with inflammation usually triggered by allergen exposure (Skoner, 2001). Most cases of rhinitis are allergic (43% of patients have allergic, 34% mixed allergic and non-allergic rhinitis and only 23% non-allergic rhinitis), and the most common symptoms are runny and itchy nose, stuffy nose, itchy and tearing eyes, sometimes reddened puffy eyes, sneezing, headaches, coughing, and others. These symptoms can appear in any combination (Kaliner, Scarupa, 2005). Although there are a number of medications available to fight the symptoms of rhinitis, the main prevention and treatment path is the avoidance of allergens and other triggers (Skoner, 2001; Sur & Scandale, 2010). According to the World Allergy Organization, the most common allergens (globally) are dust mites, tree and grass pollens, pets' allergens, cockroaches, moulds and weed pollens (Pawankar, Canonica, Holgate & Lockey, 2011).

Rhinitis is a very common condition, its prevalence estimated at between 24-28% (Kaliner, Scarupa, 2005). Although it is rarely a cause of death, it accounts for lower quality of life, worse school performance, and absenteeism (Jáuregui et al., 2009; Mir, Panjabi, & Shah, 2012).

Asthma and rhinitis are two strongly associated diseases. Both are caused by inflammation of the airways, often triggered by allergens and other common risk factors

(Compalati et al., 2010; Leynaert, Neukirch, Demoly, & Bousquet, 2000; Simons, 1999; Valero et al., 2009). The intensity, duration, control, and remission of asthma have been associated with the severity of rhinitis (Togias, 2003). The strong association between the two conditions induces the necessity of a concomitant approach to their exploration.

As mentioned before, both asthma and rhinitis are associated with a westernized lifestyle. More specifically, the putative elements contributing to the increase in the prevalence of these diseases are, among others, changes in diet (both the change in quantity and the quality of such) (Barros et al., 2008; Sexton et al., 2013), sedentary lifestyle (Konstantaki et al., 2013; Mitchell et al., 2013), air pollution (Clark et al., 2010; Rob McConnell et al., 2010; Patel & Miller, 2009), time spent indoors (Gent et al., 2009; McCormack et al., 2011), altered exposure to infectious agents ("hygiene hypothesis") (Figueiredo et al., 2013; Okada, Kuhn, Feillet, & Bach, 2010; Umetsu, 2012), and medication use (Muc, Padez, & Mota Pinto, 2013).

1.4. Association between asthma and obesity

The parallel increase in prevalence of obesity and asthma in childhood suggests a link between the two. Indeed, numerous cross-sectional (Black, Smith, Porter, Jacobsen, & Koebnick, 2012; Okabe et al., 2012) and longitudinal studies (Jeong et al., 2010; Taveras et al., 2008) tend to concur in confirming such an association. As presented in the recent review by Papoutsakis et al., (2013) 12 out of 13 cited prospective studies run between 2006-2010 confirmed the association between high body weight and subsequent development of asthma; however, there is still no consensus about the causality or mechanism of that link (Farah & Salome, 2012).

A recent study on allergies and asthma involving 8 European birth cohorts of 12,050 children found an association between the gender and age specific Body Mass Index (BMI) trajectories during the first 6 years of life and the incidence of asthma. The rapid increase in body mass in the first 2 years of life appeared to be the strongest predictor of asthma incidence later in childhood (Rzehak et al., 2013).

Although BMI is the most common and easiest measure of adiposity, obtaining it assesses total body mass, without clarifying the real contribution of fat tissue in the total mass or the distribution of it there. There is strong evidence demonstrating that not only total body mass but also fat distribution can modify the effect of adiposity on health. Abdominal obesity is the clinical name for accumulation of fat tissue in the abdominal area, also known as abdominal obesity; it seems to be an additional strong risk factor for comorbidity in relation to obesity for diseases including asthma (Musaad et al., 2009). Abdominal obesity, often measured by waist circumference and its derivative waist-to-height ratio (WHtR), is considered more accurate than

BMI, as it has been shown that fat distribution is an important factor in obesity-related comorbidities in children (Silva et al., 2013).

In the literature there are several links concerning the association between asthma and rhinitis with obesity (Ali & Ulrik, 2013). Epidemiological studies have shown and highlighted that the risk of developing asthma and rhinitis is significantly higher with a positive family history of atopic diseases, with a very significant increased risk when there is a history of maternal atopy (Bjerg et al., 2007; Burke, Fesinmeyer, Reed, Hampson, & Carlsten, 2003; Litonjua, Carey, Burge, Weiss, & Gold, 1998). Likewise, a family history of obesity is a strong risk factor for this condition (Whitaker, Jarvis, Beeken, Boniface, & Wardle, 2010). This highlights the need to research the genetic contribution to the obesity and related problems of asthma patients. Indeed, investigating the putative genetic background for both asthma and obesity highlighted some genes as candidates (Melén et al., 2010).This does not, however, explain the full variation of the disease, and further hypotheses had to be tested to reach a deeper understanding of the phenomenon.

One hypothesis has been designed, suggesting that higher prevalence and severity of asthma among obese patients could be the result of misclassification. Asthma-like symptoms such as shortness of breath and wheezing could appear as the result of the excess of thoracic and abdominal fat mass that mechanically restricts respiration (Salome & King, 2013). This would stiffen the movement of the lungs and diaphragm and cause shortness of breath, oxidative stress, and, as a result, reduction of resting lung volumes such as functional residual capacity (FRC) (Brashier & Salvi, 2013). There are voices claiming that there might be an over-diagnosis of asthma among obese patients due to the dyspnoea resulting in mechanical restriction (Sah et al., 2013) and indeed this has been shown to be truth in some cases, with a substantial amount of underdiagnoses observed as well (van Huisstede et al., 2013). Another study, however, showed that over diagnosis is no more likely in cases of obesity than it is in non-obese individuals (Aaron et al., 2008).

There might also be a pharmacological contribution to the increased body mass in asthmatic individuals. Evidence exists indicating that treatment with steroids, very commonly used for asthma, is associated with a higher annual body mass gain, and the association might be dose-dependent (Jani, Ogston, & Mukhopadhyay, 2005).

Although these factors might indeed contribute to the association between these two conditions, one of the strongest pieces of evidence points to the physiological activity of the fat tissue. Adipocytes, the cells constituting the fat tissue, produce hormones called adipokines. Adipokines (or adipocytokines) are cytokines secreted by adipose tissue, and their main role is the regulation of the hunger and satiety and therefore are the mediators controlling the energy

homeostasis (Trayhurn, Bing, & Wood, 2006; Trayhurn & Bing, 2006). These hormones have also been shown to be the mediators of inflammation processes (Balistreri, Caruso, & Candore, 2010; Maury & Brichard, 2010). Adipokines such as leptin or resistin produced in excess due to obesity (and consequently high fat tissue levels) (Muc, Todo-Bom, Mota-Pinto, Vale-Pereira, & Loureiro, 2013) play a role in the course of inflammation, promoting pro-inflammatory responses (Monti, Carlson, Hunt, & Adams, 2006). Due to this aspect of the adipokines, their role in asthmatic inflammation has been studied. Indeed, receptors for leptin have been found in lung tissue (Bergen, Cherlet, Manuel, & Scott, 2002), which has strengthened the hypothesis relating adipokines to asthma pathogenesis. Various studies have observed increased concentrations of adipokines in asthmatic and allergic patients (Baek et al., 2011; Tsaroucha et al., 2013), and lately, leptin has been shown to regulate the dilution of airways through the neuro-immune pathways regulating the activity of the parasympathetic nervous system (Arteaga-Solis et al., 2013). This all indicates that pro-inflammatory processes, which activate adipose tissue endocrine pathways, are a strong factor linking obesity and asthma.

Both obesity and asthma, as described above, are classified as diseases of affluence, and their prevalence has increased significantly over the past few decades. It has been suggested that the westernized lifestyle played a significant role in these disease epidemics (Huneault, Mathieu, & Tremblay, 2011). Patterns of prevalence have increased, seeming to prove this hypothesis, since they follow the countries' development and westernization (Douwes, 2002; Wang & Lim, 2012b). As a natural consequence of this analysis, the question arose whether the association between asthma and obesity could be explained by the existence of common risk factors due to changing environment and lifestyle. The risk factors related to the westernized lifestyle that led to an increase in cases of obesity and asthma could also have led to the increase in the number of obese asthmatics. There are a number of common factors observed to be promoting both conditions, such as sedentary lifestyle (Konstantaki et al., 2013; Prentice-Dunn & Prentice-Dunn, 2012), dietary changes (Esposito, Kastorini, Panagiotakos, & Giugliano, 2011; Myers & Allen, 2011; Patterson, Wall, Fitzgerald, Ross, & Stanton, 2012; Popkin, Adair, & Ng, 2012; Sexton et al., 2013), vitamin D insufficiency due to lower exposure to sunlight (Foss, 2009; Hollams et al., 2011; M. L. Olson, Maalouf, Oden, White, & Hutchison, 2012; Sutherland, Goleva, Jackson, Stevens, & Leung, 2010), and tobacco exposure (Ino, 2010; Neuman et al., 2012; Tsai, Huang, Hwang, & Lee, 2010), among others.

One of many questions frequently posed in discussions of this topic is: what appears first in this specific group of patients, asthma or obesity? Although the association may be bi-directional, prospective studies suggest that obesity precedes and is a risk factor for development of asthma (Beuther & Sutherland, 2007). However this "chicken or egg" question is much harder to answer than it might seem, due to the difficulty of determining the exact

moment when the two diseases set in. What we usually treat as the onset of asthma is the moment when the first symptoms are observed and when the diagnosis is made. This, however, does not mean that the pathological state leading to these symptoms or to other physiological alterations did not appear earlier. Prospective studies show that children who are diagnosed with asthma in childhood already have altered respiratory function in their infancy, which suggests that the disease might originate in the prenatal state (Bisgaard, Jensen, & Bønnelykke, 2012).

A similar situation exists with regard to obesity. We know by now that prenatal and perinatal factors such as birth weight, maternal weight gain, and diet considerably alter the risk of developing obesity later in the child's life (Levin, 2007; Picó, Palou, Priego, Sánchez, & Palou, 2012). Moreover, the impact of the increased neonatal size on the development of asthma at the age of 7 has been observed in a Danish cohort from the COPASAC (The Copenhagen Prospective Study on Asthma in Childhood) study, and the children developing asthma by the age of 7 already as neonates expressed lung function deficit and increased bronchial responsiveness (Sevelsted & Bisgaard, 2012). As both diseases often begin before the moment of birth, claiming a causal relationship is difficult.

Although the association appears at all ages, its relation with regard to gender changes in proportion as people age, being stronger in males in childhood (Chen, Dong, Lin, & Lee, 2013) and skewing towards females in the adulthood (Chen, Dales, Tang, & Krewski, 2002).

The state of being obese and asthmatic is much more consistent in adulthood. There is strong evidence in literature that the phenotype of obese asthmatic is more prevalent among adult women, especially at the post-menopausal age (Sood, 2011; Sood et al., 2013). Hormonal changes related to menopause could be one indicated factor which could explain this dimorphism, suggesting that the postmenopausal estrogen-based therapy increases the development of asthma symptoms in women (Troisi, Speizer, Willett, Trichopoulos, & Rosner, 1995). The answers could also lie in fat distribution and composition. Adipokines have been shown to be more strongly associated with asthma symptoms in women than in men (Sood et al., 2012). This once again points toward the endocrine function of adipose tissue. Not every type of fat has the same physiological activity; ectopic fat (deposition of triglycerides within cells of non-adipose tissue) has been shown to be more physiologically active within the viscera and skeletal muscle, and therefore to produce more adipokines, which can promote asthmatic inflammation. This fat, although it exists in lower quantities in women, is more physiologically active (Sood, 2011). This could partly be the reason for higher prevalence of obesity-related asthma in adult women than in men.

The situation is less clear and more difficult to explain in children. There are many inconsistencies in the reports on obesity-related asthma among children (Chen et al., 2013;

Willeboordse et al., 2013). Discrepancies may reflect differences in methodology, as there are not only various markers of obesity used but also different definitions of asthma. The mechanism justifying higher prevalence of obesity related to asthma among boys is fairly unclear, but those sources reporting a stronger association among girls suggest similar explanations to those in adults, pointing at adipokines production (Sood, 2011) and early menarche caused by increased body mas, associated with higher risk for asthma(Varraso, Siroux, Maccario, Pin, & Kauffmann, 2005). Genetic predisposition of girls toward this asthma phenotype has also been mentioned in the literature (Arriba-Méndez et al., 2008).

Despite the growing evidence on the asthma-obesity association, there is no consensus on causality and mechanism.

Regardless what the links of mechanism and causality are between the two diseases, the fact is that obesity is related to higher hospitalization rates for asthma as well as higher doses of medications required for control of the disease, and it seems to be a dose-dependent association (Quinto et al., 2011). For obese patients with asthma and their families this equals higher medication costs, and a more difficult and less effective treatment, which constitutes a heavy burden and results in the lowering of their quality of life. Moreover, this problem is related to increased economic costs for public health systems as well. To avoid these issues, prevention and lifestyle interventions are of great importance. As the phenotype of asthma, associated with obesity, seems to be a specific condition, it is necessary to study it independently. This distinct group of patients may be characterized by different environmental, socioeconomic and family risk factors than non-obese asthmatics and non-asthmatic obese children. An in-depth knowledge of the risk factors for development of obesity-related asthma and rhinitis is essential in order to design effective, evidence-based prevention and intervention programs.

2. Aims and objectives

The main aim of this work was to investigate the role played by environmental and socioeconomic factors in the association between asthma and rhinitis symptoms and obesity (See Figure 2.1.).

To achieve this goal we have set ourselves the following specific objectives:

- Estimate the prevalence of obesity and overweight among 6-8 year-old children from the Coimbra district
- Estimate the prevalence of asthma and rhinitis symptoms
- Recognize the risk factors for obesity in the studied population
- Recognize the risk factors for asthma and rhinitis in the studied population
- Investigate how common environmental and socioeconomic risk factors for these diseases modulate the association between obesity, asthma and rhinitis, and therefore whether the link between obesity and asthma and rhinitis can partly be explained by these epidemiological similarities.
- Verify whether the differences between obese and non-obese asthmatics can be identified at birth

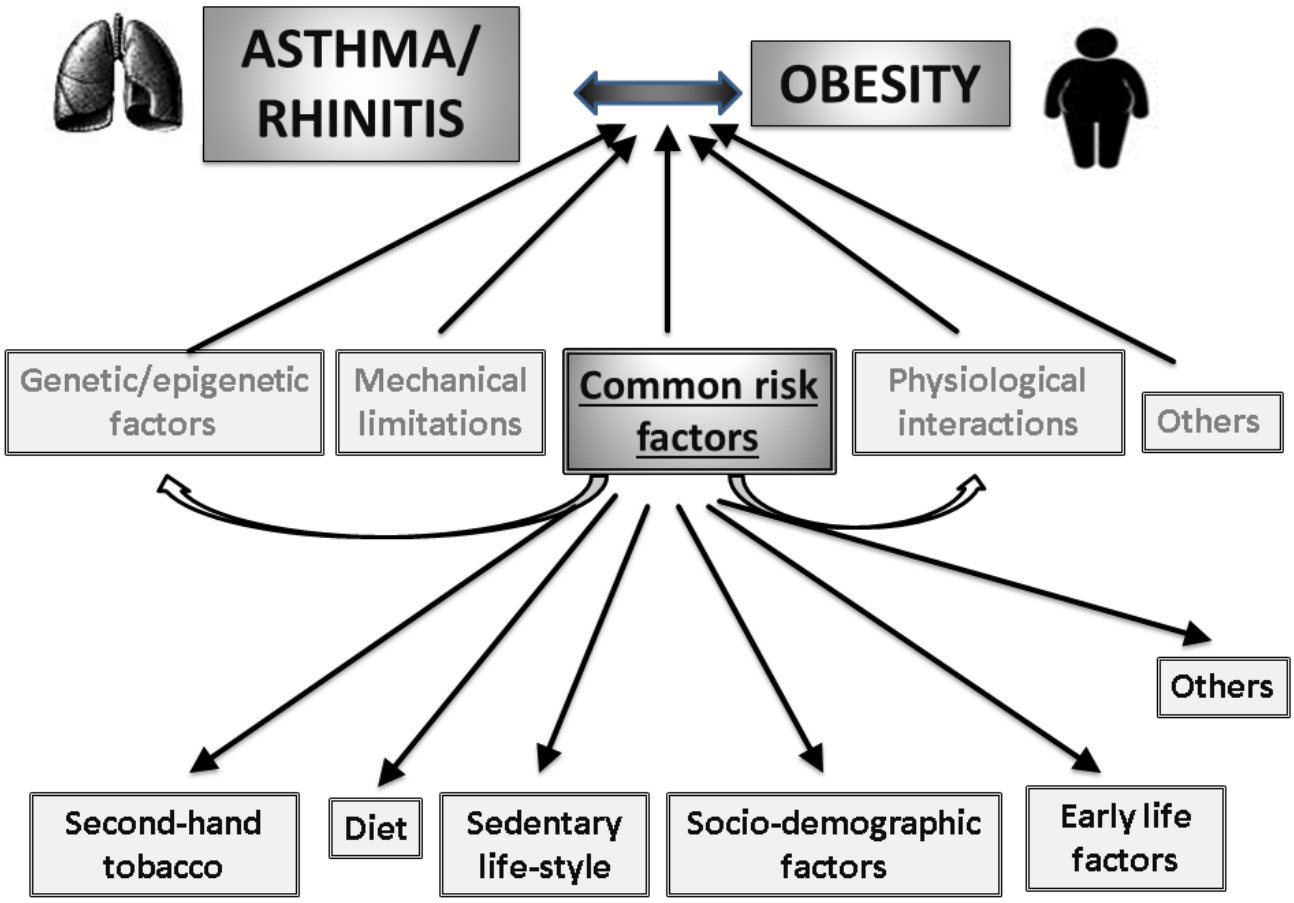


Figure 2.1. Graphical representation of the study hypothesis.

We hypothesized that there was an association between asthma, rhinitis and obesity in studied population of 6-8years old children living in Coimbra, and that this association could party be explained by the existence of the common risk factors modulating the risk of developing these two

3. General Methodology

3.1. Design and study participants

A cross-sectional study was done in a sample of children 6-8 years old from Coimbra district, attending elementary school. Children from both public and private schools, located in urban, suburban, and rural areas of the district, were invited to participate in the study. No pre-selection, apart from the geographical location within the district, was applied. Information on children's asthma and rhinitis symptoms was obtained using questionnaires, and the obesity evaluation was made using anthropometric measures. School clusters (*Agrupamentos* in Portuguese) were initially asked to collaborate through letters containing a request for their participation, ethical authorizations of the project, sample questionnaires, and letters addressed to the children's legal guardians. The authorization of these cluster requests was obtained by telephoning each school's headquarters. If authorization was granted, questionnaires containing questions about the respiratory health of children and their families and various environmental and family factors were distributed among the parents/legal guardians of children from 1st and 2nd grade in primary school. Attached was the authorization form to take the anthropometric measurements of each child. Parents/legal guardians had approximately a week to return the questionnaires, unless requested otherwise by the school headquarters. Only children with the signed authorization were measured and included in the further process. Authorization used can be found in the Appendix 1.

Data on children's asthma and rhinitis symptoms were obtained using the ISAAC (The International Study of Asthma and Allergies in Childhood) asthma and rhinitis and questionnaires. Similarly, environmental and family factors were verified using methodology provided by ISAAC. The questionnaire had previously been translated and adapted to Portuguese realities for the purposes of an ISAAC study in Portugal. The questionnaire can be found in the attachments (Appendix 2). The ISAAC questionnaires were expanded to include questions we deemed necessary for the objective of the study and which are marked with stars (*).

3.2. Anthropometric measurements

The weight of each child was measured using digital scales (Seca, United Kingdom, Birmingham, England), registered with accuracy of 100 grams. Height was measured with stadiometer (Seca, United Kingdom, Birmingham, England) and registered with accuracy of 5mm. Measurements of the waist and upper arm circumferences were taken using the tape measure with the accuracy of 5mm (Seca, United Kingdom, Birmingham, England). Using the skinfold clipper, triceps, suprailiac, and subscapular skinfolds were measured, all from the left side of the body (Seca, United Kingdom, Birmingham, England).

Using the measures described above, the following indexes of body mass and composition were calculated:

Body Mass Index (BMI) calculated with the formula: BMI= kg/m^2, where "kg" stands for weight in kilograms and "m" for height in meters.

Waist-to-Height Ratio (WHtR) calculated as the waist circumference divided by the height, with both given in cm.

Fat percentage using the Slaughter (Slaughter et al., 1988) equation = 1.33* (TSF+SSF) – 0.013* $(triceps+subscapular)^2$ – 2.5 for girls and 1.21* (triceps+subscapular) – 0.008* $(triceps+subscapular)^2$ – 3.2 for boys where TSF stands for the Triceps Skin Fold and SSF for the Subscapular Skin Fold in mm.

MUAMC (mid-upper arm muscle circumference) = MUAC – (Π*TSF), where MUAC stands for the Mid-Upper Arm Circumference in cm and TSF for the Triceps Skin Fold in cm.

MUAMA (mid-upper arm muscle area) =$MUAMC^2/4Π$

MUAA (mid-upper arm area)= $MUAC^2/4Π$

MUAFA (mid-upper arm fat area) = MUAA - MUAMA

AFI (arm fat index) = 100*(MUAFA/MUAA)

3.3. Obesity and overweight definitions

Obesity was assessed using the gender and age standardized BMI z-score, based on the WHO's methodology and calculated using the WHO reference population. BMI z-score was used both as a continuous variable and categorized into groups as indicated by the WHO:

Cut-offs:

Overweight: >+1SD (equivalent to BMI 25 kg/m2 at 19 years)

Obesity: >+2SD (equivalent to BMI 30 kg/m2 at 19 years)

Thinness: <-2SD

Severe thinness: <-3SD

(http://www.who.int/childgrowth/standards/en/)

In addition, to be able to compare the prevalence of obesity with data obtainable from studies using the IOTF cut-off points (Cole, Bellizzi, Flegal, & Dietz, 2000), we decided to apply those in our sample. The comparison using these two major definitions of obesity has been used before in other studies (Monasta, Lobstein, Cole, Vignerová, & Cattaneo, 2011; Shields & Tremblay, 2010) and is of great importance for taking into account differences in the prevalence of obesity encountered that depend on the chosen methodology.

3.4. Abdominal obesity

Waist-to-Height Ratio values were categorized to define abdominal obesity. For categorization we used the cut-off point of WHtR=0.5, as it has been shown in a large review of the literature available on this topic that values of waist circumference superior to the half of the height were representing a risk for .cardiovascular diseases and diabetes for adult and paediatric populations (Browning, Hsieh, & Ashwell, 2010).

3.5. Body composition

Body composition is the indicator of the proportion of body fat in the total body mass of the person. Body fat percentage values were categorized. We have used cut off points proposed by the McCarthy et al. (McCarthy, Cole, Fry, Jebb, & Prentice, 2006) Obesity defined by this measure was classified as:

Normal: $<85^{th}$ age and gender specific percentile

Overfat: $\geq 85^{th} > 95^{th}$ age and gender specific percentile

High fat: $\geq 95^{th}$ age and gender specific percentile

For the purposes of some tests, anthropometric measures were used as continuous variables.

3.6. Definition of asthmatic and rhinitis variables

Variables describing the respiratory health of the child were obtained through the ISAAC asthma and rhinitis questionnaire, in an English translation adapted to accommodate Portuguese vernacular and realities. The questionnaire was distributed to the parents/legal guardians of children from the 1st and 2nd grade classes of primary schools in Coimbra.

Asthma variables used in the study were defined as follows:

- **"Wheeze ever"** (also referred to as "Lifetime wheeze") - child ever having had a wheeze attack.
- **"Wheeze 12m" -**at least one wheezing episode in the past 12 months
- **"Asthma ever"** (also referred to as "Lifetime asthma") - child ever having had an asthma attack.
- **"Exercise-induced asthma 12m**"- child having chest sounded wheezy during or after exercise in the past 12 months
- **"Night cough 12m"-** at least one night of a cough attack not related to infection in the past 12 months.

In addition, it was asked whether the reported asthma was diagnosed by a medical doctor and, in the event of the child's being under any treatment, which medication was being used.

Severity of the disease was estimated based on the responses to three questions about the **number of wheeze attacks in the past 12 months, number of wake-up episodes caused by wheezing, and problems in speaking caused by wheezing.**

Rhinitis variables used in the study were as follows:

"Rhinitis ever" (also referred to as "Lifetime rhinitis") - was defined as ever having had a problem with sneezing or runny or blocked nose not caused by infections

"Current rhinitis" (also referred to as "Rhinitis 12m") **-**defined as having had a problem with sneezing or runny or blocked nose not caused by infections in the past 12 months.

"Itchy and watery eyes"- nose problems accompanied by itchy-watery eyes.

Severity of the rhinitis was assessed through a question about **disturbances in daily activities brought on by rhinitis symptoms**. The questionnaire further contained questions concerning **hay fever** and **months of rhinitis crisis in the past 12 months**. See Appendix 3.

3.7. Risk Factors included in the study

3.1.1. Family history

As the family history of both asthma and rhinitis are very strong risk factors for the development of these diseases in children, we asked the children's guardians whether anybody in the family suffered from either asthma or/and rhinitis, and if so, what was the degree of kinship.

3.1.2. Birth factors

Basic information about the birth circumstances of each child was obtained, such as the date of birth, length (in cm) and weight (in kg) at birth, and gestational age in weeks. The Ponderal Index was calculated from the length and weight at birth; due to its sensitivity to very large and very small height/lengths, the Ponderal Index is often applied as a substitute for the BMI in taking the measurements of new-borns. The formula of the index is: $PI=weight/lenght^3$.

3.1.3. Breastfeeding

Apart from the basic information regarding whether the child had been breastfed or not, we asked the parents/legal guardians about the period during which the child had been breastfed exclusively (without the introduction of any other nutrients into the child's diet) andin total.

3.1.4. Dietary patterns

Noting the frequency of the child's consumption of various food types was introduced as part of the study. The foods included in the analysis were: meat, fish, potatoes, pasta, rice, legumes, fruits, butter, margarine, eggs, milk, cereals (including bread), dried fruits and fast food. Parents/legal guardians of the child had to choose between 3 options in describing the number of times per week that the child ate each food type. The options were: never or occasionally, once or twice per week, and three or more times per week.

Factorial analysis was applied running the Principal Components Analysis (PCA) including all items except those which did not cluster well in the model, namely Cereals, Milk,

Margarine and Dried Fruits. The remaining dietary elements were included in the PCA model; the varimax rotation was chosen with Kaiser Normalization, and three components were pre-defined. Based on the clustering of foods, three components were created as follows:

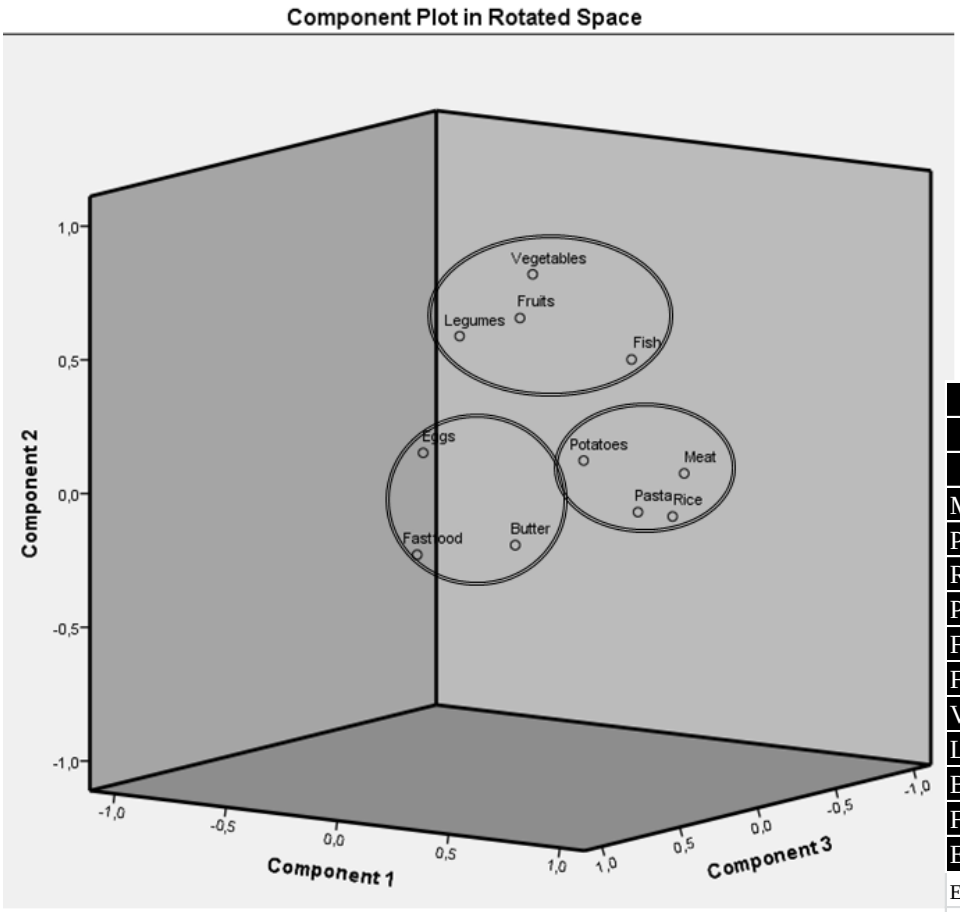
Component 1**. Base of the Portuguese diet**: component including meat, pasta, potatoes and rice.

Component 2. **Mediterranean diet**: component consisting of fruits, vegetables, legumes and fish

Component 3. **Saturated fat diet**: composed of fast food, butter and eggs.

The clustering of the elements in a three-dimensional matrix and the exact values of scores for each element within the three components are presented in the Figure 3..

The Bartlett method was applied to generate the scores for the three components and continuous variables were used to determine the degree of adherence to each dietary pattern (the higher the score, the higher adherence). Three variables for each component were created, describing the representation of each type of diet in nutritional habits of each child.



Rotated Component Matrix			
	Components		
	PC1	PC2	PC3
Meat	**0.54**	0.03	-0.35
Potatoes	**0.51**	0.16	0.25
Rice	**0.79**	-0.04	0.09
Pasta	**0.69**	-0.02	0.17
Fish	0.42	**0.47**	-0.18
Fruits	-0.05	**0.58**	-0.14
Vegetables	0.09	**0.78**	-0.02
Legumes	-0.01	**0.59**	0.32
Butter	0.21	-0.18	**0.27**
Fast-Food	0.05	-0.18	**0.67**
Eggs	0.07	0.21	**0.66**
Extraction method: Principal Component Analyses			
Rotation method: Varimax with Keiser Normalization			

Figure 3.1. Clustering of the foods in the studied sample.

Principal Component Analyses Plot in rotated. Next to the graph we placed the rotated component matrix with the representation of each food in the component 1 (Base of Diet), 2 (Mediterranean diet) and 3 (Saturated fats)

3.1.5. Physical activity and sedentary behaviour

To evaluate the level of sedentary behaviour, we asked parents/legal guardians how many times per week the child practiced vigorous exercise that would leave the child breathing heavily and how many hours per day the child watched television, during an average week.

3.1.6. Environmental factors - Heavy Trucks Traffic

Exposure to traffic pollution was evaluated by means of a question about the frequency of big trucks passing on the street where the child lived (almost all day/often during the day/rarely/ never).

3.1.7. Tobacco

Information about current smoking by the mother as well as the number of cigarettes per day was acquired. We further asked whether the mother smoked during pregnancy, and if so, for how long. To verify the effects of second-hand smoking, data on the mother's smoking in the first year of the child's life and the total number of the smokers in each household was obtained.

3.1.8. Degree of urbanization of the residential area

The postal code of each family residence was obtained through the questionnaire. Based on this code, we determined the residence parish (freguesia). The degree of urbanization of each zone was assessed using the new Urban Zones Typology (Tipologia de Área Urbanas - TIPAU) released by the National Statistics Institute (Insituto Nacional de Estatistica - INE) in 2009 (Instituto Nacional de Estatística, 2009) for each of the parishes in the country. As indicated by the INE, three types were listed: Predominantly Urban Zone (APU- Area Predominantamente Urbana), Moderately Urban Zone (AMU – Area Mediatamente Urbana) and Predominantly Rural Zone (Area Predominantamente Rural). The zones are classified as follows:

In the category of Predominantly Urban Area (APU) we classified those parishes, which met at least one of the following requirements:

1) The highest mean value between the weight of the resident population divided by the total population of the parish and the weight of the area divided by the total area of the parish corresponds to the urban zone, and the weight of the predominantly rural area of occupied space does not exceed 50% of the total area of the parish or

2) The parish includes the headquarters of the City Council and has a resident population of more than 5000 inhabitants or

3) The parish integrates wholly or partially an area with a resident population equal to or above 5000 inhabitants and the weight of the population of the place divided by the total resident population of the parish or on the total population of the place is less than 50%.

In the category of Moderately Urban Area (AMU) we classified those parishes, which met at least one of the following requirements:

1) The highest value of the mean between the weight of the resident population in the total population of the civil parish and the weight of the area on the total area of the civil parish corresponds to the urban zone, and the weight of the predominantly rural occupancy does not exceed 50% of the total area of the civil parish or

2) The highest mean value between the weight of the resident population in the total population of the civil parish and the weight of the area on the total area of the civil parish corresponds to the urban zone in conjunction with semi-urban space, and the weight of the predominantly rural occupancy does not exceed 50% of the total area of the civil parish or

3) The civil parish includes the headquarters of the City Council and has a resident population equal to or less than 5000 inhabitants or

4) The civil parish integrates fully or partially a place with a resident population above or equal to 2000 inhabitants and under 5000 inhabitants, and the weight of the population of the place on the total resident population of the parish or on the total population of the place is less than 50%.

The category of Predominantly Rural Area (APR) was applied to:

Parishes not classified as either APU or AMU.

3.1.9. Socioeconomic status

The survey used in this study contained questions about the socio-economic situation of the child's family, such as the level of education and the occupation of both parents/legal guardians.

Additional questions about the family situation dealt with the number of older and younger siblings (in order to assess the size of the household and the birth order), whether the child was born in Portugal, and if not, how many years the child had lived in the country.

To create an indicator of the family's socioeconomic status we used the maternal and paternal level of education and their profession, information we obtained through the questionnaire. The level of education was categorized based on the levels in the Portuguese educational system:

Basic education (4 years)

Basic education (6 years)

Secondary education (9 years)

Secondary education (12 years)

Higher education (at least a Bachelor degree).

The profession of the mother and father was determined by using an open question and the professions were further classified into a 10-point scale of large groups ("grupos grandes") taken from the Portuguese Classification of Professions from 2010 (INSTITUTO DO EMPREGO E FORMAÇÃO PROFISSIONAL, 2010).

Representatives of the legislatures and of executive bodies, officers, directors and executive managers (Representantes do poder legislativo e de órgãos executivos, dirigentes, directores e gestores executivos)

Specialists in intellectual and scientific activities (Especialistas das atividades intelectuais e científicas)

Technical and intermediate-level professions (Técnicos e profissões de nível Intermédio)

Administration (Pessoal administrativo)

Workers in personal services, protection and security, and sellers (Trabalhadores dos serviços pessoais, de proteção o e segurança e vendedores)

Farmers and qualified workers in agriculture, fishing, and forestry (Agricultores e trabalhadores Qualificados da agricultura, da pesca e da floresta)

Skilled workers in industry, construction and crafts (Trabalhadores qualificados da indústria, construção e artífices)

Operators of installations and machines and installation workers (Operadores de instalações e Máquinas e trabalhadores da montagem)

Trabalhadores não qualificados (Non-qualified workers)

For the purpose of the study, the category of unemployed/retired/pensioner was created and assigned as 0.

Socioeconomic Status (SES) index of the family was calculated using both the parents' education background and their professions. Factorial analysis (Principal Components Analyses, varimax rotation) resulted in the creation of the variable of the SES. Only one component reached an eigenvalue above 1 and was taken into consideration in the further process. Object scores were saved using the Bartlett method. This variable was additionally dichotomized to create two categories where the values above and including the median were assigned to the higher SES level and those below the median to the lower SES level.

3.8. Risk Factors NOT included in the study

Some factors appearing on our questionnaire did not encounter the criteria of the risk factors commonly described as being associated with asthma, rhinitis as well as obesity, and were therefore not considered for the further analyses of this thesis. These factors were as followed:

3.8.1. Food shopping habits

To obtain a broader view of the behavioural patterns of the group of subjects, we introduced questions concerning the food shopping habits of the family. The questions referred to the kind of shopping establishment habitually chosen by the family as well as the motivations of such a choice and the mode of transportation used to reach the place.

3.8.2. Contact with animals

The respondents were asked whether the child had had contact with farm animals, a dog or/and a cat during the first year of life. Information about exposure to dogs and/or cats in the last 12 months of life was also obtained, as well as maternal contact (at least once a week) with farm animals during the pregnancy period. All of the above-mentioned variables were measured dichotomously (yes/no).

3.8.3. Use of medication

The intake of paracetamol and antibiotics in the first 12 months of the children's life was studied as a dichotomized variable (yes/no). In addition, the intake and dose of paracetamol were assessed for the last 12 months of life (at least once per year, at least once per month, or never).

3.8.4. The household energy source

As differences in respiratory health have been reported depending on household energy sources, we asked the respondents what the source of the cooking and heating energy in the children's homes was.

3.9. Statistical analyses

To perform the statistical analyses, SPSS vs.21 software was used. Since all of the respiratory variables are categorical, they were used as such (dichotomic or multinominal) in the analyses. Anthropometric measurements provided continuous variables reflecting adiposity. Likewise, birth data such as birth weight and length, Ponderal Index and gestational age were included in the analyses as continuous data. Due to the large sample size (N>1000) and normal distribution of the continuous variables parametric tests were used to analyse the associations.

For the purposes of some hypotheses tested within the study, some of the continuous variables were categorized as described above.

As the evidence for gender differences in asthma and obesity is widely described in the literature, depending on the particular hypothesis, some tests were also performed separately for each gender.

3.9.1. Associations between obesity and risk factors

In order to perform comparisons of the mean values of each continuous measure describing adiposity levels between categorical risk factors, two tests were used alternatively: the Student's t-test (for the dichotomous variables of the risk factors) and the one-way ANOVA (for the polychotomous variables). For each one-way ANOVA test, the Post-hoc test was performed using the LSD method (Least Significant Difference test) to examine pair-wise comparisons between the groups. Although this test is characterized by an inflated risk of type I errors, it has been chosen for the purpose of our study due to its higher (compared to other Post-hoc tests) detection power (higher probability of the rejection of the null hypothesis when the alternative hypothesis is true).

In the event of the categorized adiposity measures' (set using the cut-off points) associations with putative risk factors, after performing the basic X^2 test, multinominal or binary logistic regressions were made to assess the odds ratios of the risk of developing obesity/overweight increasing by each risk factor. If necessary, these tests were adjusted for the confounding variables (Multinominal Logistic Regression).

For continuously represented risk factors, such as birth weight, Ponderal Index or gestational age, correlations with continuous markers of current adiposity were performed using the Pearson correlation test. To adjust for the covariates, partial correlation tests were used.

3.9.2. Associations between respiratory symptoms and risk factors

All of the respiratory variables are categorical (binominal or multinominal). To test their association with the risk factors that had the same character a multinominal or binary logistic regression to assess the odds ratios of the risk of developing these symptoms increased by each risk factor. If necessary, these tests were adjusted for the confounding variables (Multinominal Logistic Regression).

To study the effect of birth characteristics such as birth weight, Ponderal Index or gestational age on respiratory health, we investigated the differences between the means of these values depending on respiratory status categories. Similarly to what was described for the adiposity measures, two tests were used alternatively, Student's t-test or one-way ANOVA. For each one-way ANOVA test, the Post-hoc test was performed using the LSD method.

3.9.3. Association between respiratory symptoms and obesity indicators

After testing the role played by the risk factors studied in the development of both obesity and asthma in our sample, we investigated the association between these two diseases.

Student's t-test or one-way ANOVA tests were used for comparison of the mean values of adiposity measures represented as continuous variables depending on the respiratory health indicators (all categorical). For each one-way ANOVA test, the Post-hoc test was performed using the LSD method.

For the created groups of adiposity status (categorized variables), a multinominal or binary logistic regressions run to assess the odds ratios of the risk of developing these symptoms increased by each risk factor. If necessary, these tests were adjusted for the confounding variables (Multinominal Logistic Regression).

For all the performed tests, the p-level of 0.05 was considered significant.

3.9.4. Other analyses

The detailed description of the statistical analyses not mentioned here can be found in each chapter of the thesis for the particular hypothesis studied, as well as in the articles attached in annexes.

4. General Results - Demographics and sample characteristics

4.1. Geographic and administrative distribution

The total number of 1777 questionnaires was distributed between 28 public schools belonging to 7 school clusters and 4 private public schools. Below in the Tables 4.1 and 4.2 we present the distribution of the children participating from each school and in each cluster. The division into school clusters used in the study refers to the situation from 2012, before they merged into a smaller group of 7 clusters.

Table 4.1 Number of children from each school (public and private) participating in our study with presented rate of participation per school.

	School	n	% of a sample	Distributed	% response
Public (79.9%)	Ademia	26	2.45	43	60.5
	Almas de Freire	44	4.14	74	59.5
	Almedina	4	0.38	23	17.4
	Areeiro	21	1.98	42	50.0
	Assafarge	23	2.16	28	82.1
	Brasfemes	15	1.41	22	68.2
	Cernache	15	1.41	15	100.0
	Condeixa a Nova I	65	6.11	93	69.9
	Condeixa a Nova III	62	5.83	110	56.4
	Eiras	17	1.6	32	53.1
	Espirito Santo das Touregas	16	1.51	16	100.0
	Fala	33	3.1	49	67.3
	Feteira	12	1.13	18	66.7
	Loreto	4	0.38	13	30.8
	Norton de Matos	33	3.1	64	51.6
	Palheira	18	1.69	19	94.7
	Pedrulha	26	2.45	37	70.3
	Pereira	40	3.76	80	50.0
	Povoa	23	2.16	28	82.1
	Quinta das Flores	62	5.83	80	77.5
	Santa Apolonia	49	4.61	89	55.1
	São Bartolomeu	15	1.41	38	39.5
	São Martinho de Bispo	39	3.67	94	41.5
	Sargento Mor	9	0.85	14	64.3
	Solum	52	4.89	102	51.0
	Solum Sul	86	8.09	145	59.3
	Souselas	22	2.07	40	55.0
	Trouxemil	18	1.69	18	100.0
Private (20.1%)	Colegio Rainha Santa	69	6.49	89	77.5
	Externato Menino Jesus	10	0.94	12	83.3
	João de Deus I	47	4.42	110	42.7
	João de Deus II	88	8.28	140	62.9
	Total	1063	100	1777	59.8

Schools from 7 school clusters from the Coimbra district agreed to participate in the study. Most of the children participating in the study attend the school within the school cluster of Pedrulha (18.4% of distributed questionnaires) and private schools (18.1%). The smallest part came from school cluster Montemor-o-Velho (5.7%). Distribution of the children from our sample between the school clusters can be found in the Table 4.2.

Table 4.2 Frequency of children from each school cluster participating in the study.

Clusters (Agrupamentos)		
	n	Percent
Pedrulha	190	18.4
Alice Gouveia	100	9.7
Eugenio de Castro	120	11.6
Inês de Castro	132	12.8
Silva Gaio	109	10.5
Condeixa-a-Nova	137	13.2
Montemor-o-Velho	59	5.7
Private schools	187	18.1
Total	1034	100.0

The response rate was 59.8% with a final total of 1063 questionnaires returned. There was no significant difference in response rate between private and public schools (p=0.88) or among urban, suburban and rural areas (p=0.42). The list of civil parishes included in the study and the number of children residing in each is included in the Table 4.3. Map of the Coimbra Municipality and the percentage of children from our sample living in each civil parish of this municipality are presented in the Figure 4.1.

Table 4.3 Frequency of children from each civil parish participating in the study.

	Civil parish/Freguesia	n	Percent			n	Percent
Coimbra Municipality	Almalaguês	1	0.09	Other Municipalities	Alfarelos	1	0.09
	Almedina	2	0.19		Anobra	4	0.38
	Ameal	1	0.09		Arazede	1	0.09
	Antanhol	7	0.66		Arganil	1	0.09
	Antuzede	4	0.38		Barcouço	2	0.19
	Arzila	3	0.28		Belide	1	0.09
	Assafarge	28	2.63		Cantanhede	1	0.09
	Botão	3	0.28		Carapinheira	2	0.19
	Brasfemes	15	1.41		Casal Comba	3	0.28
	Castelo Viegas	11	1.03		Condeixa-A-Nova	37	3.48
	Ceira	5	0.47		Condeixa-A-Velha	54	5.08
	Cernache	22	2.07		Ega	12	1.13
	Eiras	88	8.28		Figueira De Lorvão	2	0.19
	Lamarosa	1	0.09		Granja Do Ulmeiro	5	0.47
	Ribeira de Frades	2	0.19		Lorvão	4	0.38
	Santa Clara	88	8.28		Lousã	3	0.28
	Santa Cruz	24	2.26		Luso	1	0.09
	Santo António dos Olivais	253	23.80		Mealhada	5	0.47
	São Bartolomeu	2	0.19		Miranda Do Corvo	3	0.28
	São João do Campo	1	0.09		São João do Campo	1	0.09
	São Martinho De Árvore	2	0.19		Montemor-O-Velho	1	0.09
	São Martinho do Bispo	64	6.02		Pampilhosa	8	0.75
	São Paulo de Frades	10	0.94		Pereira	24	2.26
	São Silvestre	3	0.28		Podentes	1	0.09
	Sé Nova	7	0.66		Porto	1	0.09
	Souselas	20	1.88		Rabaçal	1	0.09
	Taveiro	6	0.56		Rio Vide	1	0.09
	Torre De Vilela	7	0.66		Santo Varão	12	1.13
	Torres do Mondego	11	1.03		São Miguel De Poiares	2	0.19
	Trouxemil	26	2.45		Sebal	21	1.98
	Vil De Matos	6	0.56		Serpins	1	0.09
	Total	723			Sinde	1	0.09
					Soure	2	0.19
	No information	92	8.65		Tavarede	1	0.09
					Tentúgal	1	0.09
					Vila Nova De Poiares	4	0.38
					Vila Seca	17	1.60
					Vilarinho	4	0.38
					Zambujal	3	0.28
					Total	248	

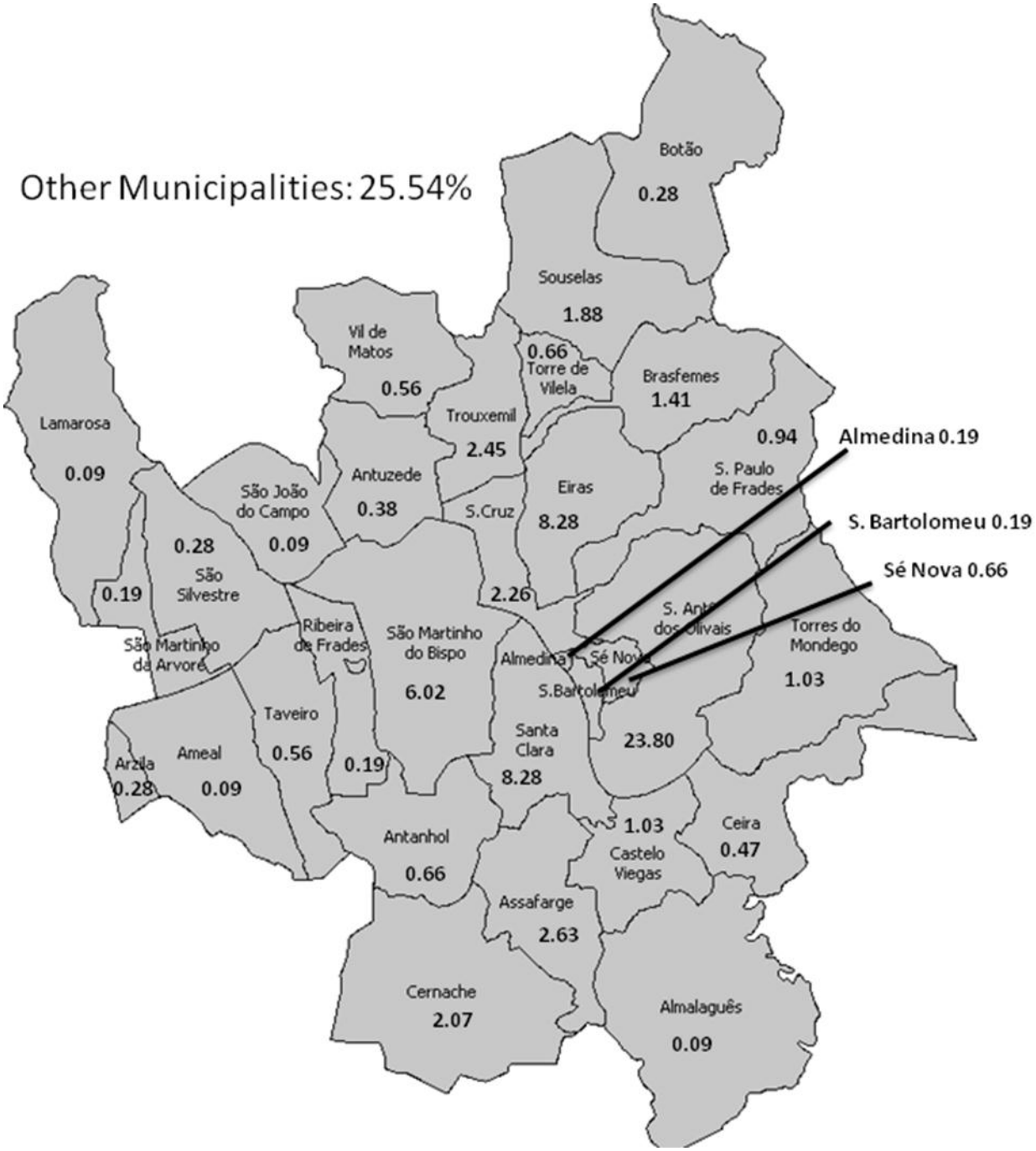


Figure 4.1 Map of the Coimbra Municipality with the names of the civil parishes and the percentage of the children from our sample living in each civil parish.

4.2. The district of Coimbra

The district of Coimbra, with a total area of 3 974 km2, is located in the central part of Portugal and has 434,311 inhabitants (4.1% of the total population of Portugal). Coimbra is the biggest city in the central region, and the 6th largest in Portugal (Comissão de Coordenacão e Desenvolvimento Regional do Centro, 2008). Its density of population is approximately 109/km2. The district consists of 17 municipalities that are divided into "freguesias" (civil parishes). Out of 31 civil parishes, 24 are classified as predominantly urban. The city of Coimbra is the biggest in the central region, and the 6th largest in Portugal (Comissão de Coordenacão e Desenvolvimento Regional & do Centro, 2008). Most of the children we studied live in the municipality of Coimbra (74.46%) and approximately one fourth in the other municipalities of Coimbra district. The administrative divisions used followed guidelines from 2012, before the merging of civil parishes in 2013.

The estimated number of children in the 1st and 2nd grades in the Coimbra district is 8200 (National Census 2011). Compared to the Census data for the corresponding proportion of the population per degree of urbanization of the residential area our sample showed a higher frequency of children from urban areas (72% comparing to 57% for the district) (Comissão de Coordenacão e Desenvolvimento Regional & do Centro, 2008); to correct for the difference, we therefore applied the post-stratification weights for the degree of urbanization of the residential area.

For the purpose of the study, 20 children with chronic diseases other than atopic diseases and obesity were excluded, leaving the final sample included in the analyses in the amount of 1043 children.

4.3. Demographic characteristics of the sample

Our sample consists of 531 girls (51%) and 510 (49%) boys; the mean age was 7.26 years old (SD=0.61) (2 children with missing gender information). Of all children 19% was born prematurely (<37 weeks of gestation), 7.6% was born with low birth weight (<2.500kg) and 4.9% with high birth weight (>4.000kg). Majority of the children had one sibling (53.3%). More than half of the mothers (52.0%) and 39.5% of the fathers of studied children had higher education. Only 7.7% of the children never were breastfed and 6.3% never exclusively breastfed. Majority of the families lived in the urban (72.2%) areas, 20% lived in suburban and 7.8% in rural civil parishes. A large fraction of parents reported a having a heavy truck traffic near the residential area (80.5). Only 26.3% of the studied children declared to practice vigorous

physical activity 3 or more times per week and 14% of them practice only occasionally or do not practice at all. Most children spent one to three ours per day watching TV (53.2%) and altogether 73% of the children watch TV over an hour a day. Full socio-demographic characteristics and behavioural patterns of the children and their families are presented in the Table 4.4.

Table 4.4 Demographic characteristic of the studied population.

Characteristic		n	%
Gender	Girls	531	51.0
	Boys	510	49.0
Gestational age [1]	Premature (<37weeks)	192	19.0
	Normal (37-42weeks)	814	80.8
	Post-mature (>42weeks)	2	0.2
Birth weight [2]	low weight (<2.500kg)	77	7.6
	normal weight (2.500-4000kg)	885	87.5
	High weight (>4.000kg)	50	4.9
Number of siblings	0 (only child)	283	27.3
	1	554	53.5
	2	149	14.4
	3 or more	50	4.8
Maternal education	Basic (4 years)	30	2.9
	Secondary (6 years)	65	6.3
	Secondary (9 years)	127	12.4
	Secondary (12 years	271	26.4
	University	535	52.0
Paternal education	Basic 4 years	39	3.9
	Secondary 6 years	100	9.9
	Secondary 9 years	192	19.0
	Secondary 12 years	281	27.8
	University	399	39.5
Breastfed	Yes	948	92.3
	No	79	7.7
Breastfed period	Not breastfed	68	6.7
	< 3 months	251	24.6
	3-6months	209	20.5
	6-9months	191	18.7
	> 9months	303	29.6
Exclusive breastfed period	Never	64	6.3
	< 3months	409	40.6
	3-6months	410	40.7
	6-9months	90	8.9
	> 9months	35	3.5
Residential area[3]	Urban	687	72.2
	Suburban	190	20.0
	Rural	74	7.8
Heavy Trucks frequency	Often or all day	824	80.5
	Never or rarely	199	19.5
Vigorous Physical Activity	Never or occasionally	143	14.0
	1-2 times per week	611	59.7
	3 or more times per week	269	26.3
TV hrs. /day	≥5	69	6.7
	3-5	136	13.2
	1-3	548	53.2
	<1hr	277	26.9

Definitions source: [1.](Berghella, 2007; WHO, 2013b); [2.](Wei et al., 2003);
[3.] Based on the INE classification (INE, 2001)

4.4. Tobacco smoking habits of the children's household members

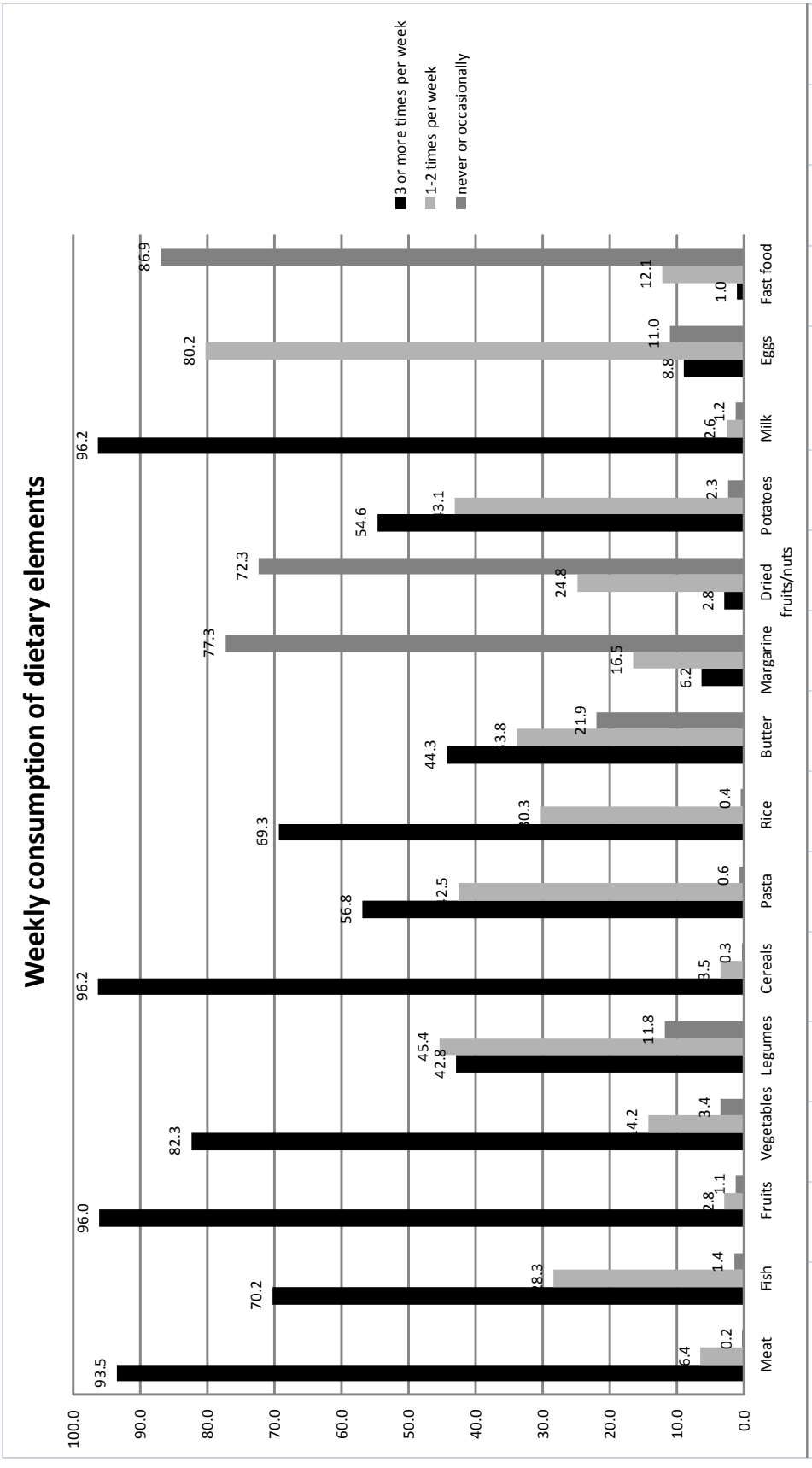
Among all the mothers of children participating on this study 18.9% are current smokers and 5.5% smoke under five cigarettes per day, 6.6% smoke between five and ten cigarettes and 6.9% smoke over 10 cigarettes per day. Approximately half of the currently smoking mothers (9.9%) smoked also during the pregnancy and most of these mothers smoked 6-9months of the pregnancy. During the first year of child's life 12.5% mothers smoked. See Table 4.5 for more details.

Table 4.5Maternal and household members' tobacco use habits.

Tobacco exposure	Status	n	%
Current maternal smoking now	No	830	81.1
	Yes	194	18.9
Number of cigarettes mother smokes per day	No	829	81.0
	< 5	56	5.5
	5-10	68	6.6
	> 10	71	6.9
Pregnancy smoking	No	928	91.0
	Yes	92	9.0
Pregnancy smoking period (months)	Nome	928	91.1
	0-3	12	1.2
	3-6	11	1.1
	6-9	68	6.7
1st year of life maternal smoking	Yes	127	12.5
	No	889	87.5
Anyone smoking at home	Yes	366	35.8
	No	656	64.2
Number of household members smoking	None	656	64.2
	1	246	24.1
	2	104	10.2
	3 or more	16	1.6

4.5. Dietary habits of the studied children

Majority of the children eat meat, fruits and cereals (including bread) three or more times per day (93.5%, 96.0%, and 96.2% respectively). Fish consumption three or more times per week was reported for 70.2% of all children and 82.3% of the children eat vegetables three or more times per week. A large number of children never or only occasionally consume dried fruits and margarine (72.3% and 77.3% respectively). Detailed information on the alimentary patterns of the studied sample can be found in the Figure 4.2.



Dietary element (n)	Meat	Fish	Fruits	Vegetables	Legumes	Cereals	Pasta	Rice	Butter	Margarine	Dried fruits/nuts	Potatoes	Milk	Eggs	Fast food
3 or more times per week	962	723	988	847	441	991	585	713	452	63	29	558	984	90	10
1-2 times per week	66	292	29	146	467	36	438	312	345	166	252	440	27	819	124
never or occasionally	2	15	12	35	121	3	6	4	224	777	735	24	12	112	886

Figure 4.2 Frequency of the consumption of dietary elements by the studied children per week.

5. Prevalence of overweight and obesity

5.1. Introduction

Obesity has increased worldwide during recent decades in both high-income and low income societies in all socioeconomic groups. In 2010 there were over 42 million overweight children under the age of five, among whom approximately 35 million from developing countries (WHO, 2014.).

The prevalence of childhood overweight (including obesity) increased worldwide from 4.2% in 1990 to 6.7% in 2010. The rate of obesity in developed countries is 11.7%, which is almost twice as high as in developing countries, where the rate is 6.1%. Nevertheless, it was the developing countries that showed a higher increase in the prevalence of overweight over these two decades, with 65% more obesity cases, compared to 48% in developed countries(Mercedes de Onis, Blössner, & Borghi, 2010). Comparing worldwide patterns of overweight and obesity, the highest rates were observed in North and South America and eastern Mediterranean regions (30-40%), followed by the European region (20-30%), with the lowest prevalence in the south-east Asian, western Pacific, and African regions (10 – 20%) (Wang & Lim, 2012b).

As obese children are much more likely to grow into obese adults, and due to the various comorbidities such as: hypertension, dyslipidaemia, type 2 diabetes, heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnoea and respiratory problems, and certain cancers (Biro & Wien, 2010), the problem has focused the attention of the scientific and medical professionals worldwide. Apart from physical adversities, there is also psychological stress affecting obese children, causing lower self-esteem (Strauss, 2000) and a predisposition toward bullying (Griffiths et al., 2006). This appears even more alarming when we take into account that it is likely to lead to involvement in other risky behaviours such as smoking or alcohol consumption (Strauss, 2000).

Although we know that weight gain is the result of the imbalance between the energy consumed and spent by the organism, there is a great complexity of factors modulating both intake and expenditure. The environmental and lifestyle changes modulating both components of this equation and interacting with genetics have been indicated as a putative cause of epidemics of obesity.

In the review by Popkin et al. (2012) authors point out the clash between the biological needs and tendencies of our bodies and the accelerated technological and industrial progress we have seen in the last several decades. Our preferences for sweets, a source of easily accessible energy, are catered to by highly-processed and caloric foods, a source of sweeteners that additionally are cheap. Similarly, our natural preferences for fatty foods have met a revolution in edible oil production with high-yield oilseeds as well as advances in developing the technology for cheap and efficient removal of oils. Furthermore, we are programmed for

energy saving and the limitation of unnecessary exertion, which has become extraordinarily easy with the development of technology and the increasing accessibility of cars as well as the urbanization of the landscape. These collisions have made our natural tendencies become our enemies, with inactivity and excessive consumption of high-energy food more common and harmful than ever.

Indeed, one of the most important and most widely described factors related to obesity in childhood is the change in quantities and qualities of consumed meals. Common and easy access to food, caused in part by increasing urbanization, often results in overeating. Evidence shows that there was an increase not only in the energy density of food and drinks but also in portion size and the number of meals and snacks per day (Duffey & Popkin, 2011). The increase in the energy density of food is especially worrying, as it is not as intuitive and easy for consumers to control as the portion size or number of meals. In the last several decades there has been an increase in the availability of highly processed food, lacking in nutrients and highly caloric. The market is dominated by manufacturers whose objective is the maximization of profits rather than the optimization of dietary nutrients (Stuckler & Nestle, 2012). The phenomenon is a cause for concern, now more than ever, due to the aggressive advertising addressed toward children (Harris, Pomeranz, Lobstein, & Brownell, 2009). In addition, modern family life with both parents working very often results in a decrease in home-prepared meals, replaced by pre-prepared meals and *fast food*. There is an observed tendency toward decreasing adhesion to traditional diets. The Mediterranean diet, traditional for Portugal, Spain, Greece, and Italy, is one of the few diets characterized by a very positive effect on health, attributable to the high intake of vegetables, legumes, fruits, olive oil and fish/seafood and low intake of meat and animal fats. The increase of obesity in these countries has been observed to be inversely correlated to adhesion to the Mediterranean diet (Bonaccio et al., 2012; Cruz, 2000; Farajian et al., 2011; Silva-del Valle, Sánchez-Villegas, & Serra-Majem, 2013).

The other factor that has contributed to the imbalance in the equation, namely energy expenditure, is the sedentary lifestyle. There has been a decline in the habits of walking or biking to school in favour of traveling by car or bus, which has been reported to have an adverse effect on the cardiovascular health of children (Davison, Werder, & Lawson, 2008). Moreover, those children who commute to school by means of physical activity are also more likely to have higher physical activity levels than those who use passive forms of transportation (Lee, Orenstein, & Richardson, 2008). Generally, there are data indicating a decline in time spent by children pursuing outdoor activities, and an important role seems to be played in the development of this trend by the influence of adult supervision (Cleland et al., 2010). The decrease could in part be explained by augmenting parental perception of risk in their neighbourhood (Ferrão et al., 2013). The decline also concerns general levels of physical

activity (defined by the WHO (2010)) as any bodily movement including sports, exercise, and other activities such as playing, walking, doing household chores, gardening, and dancing) (Adams, 2006; Craggs, Corder, van Sluijs, & Griffin, 2011; Dollman, Norton, & Norton, 2005).

As time spent by children on physical activity has decreased, and an increase in sedentary behaviours has been observed, both of these factors underlie the lower rates of the actual energy expenditure in children now (and in the recent past) than several decades ago. An association has been observed between time spent on play not involving physical activity, such as playing video games, computer use, and watching TV, and increased rates of obesity in children (Carvalhal, Padez, Moreira, & Rosado, 2007; Goldfield et al., 2011, 2013; Stamatakis et al., 2013). Access to electronic devices and their increasingly common use among children adds to the problem. As a link has been discovered between sleep duration and obesity (Padez, Mourao, Moreira, & Rosado, 2009) and more recently the use of electronics was shown to shorten sleep duration, the use of devices such as mobile phones, computers or tablets could contribute to the obesity increase independently of the sedentary lifestyle.

The causes of the increased rates of obesity and overweight can be trucked back as far as pre-natal life, or perhaps even earlier, through the mother's lifestyle before conceiving or, in particular, to a high pre-pregnancy weight. Besides that, the effects of *in utero* exposures to high-fat food and other unhealthy food choices by the mother, among several other factors, can be observed already in the birth weight of the child and later in life and have long-lasting effects on health. This seems also to be the case with the risk of increased body mass. Not only maternal body mass during early pregnancy (Olson, Strawderman, & Dennison, 2009; R. C. Whitaker, 2004) but also weight gain in that period has been showed to significantly increase the risk of obesity in offspring.

Moreover, second-hand exposure to tobacco *in utero* and during childhood and infancy has been showed to affect children's body mass, in addition to other severe health outputs (Gorog et al., 2011; Raum et al., 2011).

As mentioned above, there are observed differences in the scale of the childhood obesity epidemic among different regions and countries. Nevertheless, the differences can be observed on lower structural levels such as the socioeconomic index of a residential area, or a family or individual's socioeconomic status. Children from families characterized by lower socioeconomic status tend to show a greater prevalence of obesity than children from higher socioeconomic status (Singh, Siahpush, & Kogan, 2010). Socioeconomic status is a strong determinant of health and acts indirectly, through changes in diet and physical activity patterns, among other factors. People's educational levels are believed to affect the process mainly through awareness and access to information, as well as through the possibility of being able to

afford healthier food. Having more consciousness of the adverse effects of obesity on health and being able to recognize and apply effective prevention or intervention actions at the family level could result in decreased prevalence of this condition and its comorbidities among this social group. Lower income is related to lower economic capacity, limiting the freedom to make healthy choices such as maintaining a well-balanced and nutritive diet and arranging extracurricular sports activities for one's children.

Variations in obesity rates have also been observed among residential areas. In developed countries, there appears to be an increased risk for developing unhealthy body mass among children living in rural zones (Bertoncello, Cazzaro, Ferraresso, Mazzer, & Moretti, 2008; Davis, Bennett, Befort, & Nollen, 2011; Itoi, Yamada, Watanabe, & Kimura, 2012) in contrast to developing countries where urban children seem to be more affected (Adamo et al., 2011; Chen, Modin, Ji, & Hjern, 2011; Mohan et al., 2004).

There have also been differences reported between genders in the prevalence of obesity and overweight, though there varied conclusions have been reached on this point, with some reporting boys to be at greater risk (Farajian et al., 2013; Julia, van Weissenbruch, de Waal, & Surjono, 2004; Ogden, Carroll, Kit, & Flegal, 2012), and others indicating a higher risk for girls (Bingham et al., 2013; Pedrosa et al., 2011). However other studies did not find any significant difference between the two genders (Bertoncello et al., 2008).

5.2. Objectives

The objective of this chapter of the study was to assess the prevalence of overweight and obesity among children aged 6-8 years living in Coimbra. In addition, we wanted to study gender differences in obesity and overweight rates and compare the mean adiposity measures between genders.

5.3. Methods

Based on the National Census data from 2011, the estimated number of children enrolled in 1st and 2nd grade in the Coimbra district was 8200. The sample size for this study was calculated based on a confidence interval of 95%, the expected prevalence for this age group of 30% (Padez, Fernandes, Mourão, Moreira, & Rosado, 2004) and a margin of error of 5%;and based on this it has been concluded that for the purpose of the study hypothesis a sample of 311 individuals would be sufficient.

Procedures relating to anthropometric measurements and calculations for adiposity markers can be found in the chapter on general methodology.

There are three main methodologies used to define children's nutritional status: cut-off points from the International Obesity Task Force (IOTF) (Cole et al., 2000), those from the Centres for Disease Control (CDC) (Kuczmarski et al., 2002) and those of the WHO (De Onis, Garza, Onyango, & Rolland-Cachera, 2009). Among the three, the WHO definition was shown to be the most accurate and sensitive for classifying obesity in Portuguese children (de Sousa Lopes, 2012), and we therefore decided to use these criteria in our study. BMI transformed into gender- and age-specific BMI z-score was used to assess the nutritional status of the studied children. Cut-off points set by the WHO were applied as described in the general methodology section (De Onis et al., 2009). Prevalence of severe thinness, thinness, normal body mass, overweight and obesity were calculated for the sample as a whole and after that separately for boys and girls. However, due to the small number of children classified as thin or severely thin, in further analyses we used only the 3 groups of normal weight, overweight and obese.

As a discrepancy was reported between the IOTF and WHO cut-off points for overweight and obesity (Sheilds 2010, Monasta 2011), in order to be able to compare our prevalence data to a larger number of studies, we repeated all the prevalence analyses using the IOTF methodology.

Next, we ran a comparison of all anthropometric measures, including skin folds, between girls and boys using the Student's t-test for Independent samples.

SPSS v20 statistics software was used to process data and to perform analyses. P-value below 0.05 was considered significant.

5.4. Results

The children in our sample had mean values of BMI equal to 16.96 kg/m^2 with mean weight 26.10kg and height 123.71cm. The mean body fat percent was 21.42% and Waist to Height Ratio (WHtR) was 0.48, as shown in Table 5.1.

Comparing the anthropometric measures along the spectrum (as continuous variables) we have found that except for crude weight, crude BMI and z-scores of weight, height and BMI (which are already gender-specific), all of the measures differed significantly between genders. Mean arm and waist circumferences were significantly increased in girls compared with boys, with differences of 0.38cm and 0.92cm respectively. The difference was even stronger for the WHtR, with girls having 0.02 higher ratios than boys. Tricepital suprailiac and subscapular skin folds were significantly higher in girls than in boys, with differences of 2.76mm, 2.45mm and 1.82mm respectively. Girls had a higher BMI mean by 0.28kg/m^2; this result was, however, not significant. They also had 2.17% higher body fat percentage compared to boys and the result was highly significant. Boys had significantly a higher mean height (difference of 1.14cm) than girls. Arm indexes defining muscle mass (Mid-upper Arm Muscle Area, Mid-upper arm muscle circumference) were higher in boys and those describing arm fat mass (Mid-upper arm fat area and Arm fat index) were higher in girls. Total mid-arm area was higher in girls (Table 5.1).

Table 5.1 Means of the anthropometric measures of the total population of 6-8 year old children living in Coimbra and per gender.

Anthropometric measures	Total			Per Gender				
Measurement	N	Mean	SD	Gender	n	Mean	SD	p-value
Height (cm)	986	123.71	6.32	Girls	496	123.14	6.33	0.01
				Boys	487	124.28	6.23	
Weight (kg)	986	26.10	5.02	Girls	496	26.08	5.36	0.90
				Boys	487	26.12	4.61	
BMI (kg/m2)	986	16.96	2.37	Girls	496	17.10	2.67	0.07
				Boys	487	16.82	2.01	
BMI z-score (SD)	984	0.68	1.05	Girls	496	0.68	1.05	0.94
				Boys	487	0.67	1.05	
Height z-score (SD)	980	0.23	0.92	Girls	494	0.22	0.90	0.68
				Boys	486	0.24	0.95	
Weight z-score (SD)	980	0.63	1.03	Girls	494	0.65	1.02	0.72
				Boys	486	0.62	1.05	
AC (cm)	986	18.97	2.06	Girls	496	19.14	2.03	0.01
				Boys	487	18.78	2.07	
WC (cm)	984	59.44	6.15	Girls	496	59.88	6.52	0.02
				Boys	486	58.96	5.67	
WHtR	984	0.48	0.04	Girls	496	0.49	0.04	<0.001
				Boys	486	0.47	0.04	
TSF (mm)	982	14.96	5.33	Girls	493	16.33	5.16	<0.001
				Boys	486	13.57	5.16	
SISF (mm)	980	9.23	5.70	Girls	492	10.44	6.00	<0.001
				Boys	485	7.99	5.09	
SSF (mm)	978	9.10	4.68	Girls	491	10.01	5.00	<0.001
				Boys	485	8.19	4.15	
BF (%)	976	21.42	5.83	Girls	491	22.50	4.94	<0.001
				Boys	485	20.33	6.44	
MAMC	982	14.27	1.46	Girls	493	14.02	1.39	<0.001
				Boys	486	14.51	1.47	
MUAMA	982	155.08	33.80	Girls	493	150.81	31.15	<0.001
				Boys	486	159.29	35.65	
MUAA	983	286.04	64.43	Girls	493	291.32	63.37	0.01
				Boys	487	280.52	64.97	
MUAFA	982	130.85	51.98	Girls	493	140.51	51.04	<0.001
				Boys	486	121.00	51.21	
AFI	982	44.81	9.55	Girls	493	47.35	8.97	<0.001
				Boys	486	42.23	9.46	

Mean values of the anthropometric measures of the studied population and their differences between genders. P values presented are the results from the Student's t-test analyses of gender's comparison. Significant results (p<0.05) were marked as underlined.

Abbreviations: BMI-Body Mass Index; AC- arm circumference; WC- waist circumference; WHtR-Waist-to-Height Ratio; TSF- Triceps Skin Fold; SISF- Suprailiac Skin Fold; SSF- Subscapular Skin Fold; %BF-body fat percentage MUAMC- mid-upper arm muscle circumference; MUAC- Mid-Upper Arm Circumference; TSF- Triceps Skin Fold; MUAMA- mid-upper arm muscle area; MUAA- mid-upper arm area; MUAFA- mid-upper arm fat area; AFI-arm fat index.

5.4.1. Prevalence of nutritional status using WHO cut-off points

As presented in the Figure 5.1 and Table 5.2 in the population studied, the prevalence of obesity was 10.8% and of overweight 23.3%, with corresponding values for thinness of 0.4% and for severe thinness 0.1%. Due to the small number of the thin and severely thin children, these 5 individuals were excluded from the further analyses. It is due to the fact, that the small number of children do not allow for using it as a separate group and the underweight status is related to its own health comorbidities (van Grieken, Renders, Wijtzes, Hirasing, & Raat, 2013), and therefore cannot be integrated into the "normal weight" group.

Although there were slightly more girls than boys with obesity and overweight status, the difference between genders was not significant ($p>0.05$).

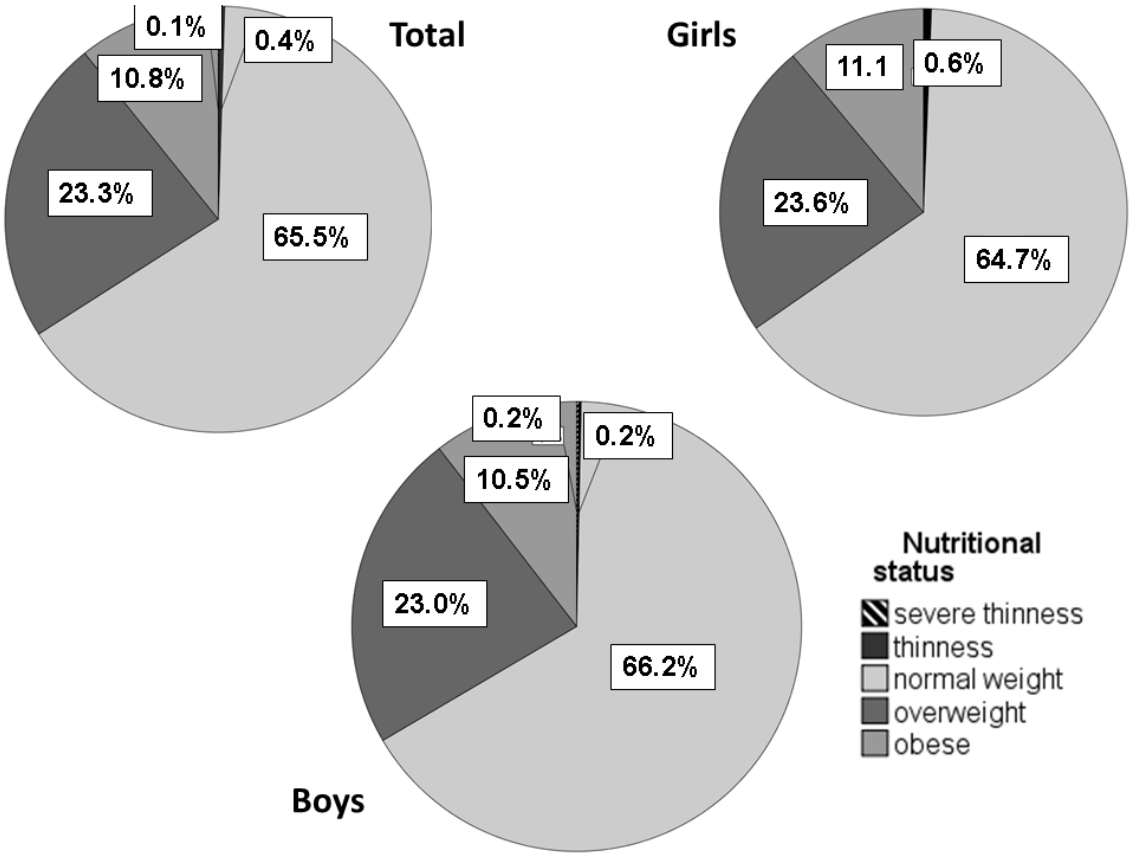


Figure 5.1 Prevalence of nutritional status among studied children, for total population and per gender (WHO criteria).

Table 5.2 Prevalence of overweight and obesity and the comparison between the two genders using WHO and IOTF criteria.

Nutritional status		WHO					IOTF				
	Total		Girls		Boys		Total	Girls		Boys	
	n	%	n	%	n	%	%	n	%	n	%
normal weight	644	65.5	321	64.7	323	66.2	75.60%	357	71.80%	388	79.80%
overweight	229	23.3	117	23.6	112	23	19.00%	108	21.70%	78	16.00%
obese	106	10.8	55	11.1	51	10.5	5.40%	32	6.40%	20	4.10%
			p=0.897					p= 0.012			

5.4.2. Prevalence of overweight and obesity using IOTF cut-off points

There was a difference in the prevalence of overweight and obesity using the IOTF methodology relative to when using the WHO tools. The prevalence of obesity and overweight calculated using IOTF methods was 5.4% and 10.9% respectively. All of the children classified as having a normal body weight with WHO guidelines remained in the same category according to IOTF standards. Among 229 children considered overweight with WHO tools, 96 (41.9%) were considered normal using IOTF cut-offs. From 106 children classified as obese according to WHO methods, 50% moved into the overweight category with applied IOTF criteria. Comparison between genders using the IOTF cut-off points showed a significantly higher prevalence of both overweight and obesity among girls. Altogether, there were 8% more girls with body weight above normal (obese or overweight). Details presented in the Table 5.2.

5.4.3. Prevalence of overweight and obesity per age

As we can see in the figure 5.2 the prevalence of both obesity and overweight increased among children from 6.5 until 7.5 years old, and decreased among children 8 years old. The highest prevalence of obesity and overweight was therefore observed in the 7.5 year-old group with 9.4% obesity and 21.9% overweight (for a total of 31.3% of children above the recommended body mass).

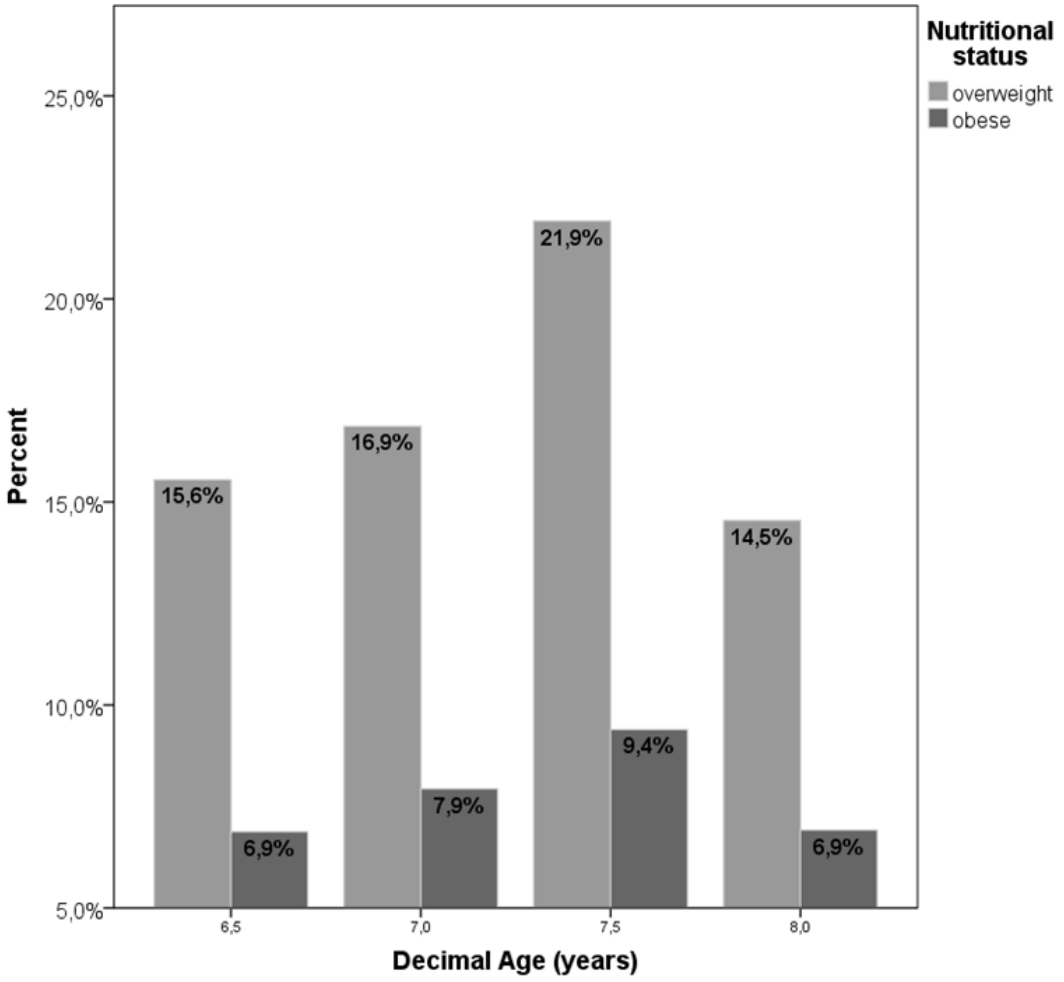


Figure 5.2Prevalence of obesity and overweight per decimal age groups.

Age interval - 0.5 years. Age intervals with fewer than 5% of children were excluded from the graph.

5.5. Discussion

This study presents an estimation of obesity and overweight prevalence among 6-8 year-old children living in the Coimbra district in 2012.

Portugal has one of the highest childhood obesity rates in Europe (Wijnhoven et al., 2013). As in many other countries, recent decades have brought an increase in the prevalence of obesity and the BMI values among children (Cardoso & Padez, 2008; Padez et al., 2004; Padez, 2006).

Our study in Coimbra district showed the prevalence of obesity at 10.8% and overweight at 23.3% using the WHO cut-offs and 19.0% and 5.4% respectively, using the IOTF standards. This means that 34.1% of the children in Coimbra district are above normal weight, which is higher than the national rates reported in the studies presented above.

The study assessing the prevalence of this condition in continental Portugal conducted in 2002-2003 reported an alarming situation among Portuguese children, with prevalence of obesity at 11.3% and of overweight at 20.3% (for a total of 31.6%) (Padez, Mourão, Moreira, & Rosado, 2005) That meant 29.4% of boys and 33.7% of girls were overweight or obese (IOTF criteria) (Padez et al., 2004). Later, in 2007, the WHO results from this study placed Portugal in first place on the list of countries of the European Region with the highest prevalence of overweight (including obesity) of children under 11 years (Branca, Francesco, Haik Nikogosian, and Tim Lobstein, eds. World Health Organization, 2007). Another study performed within the Childhood Obesity Surveillance Initiative (COSI) from 2008 shows even higher rates among Portuguese 6-9 year-old children with 37.9% of children being overweight (including obese) and 15.3% obese (WHO criteria). Among those, 40.5% of boys and 35.5% of girls were either obese or overweight (Rito, Paixão, Carvalho, & Ramos, 2011). Comparing the COSI results among nations, that is the second highest prevalence among the 12 countries studied, with only Italy having higher rates (Wijnhoven et al., 2013).

A study of slightly older children aged 9-11 years old from 2000 showed much higher prevalence of overweight, including obesity. It reported that 47.3% of 9 year-olds, 35.5% of 10 year-olds and 36.6% of 11 year-olds had body mass above that recommended for their age and gender (IOFT criteria) (Cardoso & Padez, 2008). Data from the same year on 18 year-old boys revealed the prevalence of 25.5% overweight including obesity and 4.2% obesity (Padez, 2006).

Eight years later another study of older children (10-18 years old) from Portugal showed that 30.6% of children were either overweight or obese and 10.2% were obese (WHO criteria) (Sardinha et al., 2011).

The results presented above indicate that over one-third of Portuguese children are afflicted with excess body mass, which can have serious adverse results on their health.

Differences have also been studied among regions within Portugal. Results published recently using the data previously mentioned from the Portuguese National Surveillance System (COSI Portugal) showed that the rates observed in central Portugal are similar to those from Lisbon (and Tagus Valley) and the North with, the prevalence of overweight (including obesity) at 38.1%, 38.3% and 38.6% respectively. The highest prevalence of 46.6% was observed among children from Azores islands (Rito et al., 2012; Rito et al., 2011).

The same year Sardinha et al., (2011) performed a study on 10-18 year-old children in Central Portugal and found the rate of overweight including obesity almost 8% lower than Rito et al. (2011) with prevalence of 30.2%, and 9.2% for obesity (WHO criteria).

In the study from Coimbra, using data collected in 2001 and 2002 on 3-5 year-old children, 20.1% of boys and 27.3% of girls (IOTF) were classified as overweight or obese (obesity 6.5% and 6.9% respectively) (Rito, 2006). The lower numbers in this study, compared to our results, could be due to the time gap of a decade between the measurements or, more likely, the younger age of the children included. As we could see in our sample, at least until the age of 7.5 years, the prevalence of obesity increases with age.

More recently, data collected in the central region of Portugal revealed 10.7% prevalence of obesity and 22.3% of overweight (Albuquerque, Nóbrega, Samouda, & Manco, 2012). This study used the IOTF tools, and therefore compared to our findings on prevalence according to IOTF guidelines, they encountered rates of obesity almost twice as high and approximately 3% higher obesity rates. Perhaps more comparable are the data from the city of Coimbra published in 2012 concerning data collected in 2009 from 6-10 years old children where the rate of overweight (including obesity) using the IOTF cut offs was 29.8% (Santana, 2013). This prevalence, also, is higher than that which we observed (a difference of 5.4%). Prevalence described in the literature within the last decade in Portugal, central Portugal and Coimbra can be found below together with the graph illustrating the differences using the IOTF and WHO criteria (See Figure 5.3 and Table 5.3).

Generally, we can see that rates of overweight and obesity are not among the highest reported within the past 15 years. They are higher than those presented by Sardinha et al. (2011) from 2008 for central Portugal but lower than those reported in Coimbra by Santana et al. (2013), Rito et al. (2011) and Albuquerque et al. (2012).

Table 5.3 Articles published since year 2000 describing the prevalence of obesity and overweight in Portugal, central Portugal and Coimbra.

	Reference	Population	Year of the study	Age	Criteria used	Overweight including obese		Obese	
						WHO	IOTF	WHO	IOTF
	Our study	Coimbra District	2011-2012	6-8 years old	WHO & IOTF	34.1%	24.4%	10.8%	5.4%
National	Cardoso et al., 2008	Portugal	2000	9-11 years old	IOTF	–	47.3% (9yo*); 35.5% (10yo*); 36.6% (11yo*)	–	–
National	Padez et al., 2006	Portugal	2000	18 years old	IOTF	–	25.5%	–	4.2%
National	Padez et al., 2005	Portugal	2002-2003	7-9 years old	IOTF	–	31.6%	–	11.3%
National	Rito et al., 2011	Portugal	2008	6-9 years old	WHO & IOTF	37.9%	28.1%	15.3%	8.9%
National	Sardinha et al., 2011	Portugal	2008	10-18 years old	WHO & IOTF	30.6%	23.5%	10.2%	5.8%
Regional	Rito et al., 2011	Central Portugal	2008	6-9 years old	WHO & IOTF	38.1	27.8%	16.9%	9.0%
Regional	Sardinha et al., 2011	Central Portugal	2008	10-18 years old	WHO & IOTF	30.2%	20.8	9.2%	4.4%
Regional	Albuquerque at al., 2012	Central Portugal	2011	6-12 years old	IOTF	–	33.0%		10.7%
Regional	Rito et al., 2006	Coimbra	2001-2002	3-5 years old	IOTF	–	20.1% boys; 27.3% girls		6.5% boys; 6.9% girls
Regional	Santana et al., 2013	Coimbra	2009	6-10 years old	IOTF	–	29.8%	–	–

***yo- years old**

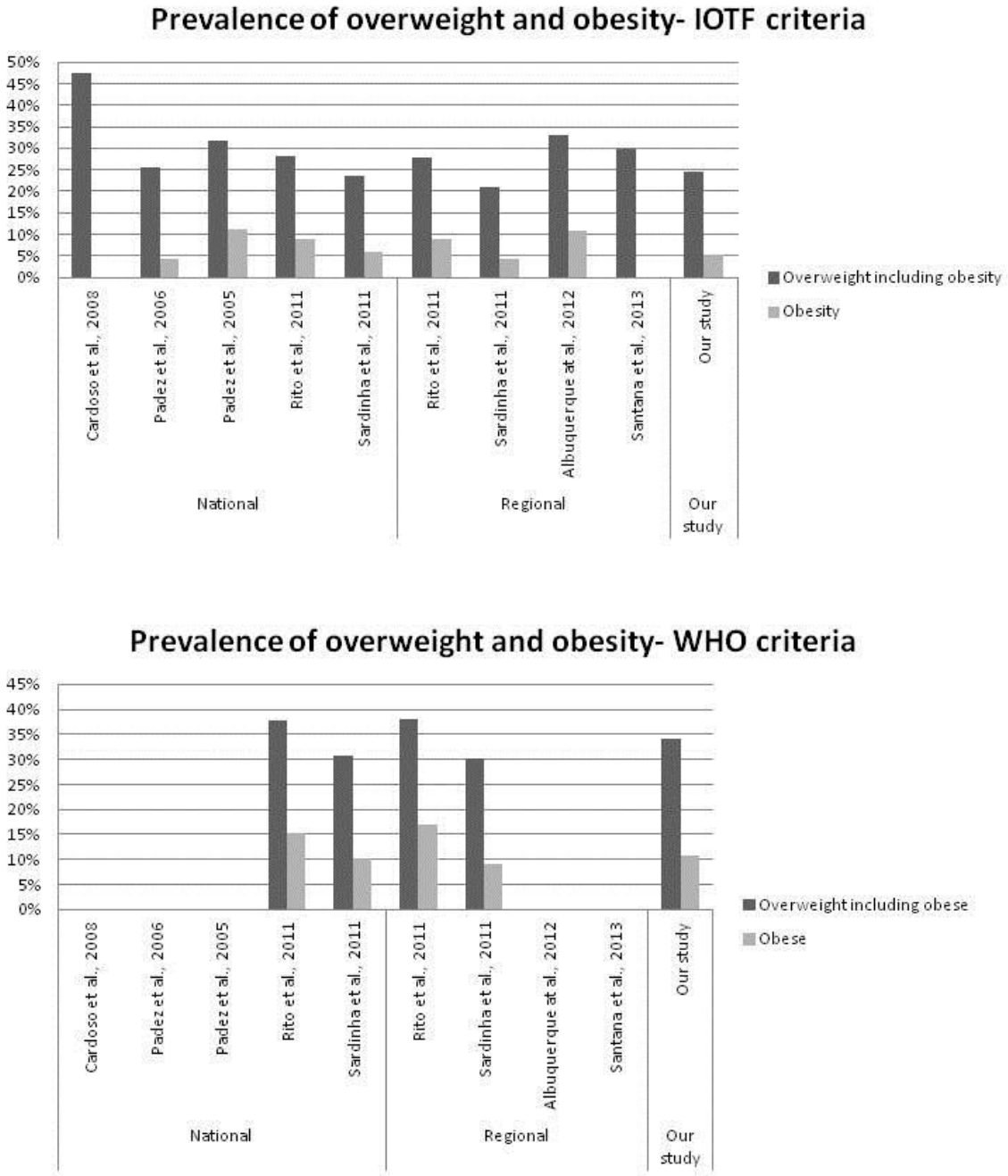


Figure 5.3 Prevalence of overweight including obesity and obesity rates reported in the past years in Portugal and Central Portugal (regional).

These discrepancies observed in the prevalence of overweight and obesity among children in Portugal and in the Coimbra region could be due to various reasons related to methodology and sampling. There are differences between the studied populations in the children's mean age, the regions included in the study, and related demographic differences. Our rates being lower compared to other descriptions of prevalence could be due to these sampling differences, or due to an actual decrease in the prevalence of excess body weight among children that occurred within the last years. Despite the lower values, the problem of obesity is still present in the population of children in Coimbra and requires attention and interventions.

We observed increased adiposity measures, including skinfolds measurements and waist circumference, in girls compared to boys, with the opposite situation in regard to muscle mass. The clear and significant differences in these measures, however, did not translate into equal differences in prevalence, with only 1.3% more girls being classified as overweight or obese. This is most likely due to the fact that we used the WHO BMI z-score cut-off points, which are already gender specific and account for the difference between genders. There is no uniformity in reports concerning gender differences in childhood obesity and overweight prevalence. Some Portuguese studies from the last decade have observed increased rates among the population of girls (Padez et al., 2004; Padez et al., 2005; Rito, 2006) and others among boys (Albuquerque et al., 2012; Mota, Flores, Flores, Ribeiro, & Santos, 2006; Ribeiro, Santos, Duarte, & Mota, 2006; Rito, Carvalho, Ramos, & Breda, 2013; Sardinha et al., 2011).

In the report of the WHO comparing national data from 12 countries, the situation appears more consistent. Independently of the general rate of obesity and overweight, prevalence is higher among girls when using the IOTF tools and higher for boys when applying the WHO methodology on the same sample (Wijnhoven et al., 2013).

We have presented our results using the WHO tools, which were shown to be characterised by higher sensitivity to the population level, to define obesity in Portuguese children (de Sousa Lopes, 2012), which, additionally, allows for continuous analyses of the BMI along its spectrum. There are, however, differences observed between the rates of prevalence reported depending on the methodology chosen, which is not only reflected in general prevalence but also in the risk factor evaluation. As we can see in our study, the prevalence of children classified as obese according to WHO standards is the double of the prevalence calculated using the IOTF tools. A similar situation appears in the case of overweight, with the difference of 4.4%. Altogether, 10% of the children classified as having a normal weight using IOTF cut-offs, are considered overweight following the WHO recommendations. In order to obtain a comparable level of information and comparison between the different centres studying the problem of childhood obesity, the authors started to apply

more than one methodology in reporting prevalence (Monasta et al., 2011; Rito et al., 2012; Shields & Tremblay, 2010; Wijnhoven et al., 2013), as we did in our study. The cut-off points for the BMI serve to indicate the assessed value above which the risk of obesity comorbidities increases significantly, therefore the selection of a more accurate definition of obesity and overweight should be based on the verification of the precision of risk estimation. The study comparing the different criteria in relation to asthma and rhinitis outputs in various populations could help to raise the alarm both for the purpose of research, and individual recommendations given to parents and children.

5.6. Conclusion

Our study shows that obesity continues to be a serious problem among Portuguese children, with Coimbra no exception. Despite growing evidence and increasing access to information, obesity rates are still at an alarming level, and complicated national conditions, attributable to the economic crisis, unemployment, and salary cuts, could contribute further to social inequalities and health disruption. Recognition of risk factors adding to the high rates of overweight and obesity is necessary in order to design evidence-based strategies of prevention and intervention which could improve the situation of the children.

6. Prevalence of asthma and rhinitis symptoms

Based on the brief report: Muc, M., A. Mota-Pinto, and C. Padez. "Prevalence of asthma and rhinitis symptoms among children living in Coimbra, Portugal." Revista Portuguesa de Pneumologia 2014 Jul-Aug;20(4):208-10. doi: 10.1016/j.rppneu.2013.08.002. Epub 2013 Dec 24.

6.2. Introduction

Asthma is the most common chronic disease in paediatrics and, according to the WHO, 235 million people currently suffer from this disease (World Health Organization, 2013). In view of the fact that in most cases, the onset of the disease appears before the age of 18 (Sa-Sousa et al., 2012), it is not surprising that in fighting the disease, the interest of the scientific and medical world has focused on this age group. The burden of asthma includes not only physical symptoms and discomfort, but also lower self-esteem and school absenteeism (Borrego, César, Leiria-Pinto, & Rosado-Pinto, 2005).

Most data on the prevalence of childhood allergic diseases comes from the ISAAC phase II, held in 1995 and phase III, held in 2002. ISAAC created a methodology for studying two age groups, children 6-7 and 13-14 years old (Asher et al., 1995). In Portugal, the study was conducted in five cities: Porto, Lisbon, Coimbra, Portimão and Funchal. During the seven-year period between the two phases of the study, from 1995 to 2002, significant increases in the prevalence of wheezing (18.2% to 21.8%), asthma (11.8% to 14.7%), nose symptoms (30.2% to 37.1%), and hay fever (6.5% to 7.5%) in the groups of 13-14 year-olds were observed. The data for the 6-7 year-old children were slightly different, with an increase in the prevalence of asthma (11.8% to 14.7%) and rhinitis (30.2% to 37.1%), but no difference in wheezing (28.2% to 28.1%) or decrease in hay-fever rates (7.3% to 7.2%) (Rosado-Pinto, 2011).

The research team from Coimbra did not study the 6-7 year-old group in either of the surveys, from 1995 or 2002. Therefore, only the data for 13-14 year-old adolescents were available. In this group, within the period between phases I and III of the ISAAC study, the prevalence of current wheezing (in the past 12 months) significantly increased, by 2.6% (from 8.1% to 10.7%). The ISAAC study conducted in Coimbra during 2001-2002 among 13-14 year-old adolescents reported 12.2% prevalence of asthma, which is lower than the national prevalence (14.7%), and lower prevalence of wheezing (20.6%) than national prevalence (21.8%) reported the same year (Rosado-Pinto, 2011).

More recent published data on prevalence of childhood asthma in Portugal comes from Lisbon in 2008, where the prevalence of asthma, allergic rhinitis and wheezing was 5.6%, 43.0% and 43.3%, respectively (Pegas et al., 2011), and from Matosinhos (data from 2009) where the prevalence of asthma among children 0-7 years old was 9.56% (de Sousa, Santo,

Colaço, Almada-Lobo, & Yaphe, 2011). A large national prevalence study based on The Portuguese National Asthma Survey reported the rate of current asthma at 6.2% for the Central region and 7.2% for the age group <18 years old in all country (Sa-Sousa et al., 2012).

In the last decade, little information on the prevalence of childhood asthma and rhinitis in Portugal has been published and, to our knowledge, none on its prevalence in Coimbra. The prevalence of asthma and rhinitis among the age group 6-8 years old has never been studied in Coimbra.

Differences in the prevalence of allergic diseases between two genders have been described (Willeboordse et al., 2013) and most of these studies observe increased prevalence for boys compared to girls (Almqvist, Worm, & Leynaert, 2008; Bjerg, Sandström, Lundbäck, & Rönmark, 2010; García-Marcos et al., 2004), in Portugal also (Rosado-Pinto, 2011), with this tendency reversing in adolescence and adulthood (Bjornson & Mitchell, 2000).

6.3. Objectives

The objective of this study was to assess the prevalence of asthma and rhinitis in the population of children 6-8 years old from the district of Coimbra. We also aimed to compare the prevalence of these diseases between genders.

6.4. Methods

Authorization to use the ISAAC methodology in our study was given to the research centre by the national coordinator of ISAAC studies in Portugal. ISAAC-based core asthma and rhinitis questionnaires, containing questions about the prevalence and frequency of asthma and rhinitis symptoms for each child in the past 12 months and in the course of his or her lifetime, were given to the legal guardians of children from the 1st and 2nd grade classes of primary schools in the Coimbra district. These questionnaires had been translated into Portuguese for the purpose of the ISAAC study in Portugal and adapted to the local reality. The questionnaires contained questions about the presence of asthma and rhinitis symptoms and their severity for each child in the last 12 months and in his or her lifetime. The questions used to define each symptom can be found in the Chapter 3 and questionnaire attached in the Appendix 3.

The estimated number of children from 1st and 2nd grade in the Coimbra district is 8200 (INE, 2011). The sample size was calculated based on a confidence interval of 95% and expected prevalence of 10% (Rosado-Pinto, 2011) and with the narrow margin of error of 2%, a sample of 782 individuals would be sufficient to test our hypothesis.

Stratification was applied to investigate the differences in disease prevalence between and among groups of children from different socioeconomic status families (Higher SES and Lower SES) and residential zones with varying levels of urbanization (Predominantly Urban Area APU=urban zone; Medially Urban Area AMU= suburban zone; Predominantly Rural Area APR= rural zone). Definitions used for each classification are given in detail in chapter 3, General Methodology). In addition, prevalence of asthma and rhinitis symptoms was compared between genders. The chisquaredtest was used to measure the significance of the differences between the groups. SPSS v20 statistics software was used to process data and to perform statistical analyses. The study protocol was approved by *Direcção Geral de Inovação e Desenvolvimento Curricular (DGIDC)* and informed parental consent was obtained. The questionnaires were filled out by parents.

6.5. Results

At least one episode of asthma in the child's lifetime was reported in 10.4% of the studied population. At least one wheezing episode had been experienced by 35.2% of the studied children and 11.8% had had at least one attack within the past 12 months. Prevalence of lifetime rhinitis and current rhinitis were 22.8 and 19.4 respectively. In our study the prevalence of lifetime asthma was 10.4%. Detailed information on each studied symptom and its severity with additional comparisons to their prevalence in the ISAAC phase III in Portugal can be found in the Table 6.1.

Table 6.1 Prevalence of asthma and rhinitis symptoms (comparison with Portuguese cities from ISAAC phase III).

	Portugal 6-7 (2002)	Portugal 13-14 (2002)	Coimbra 6-8 (2012)	Coimbra 13-14 (2002)	Oporto 6-7 (2002)	Oporto 13-14 (2002)	Lisbon 6-7 (2002)	Lisbon 13-14 (2002)	Portimão 6-7 (2002)	Portimão 13-14 (2002)	Funchal 6-7 (2002)	Funchal 13-14 (2002)
	Prevalence % (n)											
Total N			1037	1177	2464	3336	2477	3024	1069	1109	1819	3161
Wheeze ever	28.1 (1512)	21.8 (2576)	34.4 (347)	20.6 (242)	10.0 (246)	22.1 (736)	30.2 (748)	25.9 (784)	28.4 (304)	18.2 (202)	25.3 (460)	19.4 (612)
Wheeze 12 m	12.9 (692)	11.8 (1398)	11.9 (120)	10.7 (126)	2.3 (56)	13.1 (437)	14.2 (351)	14.6 (443)	13.2 (141)	9.7 (108)	11.0 (200)	(284)
≥4 attacks of wheeze 12 m			3.1 (31)	2.6 (31)	2.7 (67)	2.6 (87)	3.4 (83)	3.5 (105)	2.5 (27)	2.2 (24)	2.1 (38)	1.9 (60)
≥1 nights/week sleep disturbance from with wheeze 12m			2.2 (22)	1.0 (12)	2.5 (61)	1.5 (51)	3.4 (84)	2.1 (62)	3.6 (38)	1.8 (20)	4.1 (74)	1.5 (46)
Speech limited by wheeze 12m			1.9 (19)	2.2 (26)	10.0 (247)	2.8 (95)	2.9 (72)	3.5 (107)	2.1 (22)	2.1 (23)	3.3 (60)	2.7 (84)
Asthma ever	9.4 (505)	14.7 (1737)	10.6 (107)	12.2 (144)	5.7 (140)	15.1 (504)	7.8 (194)	15.6 (472)	4.9 (52)	12.4 (138)	14.2 (259)	15.2 (479)
Exercise-induced asthma 12m			6.4 (65)	19.5 (229)	30.8 (759)	21.0 (701)	7.1 (176)	24.8 (751)	5.5 (59)	18.2 (202)	7.0 (117)	21.2 (670)
Night cough 12m			24.2 (245)	30.5 (359)	26.1 (644)	32.9 (1097)	32.7 (809)	35.4 (1070)	29.4 (314)	31.4 (348)	32.9 (599)	34.1 (1079)
Rhinitis ever	29.1 (1565)	37.1 (4383)	23.1 (234)	31.8 (374)	22.1 (544)	41.8 (1394)	31.2 (774)	39.7 (1202)	28.0 (299)	34.4 (382)	27.0 (492)	32.6 (1031)
Rhinitis 12m	24 (1291)	26.5 (3131)	19.7 (199)	23.9 (281)	7.5 (186)	31.7 (1056)	26.3 (651)	29.0 (878)	23.1 (247)	21.7 (241)	21.6 (393)	21.4 (675)
Itchy and watery eyes 12m			9.3 (94)	6.5 (76)	0.7 (18)	10.3 (344)	10.1 (249)	10.6 (320)	8.2 (88)	7.2 (80)	9.4 (171)	8.9 (280)
Rhinitis affecting activities a lot 12m			1.6 (3)	0.3 (3)	2.7 (67)	0.5 (18)	1.0 (25)	0.6 (17)	0.9 (10)	0.2 (2)	1.5 (28)	1.1 (36)
Hay fever ever	4.2 (227)	7.5 (134)	1.0 (10)	14.0 (165)	7.4 (182)	5.0 (168)	2.7 (67)	6.4 (194)	3.6 (38)	7.3 (81)	6.7 (122)	8.7 (275)

Prevalence of asthma and rhinitis symptoms from our study in comparison to the data from Portuguese cities from 2002 obtained within the ISAAC phase III.

6.5.1. Prevalence per gender

Among all symptoms there was a general tendency observed toward greater prevalence of both asthma and rhinitis in boys than in girls; however, no difference was shown to be statistically significant. In the case of night cough episodes, girls showed statistically significant differences with a higher prevalence (27.1%) than among boys (21.3%), ($p<0.05$). The other two symptoms higher among female children were limited speech due to wheezing and strongly affected daily activities in the past 12 months, although the results were not significant, most likely due to the small numbers in each studied group. Detailed results of the analyses can be found in the Table 6.2 .

Table 6.2 Prevalence of the asthma and rhinitis symptoms stratified per gender.

	Prevalence in % (n)		
Symptom	Girls (n=531)	Boys (n=510)	p-value
Wheeze ever	32.4 (164)	36.5 (183)	0.10
Wheeze 12m	10.5 (53)	13.2 (67)	0.10
≥4 attacks of wheeze 12m	2.9 (15)	3.3 (17)	0.51
≥1 nights/week of sleep disturbance with wheeze 12m	1.9 (9)	2.5 (13)	0.47
Speech limited by wheeze 12m	2.2 (11)	1.6 (8)	0.33
Asthma ever	9.5 (48)	11.7 (59)	0.15
Exercise induced asthma 12m	6.4 (32)	6.5 (33)	0.51
Night cough 12 m	27.1 (137)	21.3 (108)	0.02
Rhinitis ever	21.5 (109)	24.7 (125)	0.13
Rhinitis 12m	18.5 (93)	20.9 (106)	0.19
Tearing and itchy eyes 12m	7.9 (40)	10.7 (54)	0.08
Rhinitis affecting activities a lot 12m	3.3 (3)	0.0 (0)	0.15
Hay-fever ever	0.5 (2)	1.6 (8)	0.06

Results are presented as percentage (with the crude number in brackets) of children whose parents reported the symptom. The last column contains the significance level of the difference in prevalence between the two genders. Chi^2 test was used to calculate the p values. Significant results ($p<0.05$) are marked as underlined.

6.6. Discussion

In this study the prevalence of asthma and rhinitis symptoms was assessed in the population of 6-8 year-old children from the Coimbra district in Portugal. This study found an increased prevalence of wheezing and decreased rhinitis symptoms compared to the national data from 2010. Moreover, there was a general tendency of boys to have higher prevalence of atopic symptoms than girls; however, the diseases' symptoms seemed to be more severe among girls. When comparing prevalence among children from lower and higher socioeconomic status, higher prevalence of symptoms was found in the former group, with the major differences in prevalence of both current and lifetime wheezing. On the contrary, rhinitis was more prevalent in the lower SES group. Differences between residential areas were less consistent and significant, however, it was the urban population that revealed the most significant increase compared to the suburban or rural populations.

In the last decade, very little information on the prevalence of childhood asthma and rhinitis in Portugal was published. Most literature available concerning this topic comes from the ISAAC study that used standardized data to obtain very extensive and comparable data on asthma and allergies from 306 research centres in 105 countries (Asher et al., 1995). In Portugal, centres in 5 cities joined the project, namely: Lisbon, Porto, Coimbra, Portimão and Funchal. The study has so far completed 4 phases. Of those, two phases were designed to assess the prevalence of allergic diseases, rhinitis and asthma. Phase I was conducted in 1995 and phase III in 2002; both used questionnaires for two age groups, children 6-7 and 13-14 years old. The centre in Coimbra studied only adolescents (13-14years old), therefore our study contains the only available data on the 6-8 year-old group in this city (Rosado-Pinto, 2011). After 2002 few data exist on the prevalence of these diseases in Portugal, and to our knowledge, none concerning Coimbra.

Due to the lack of the data related to our age group in Coimbra, we used the data on adolescents (13-14 years old) from the same city as a reference, as well as data on 6-7 year-old children from other Portuguese centres.

Compared with groups in the same age group, the prevalence of lifetime asthma in our population was 10.4% which is slightly higher than the national prevalence recorded in 2002 (9.4%) and higher than in most cities with the exception of Funchal, which has the highest overall prevalence, 14.2% (Table 1). Our study revealed a very high prevalence of confirming at least one wheezing episode in child's life, 35.2% in children aged 6-8 years old, compared to the national prevalence in 2002 (28.1%). This is not only higher than all of the values reported in 6-7 year-old children in 2002, but also higher than all of the values reported for prevalence

among adolescents (Rosado-Pinto, 2011). Although the prevalence could be biased by the understanding of the term "wheeze" (in Portuguese "pieira"), which differs between health specialists and parents (Fernandes et al., 2011), this is improbable, as the methodology used in all the studies was the same. There is no reason to think that the common understanding of this term could change significantly over a decade. Taking into account the lack of data from the Coimbra centre in our age group, from both 1995 and 2002, and the 10-year interval between the studies, we cannot be sure whether the prevalence increased during this period, or Coimbra definitely has a higher prevalence of lifetime wheezing than other Portuguese cities. The effect of age on the prevalence and severity of the symptoms is not unequivocal. When comparing the results among 6-7 year-olds with those for the groups of 13-14 year-olds from the same city at the same point in time (2002), it was observed that the lifetime asthma prevalence and the prevalence of night cough episodes in the past 12 months were higher among adolescents in each participating centre and that the lifetime prevalence of wheezing tended to be higher among 6-7 year-olds. Therefore, we cannot be sure which of these factors - the decade difference between the ISAAC phase III and our study or the 7-year difference between 6-7 and 13-14 year-old groups could contribute more to the differences observed.

In Lisbon in 2008, when a group of 342 students between 5 and 12 years of age participated in a study, the lifetime asthma rate was lower than in phase III of the ISAAC study (5.6% comparing to 7.8% in the phase III); however, at least one wheezing episode in their lifetime was reported in 13.1% more children than in 2002 (Pegas et al., 2011). These results suggest that the prevalence of wheezing may indeed have increased among Portuguese children.

Nose symptoms in the past 12 months 19.4% and lifetime nose symptoms 22.8%, were lower in our population than the national level of prevalence from 2002 (24% and 29.1% respectively) in the same age group. We also compared the values for our population to those for the 13-14 year-olds from Coimbra (23.9% and 31.8%, respectively). The full table with prevalence comparisons between our study and data gathered during the phase III of ISAAC in Portugal can be found in the Table 6.1.

In a study conducted between February and July 2009 in Matosinhos, based on a random sample of 540 patients, with the mean age of 33.2 years old (SD= 28.1 years), prevalence was tabulated by age and gender. The values of asthma for children between 0 and 7 years of age were 9.56%, while in the group between 8 and 19 prevalence was higher, 13.13% (de Sousa et al., 2011).

Although most of the symptoms did not reach a high enough level to be significant, they were higher among boys than among girls, which fact accords with data from other studies (Bjornson & Mitchell, 2000). In a recent study on children 6-16 years old in the Netherlands,

the authors found that 58.8% of the asthmatic children were boys and 41.2% girls. They also found, however, that whilst males had higher asthma prevalence among children with normal body mass and overweight, in the obese group there was a higher rate of girls with asthma than boys, suggesting the association between asthma and obesity may be stronger for girls (Willeboordse et al., 2013).

Studies of asthma and rhinitis during childhood in Portugal, using the same ISAAC tools as were used in the project presented here, have also confirmed the higher prevalence of allergic diseases in boys, within the same age group (Rosado-Pinto, 2011). Since at this age hormonal differences are not that strong, the differences are most likely due to the gender-specific environment and lifestyle which has been suggested before as a plausible explanation of these inequalities. In their review paper from 2008, Almqvist et al. found that in most studies, around two-thirds of the children reporting asthma or wheezing were boys and one-third were girls, a proportion which reverses around puberty: among adolescents, asthma was more prevalent among girls. The explanations proposed by the authors include the physiological differences consisting in differential growth of the airways and immunological differences. Boys show higher Immunoglobulin E levels and have higher susceptibility to sensitization. Another plausible reason for the gender differences described may lie in the diagnostics patterns. The authors argue that girls are undertreated and only seek out a consultation if having a more severe form of the disease than boys. This is reflected in the proportion of wheezing to the actual diagnosis of asthma being higher for girls, which could bias the prevalence data. On the other hand, the review mentions the higher susceptibility of girls to environmental pollutants, ozone and tobacco (Almqvist et al., 2008). Despite these trends which were not significant, there was one which symptom reached the level of significance: the Night cough, which on the contrary, was higher in girls. Similar results of a Night cough being more frequent among girls were found in the study performed within the ISAAC project in Poland; so, too, however, were other symptoms, such as lifetime wheezing and exercise-induced wheezing (Lis, Pietrzyk, Cichocka-Jarosz, Szczerbiński, & Kwinta, 1997). Although not at a high enough level to be considered significant, in our sample there also was increased occurrence of limited speech caused by respiratory problems and nose symptoms affecting a lot of daily activities, both noted in the past 12 months among girls. This could suggest that although prevalence is higher for boys, symptoms might be affecting the females with greater severity. Notably, although very low in number (n=3), the only individuals reporting strongly affected daily activities related to rhinitis were all girls. Perhaps an increased sample could bring more consistent and clear results. It has previously been observed that clinically measured severity of the inflammatory diseases is markedly higher in female children than in male. Casimir et al. in Belgium studied inflammatory markers of 50 children under the age of 8 hospitalized with

asthma diagnosis (years 1999-2001). They found that the neutrophils count (cells involved in inflammatory symptoms related to asthma (Macdowell & Peters, 2007)) and doses of cortisone or inhaled bronchodilators used in treatment were significantly higher for girls than for boys (Casimir et al., 2010).

6.7. Conclusion

The prevalence of lifetime asthma, lifetime wheezing and current wheezing episodes observed in our population were higher than the national values from 2002, whereas the prevalence of nose symptoms, both lifetime and in the last 12 months was lower. It has been estimated that in Portugal, we can expect 20.250 new cases of asthma annually (Correia de Sousa, Silva, Lobo, & Yaphe, 2010). Despite increasing interest from the medical and scientific communities in the topic of asthma and rhinitis, these pathologies continue to be a health concern in many countries, and Portugal does not seem to be an exception. The prevalence of atopic diseases still does not seem to have reached a plateau, and worldwide studies continuously report an increase in the scale of the problem (Anandan, Nurmatov, van Schayck, & Sheikh, 2010; Asher et al., 2012; Ekerljung et al., 2010). The issue is a burning topic, as it is associated with a high direct economic costs for public health systems (Milton, Whitehead, Holland, & Hamilton, 2004) as well as indirect costs, related to the higher level of absenteeism among affected children and poorer school performance (Bener, 2011; Jáuregui et al., 2009; Mir et al., 2012), also reported previously in Portugal (Borrego et al., 2005).

There is a general agreement on the impact of environment on asthma and rhinitis occurrence; in-depth recognition of risk factors, which often vary among studied populations, is therefore of great importance. Lifestyle interventions and prevention programmes that can subsequently be introduced are important tools to combat the global epidemic and its consequences. Risk factors related to increased risk of these diseases in our studied sample can be found in Chapter 9.

7. Obesity risk factors

7.1. Introduction

Obesity is a disease with multi-factorial aetiology, and although genetic inheritance has been shown to play an important role (Albuquerque, Nóbrega, & Manco, 2013; Bradfield et al., 2012), the increasing prevalence of this condition within genetically stable populations underscores the importance of the environmental and socioeconomic factors in the disease modulation.

Exposure to risk factors for developing obesity starts as early as the prenatal period or even before. Factors such as maternal body mass before the pregnancy and weight gain during this period have already been shown to be significantly associated with childhood obesity of offspring (Olson et al., 2009; Yu et al., 2013). Several studies have confirmed the correlation between birth weight and increased body mass later in childhood (Cnattingius, Villamor, Lagerros, Wikström, & Granath, 2012) and adulthood (Phillips & Young, 2000). This highlights the role of the intrauterine environment in the development of obesity and its comorbidities as well as the necessity of early prevention (Picó et al., 2012).

Breastfeeding is another early life factor related to childhood obesity (Vafa, Moslehi, Afshari, Hossini, & Eshraghian, 2012). It is currently the recommendation of the WHO to breastfeed exclusively during the first 6 months post-partum and to continue breastfeeding with the introduction of complementary foods for a period of two years or longer (WHO, 2014). In addition to other health benefits, breastfeeding also seems to protect against childhood obesity (Armstrong & Reilly, 2002; O'Tierney, Barker, Osmond, Kajantie, & Eriksson, 2009). However, this association was not found in some studies (Kramer et al., 2007; Vafa et al., 2012).

Another putative predictor of adiposity in childhood is second-hand exposure to tobacco (also called involuntary or passive smoking) early in life as well as later in life. The adverse effects on children's health caused by their involuntary environmental exposure to tobacco are commonly known and cited in relation to paediatric diseases such as cancer, respiratory diseases including asthma and allergies, neurological outcomes, sudden infant death syndrome, infections, middle ear disease, and others (Hofhuis, 2003). Obesity has been added to the list of the conditions influenced by second-hand tobacco exposure and foetal environmental smoke (Braun et al., 2010; Power, 2002; Raum et al., 2011). There may also be a dose-dependent effect, with the higher number of cigarettes smoked by the mother during pregnancy raising the risk of obesity in children, and with the effect being even stronger if both parents were smokers during this period (Koshy, Delpisheh, & Brabin, 2011).

Later in childhood, lifestyle, behavioural factors and exposure, including second-hand tobacco exposure, continue to influence children's predisposition to developing higher adiposity levels. Indeed, not only prenatal but also post-natal exposure to tobacco use by both (or either) parent(s) were found to be associated with increased risk of the disease later in life. It has been shown that independently of pregnancy and early life exposure, second-hand smoking during childhood (until the age of 6 in this study) significantly increases the risk of obesity in children (Raum et al., 2011). Also, the father's smoking when the child is 6-7 years old was shown to increase the risk of the child being obese (Hui, Nelson, Yu, Li, & Fok, 2003).

The dietary patterns of children and adults have a great influence on the nutritional status of their organism. Increased consumption of high-fat and high-sugar products and decreased consumption of vegetables and fruits lead to weight gain and to obesity (Epstein et al., 2001; Nicklas, Yang, Baranowski, Zakeri, & Berenson, 2003; Wang & Beydoun, 2009). However, in some studies the authors did not find a significant association between these behaviours and childhood obesity due to methodological problems in the evaluation of the children's diet (Epstein et al., 2001; Field, Gillman, Rosner, Rockett, & Colditz, 2003; Newby et al., 2003).

Insufficient levels of physical activity among children, as described in the previous chapter, have contributed to the epidemic in childhood obesity (Prentice-Dunn & Prentice-Dunn, 2012). Various kinds of activity, such as walking, active playing, and practicing sports, were described to be a protective factor against childhood obesity (Bingham et al., 2013), through an increase in energy expenditure and improvement of metabolic rate. Again, many studies did not find any statistically significant association between physical activity and obesity, probably due to methodological problems in the evaluation of the physical activity pattern (Ferreira Pronto, 2013; Mota & Ribeiro, 2006; Romanella, Wakat, Loyd, & Kelly, 1991; Suton et al., 2013). An optimal methodology for such studies is the use of accelerometers, which is difficult to apply in large samples (Prince et al., 2008).

The environment where families live is also very important, specifically the car traffic in residential areas. The intensity of traffic could indirectly influence the nutritional status of children by limiting their opportunities to play safely in their neighbourhood (Carver, Timperio, & Crawford, 2008; Kirsten Krahnstoever Davison & Lawson, 2006). Active playing constitutes a big part of children's physical activity. It is defined as a form of activity that is not a part of their extracurricular or school schedule, but simply a spontaneous activity in which they engage (Burdette & Whitaker, 2005b). Therefore, having conditions favourable to playing outside the house can protect against childhood obesity. Traffic was also shown to have an impact on television viewing among children (Burdette & Whitaker, 2005a) which is another important

risk factor for childhood obesity. Furthermore, not living in close proximity to roads with heavy trucks passing was shown to promote walking or biking to school or to other destinations, rather than using passive forms of transportation (Evenson, Scott, Cohen, & Voorhees, 2007; Oluyomi et al., 2014; Timperio, Salmon, Telford, & Crawford, 2005).

A sedentary lifestyle is defined not only by lack of physical activity, but also by an increase in passive activities, such as TV watching, playing on the computer (or otherwise using it), and console games, and time spent using the phone, among others. These activities are common among children, and many studies showed an association between obesity and particularly time spent watching television (Padez et al., 2005; Stamatakis et al., 2013), independently of physical activity (J. A. Mitchell, Pate, Beets, & Nader, 2013; Sisson et al., 2009), although there were some contradictory results (Crespo et al., 2001; Lioret, Maire, Volatier, & Charles, 2007; Ortega, Ruiz, & Sjöström, 2007). Concerning time spent using computers or electronic games, the results are more confusing, with some studies showing a positive association (O'Loughlin, 2000; Stettler, Signer, & Suter, 2004) and others that did not find any statistically significant association with child obesity (Stamatakis et al., 2013; Wake, Hesketh, & Waters, 2003),

Variations in obesity rates have also been observed among residential areas with different levels of urbanization. Geographical inequalities in health are related to the accessibility of shopping, gastronomic, sport objects, hospitals, health centres, and green areas, among other things (Cummins & Macintyre, 2006; Michimi & Wimberly, 2010; Nogueira & Santana, 2004; Smith et al., 2010). Moreover, different types of residential areas very often imply differences in housing conditions (Dunn, 2002). These elements can modulate levels of activity, diet, and exposure to other risk factors for childhood obesity (Farajian et al., 2013).

In developed countries, there appears to be an increased risk of developing a high body mass among children living in rural areas (Bertoncello et al., 2008; Davis et al., 2011; Itoi et al., 2012), in contrast to developed countries where urban children seem to be more affected (Adamo et al., 2011; Chen et al., 2011; Mohan et al., 2004).

As described in previous chapters, obesity is considered to be a disease of affluence (Ezzati et al., 2005), and compared to underdeveloped countries, a higher prevalence of obesity is observed in developed countries (Mercedes de Onis et al., 2010).

Also within each country, the prevalence of childhood obesity varies depending on the socioeconomic status and degree of urbanization of the individuals studied, among many other factors (Chen et al., 2011). The socioeconomic status of the child's family influences their financial capabilities as well as their access to health information and to the correct

interpretation of such information (through, for example, education). Lower income might result in poorer health choices due to the lack of resources. Products rich in sugars and fat, i.e., foods with high energy density, are often cheaper than healthy diets rich in nutrients and with lower energy density (Drewnowski & Darmon, 2005). It has also been shown that price reductions leads to an increase in the sales of healthy products, which shows how important economic capacity is in applying a healthy diet (French, 2003). Lower education, can result in impaired capacity of recognition of the obesity as a problem, incapacity of making healthier lifestyle choices (He & Evans, 2007). It has also been shown that children of parents with lower levels of education are more likely than those of parents with higher levels to consume high-fat and high-sugar products and less likely to eat vegetables, fruits, pasta/noodles/rice and wholemeal bread (Fernández-Alvira et al., 2013). Therefore, the adverse effect of lower socioeconomic status might manifest itself through the inability to make informed decisions about prevention or intervention and/or lack of the economic capacity to pass from decision to action. These limitations can occur all together or separately (Cutler, Lleras-Muney, & Vogl, 2008).

There are discrepancies among different definitions of socioeconomic status, which is problematic, especially when performing international comparisons (Psaki et al., 2014). There are, however, some elements which most of the classifications have in common, which are: parental level of education and occupation as well as family income (Farajian et al., 2013). In developed countries, parental (especially maternal) educational level and income was shown to have an inverse correlation to obesity rates (Bingham et al., 2013; Wang & Zhang, 2006). Differences have also been observed among different ethnic groups, with local minorities typically being at greater risk of obesity (Taveras, Gillman, Kleinman, Rich-Edwards, & Rifas-Shiman, 2010; Wang & Zhang, 2006). Despite smaller numbers of studies, there are some published results showing that contrary to the situation in the developed world, where obesity is more common among children from families of lower socioeconomic status, obesity in developing countries is more strongly associated with higher socioeconomic status (Chen et al., 2011; Julia et al., 2004).

As it is clear that environmental and socioeconomic factors have a strong influence on the growing epidemics of obesity among children, identification of the risk factors contributing to this problem is crucial in order to reverse the rapid increase in its prevalence. Each population is different, with a distinct cultural, historical, genetic background, climate, and environmental niche, characterised by diverse levels of access to natural resources, different habits, and different beliefs, among other things. Multidimensional interplay between these elements determines habits and susceptibility to obesity. Therefore, investigation of the risk factors for

obesity serves as a tool for developing evidence-based intervention programmes designed to reach particular local communities.

7.2. Objectives

Our aim was to study the environmental and socioeconomic risk factors associated with childhood obesity, abdominal obesity and high body fat, in the studied population of 6-8 year-old children living in the Coimbra District.

7.3. Methodology

7.3.1. Obesity indicators

Nutritional status

Obesity and overweight definition was applied using the WHO criteria as described in the general methodology section in Chapter 3.

Body composition

To study body composition categorized body fat values were used with categories normal body fat levels, overfat and high fat as described in the general methodology section in Chapter 3.

Fat distribution

To assess the risk related to abdominal obesity we used categorised WHtR. BMI z-score, %BF and WHtR were also used as continuous variables when appropriate.

7.3.2. Risk factors

We selected risk factors associated with the risk of developing obesity in children such as birth weight, breastfeeding, exposure to tobacco, diet, physical activity, time spent watching TV, heavy truck traffic in the residential area, degree of urbanization of residential area, and socioeconomic status.

7.3.2.1. Early life factors

7.3.2.1.1. Birth weight

Birth weight was used as a continuous variable and parametric Pearson correlation was applied with the continuous variables of BMI z-score, %BF and WHtR; partial correlation was used in order to adjust the test for the child's gestational age, age and gender.

7.3.2.1.2. Breastfeeding

Breastfeeding (whether or not the child had ever been breastfed), the total duration of breastfeeding, and the duration of exclusive breastfeeding were studied and multinominal logistic regression was used to assess the risk of the three obesity indicators. The period of breastfeeding, total or exclusive, was evaluated using the reference of never being breastfed/exclusively breastfed. Multivariate logistic regression was used to test the association with obesity indicators and all tests were adjusted for child's age, gender and SES.

7.3.2.1.3. Prenatal and early childhood second-hand tobacco exposure

Maternal smoking during pregnancy and the 1st year of child's life and overall smoking tobacco by anyone in the household were studied. Periods of smoking during pregnancy were excluded from the analyses as the number of children whose mothers smoked in this period was too small (n=92; 9%) to perform further stratifications (see the section General Results in Chapter 4). Multivariate logistic regression was used to test the association with obesity indicators and all tests were adjusted for the child's age, gender and SES.

7.3.2.2. Risk factors at 6-8 years of age

7.3.2.2.1. Second-hand tobacco exposure at 6-8 years of age

The role of maternal and household members' tobacco use was studied as a potential predictor of childhood obesity. In addition, to estimate the dose-dependent effect, we examined the role of the number of cigarettes that the mother smoked at the time of data collection per day and the number of household members smoking tobacco. Due to the small number of individuals in each group we recoded the "number of cigarettes" variable. The option of 5-10 cigarettes together with 10 or more cigarettes became: over 5 cigarettes per day. The duration of smoking during pregnancy was not evaluated due to the small number of mothers reporting smoking while pregnant, which made a reliable analysis impossible.

For these particular analyses, Multivariate logistic regression was used to test any association with obesity indicators and all tests were adjusted for child's age, gender and SES. In cases of binary (yes/no) variables, not smoking tobacco was used as reference. In the multinominal variables the references were: no cigarettes smoked by mother and nobody smoking in the household.

7.3.2.2.2. Diet

The role of dietary patterns rather than the intake of individual foods was studied in relation to childhood obesity indicators. Three types of dietary patterns were used as described in the chapter 3.6.4. Based on the clustering of foods, three components were as follows:

Base of the Portuguese diet: component including meat, pasta, potatoes and rice.

Mediterranean diet: component consisting of fruits, vegetables, legumes and fish

Saturated fat diet: composed of fast food, butter and eggs.

These variables were used as continuous and parametric Pearson correlations with the BMI z-score, %BF and WHtR were performed. Partial correlations were performed to adjust tests for the child's age, gender and SES.

7.3.2.2.3. Physical activity

We studied the frequency of vigorous physical activity among the children in relation to obesity outputs. The option "exercising 3 or more times per week" was selected as the reference and a multinominal logistic regression was run to assess the risk of increased body mass, body fat and abdominal obesity. A multivariate logistic regression was used to test the association with obesity indicators and all tests were adjusted for the child's age, gender and SES.

7.3.2.2.4. Television watching

We also examined the daily amount of time spent watching television in relation to the three obesity indicators. The reference chosen was under one hour per day TV watching and a multinominal logistic regression was applied. A multivariate logistic regression was used to test the association with obesity indicators and all tests were adjusted for child's age, gender and SES.

7.3.2.2.5. Heavy truck traffic in the residential area

The effect of the heavy traffic of trucks near the child's residence was studied in relation to obesity in children. Truck traffic was dichotomised into heavy trucks passing near the family residence "never or rarely" and "often during the day or all day". The former was used as the reference and the multinominal logistic regression was performed to assess the risk.

A multivariate logistic regression was used for these analyses; in addition, the tests were adjusted for the child's age, gender, degree of urbanization of their residential area, and SES.

7.3.2.3. Socio-demographic factors

7.3.2.3.1. Degree of urbanization of the residential area

We studied the risk of developing obesity, abdominal obesity and high body fat depending on the degree of urbanization of the residential area. Rural (R) residence was used as

the reference and the risk was calculated for children living in Urban (U) and Suburban areas (SU). To do that, we used a Multivariate logistic regression test and further adjusted for child's age, gender and SES.

7.3.2.3.2. Socioeconomic status

The role of family socioeconomic status was investigated, using the definitions of low/high SES as described in the general methodology section. Multinominal logistic regression was used to assess the risk of the three obesity indicators depending on SES. Adjusted models included child's age, gender and degree of urbanization of the residential area as covariates.

7.3.3. Multivariate analyses

Finally, for all three indicators: obesity, abdominal obesity, and high body fat, we built a multivariate model including all factors that were shown to be significantly associated with all three indicators of obesity in univariate analyses. The final, fully adjusted models served to examine which risk factors continue having a significant effect on childhood obesity adjusted for all the encountered significant risk factors.

For all the tests described in this chapter, SPSS v20 statistics software was used to process data and perform analyses and prepare figures. P-values below 0.05 were considered significant.

7.4. Results

7.4.1. Early life factors

7.4.1.1. Birth weight

We found a positive and significant, if not very strong, correlation between the birth weight and the BMI z-score ($r=0.169$; $p<0.01$), WHtR ($r=0.079$; $p=0.015$) and %BF ($r=0.087$; $p<0.01$) at measurement time. After adjustment for gestational age, age and gender, the correlations remained significant for the BMI z-score ($r=0.120$; $p<0.01$) and %BF ($r=0.075$; $p<0.01$). Below, in the Figure 7.1 we present a graph illustrating the results.

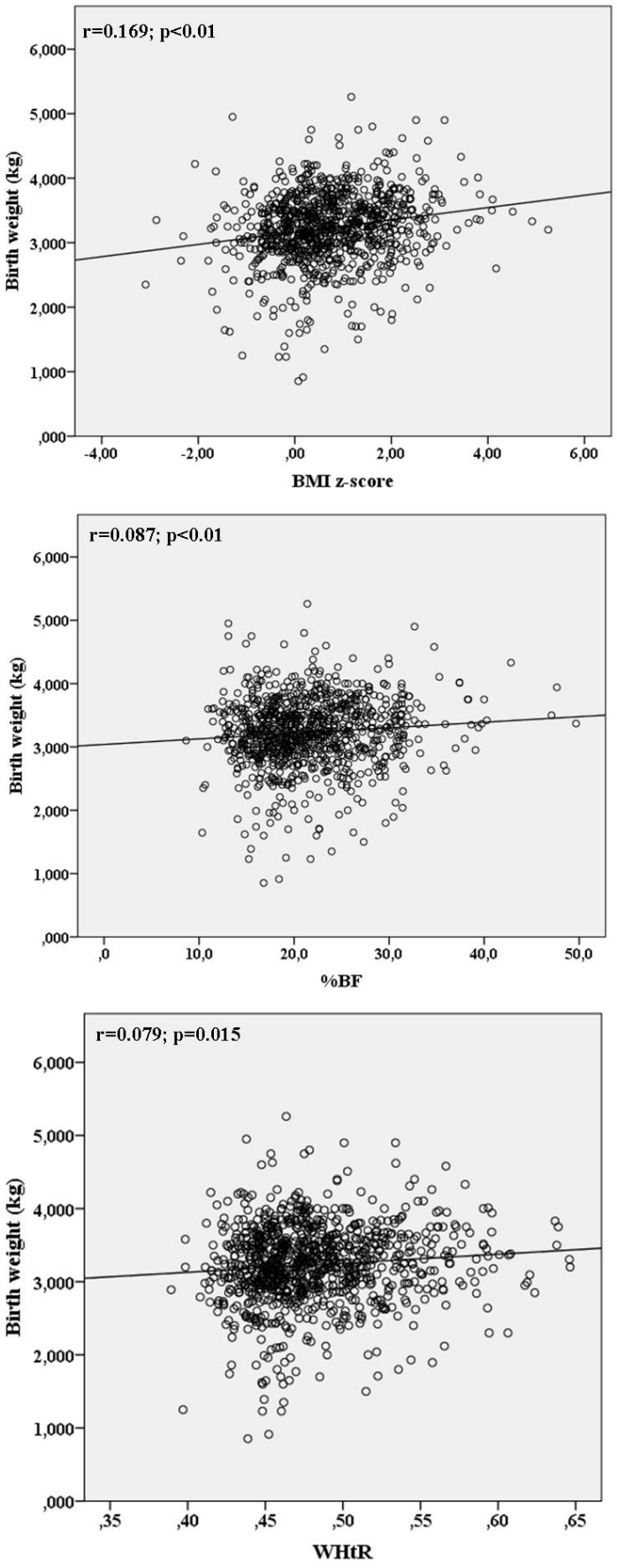


Figure 7.1Correlations between the birth weight and childhood adiposity indicators.

Scatter dots graphs with the regression lines illustrating the correlations between the birth weight and childhood BMI z-score (a), WHtR (b) and BF% (c). Results presented as r (correlation coefficient) and p values obtained using Pearson correlation test.

7.4.1.2. Breastfeeding

When considering the variable breastfeeding as a dichotomous variable (ever being breastfed- yes/no) there were no significant associations between adiposity in childhood and the fact of the child having been breastfed or not. However, we could see a tendency of lack of breastfeeding to increase the risk of obesity (crude OR=1.48; p=0.25; adjusted OR=1.53; p=0.24), abdominal obesity (OR=1.40; p=0.20; OR=1.46; p=0.18), overfat (OR=1.39; p=0.26; adjusted OR=1.46; p=0.22) and high fat (OR=1.43; p=0.25; adjusted OR=1.42; p=0.28).

7.4.1.3. Total breastfeeding period

The Table 7.1 describes the association between obesity parameters and the total time, in months, of breastfeeding. In relation to the children who were never breastfed, those who were breastfed during <3 months, 3-6 months, 6-9 months and >9months were all characterized by an increased risk of the child's being overweight with significant results only for being breastfed for over 9 months, causing a triple increase in the risk (OR=3.03; p=0.01).

There was a significant protective effect observed against obesity for children breastfed 6-9 months (OR=0.39; p=0.04) and although not significant, all other periods of breastfeeding were protective against obesity compared to never being breastfed.

No results were significant for the WHtR, although periods 3-6months and 6-9 months were also protective against abdominal obesity comparing to never being breastfed. Being breastfed for over 9 months, although not significantly, increased the risk of abdominal obesity (OR=1.15; p=0.64; AOR=1.11; p=0.76) suggesting a U-shaped association between total breastfeeding period and the risk of abdominal obesity.

For body fat no results were significant although all periods were protective against being overfat with the strongest protection for period up to three months and weakest for over 9 months, with dose effect observed. All periods besides >9 months were found to lower not significantly the risk of high body fat and being breastfed for over 9 months although not significantly increased this risk suggesting a U-shaped association between total breastfeeding period and the risk of high body fat levels. All these associations remained significant after adjustment for covariates.

7.4.1.4. Exclusive breastfeeding period

All periods of exclusive breastfeeding increased significantly the risk of child being overweight. An exclusive breastfeeding period of 3-6 or over 9 months turned out to be significantly associated with increased risk of overweight (OR=2.77; p=0.02 and OR=3.42;

p=0.03 respectively) which remained significant after adjustment (OR=2.70; p=0.03 and OR=3.59; p=0.03 respectively).

Again, although not significant, exclusive breastfeeding during any period, comparing to never being breastfed, was protective against obesity, although not significantly.

Besides the period of 3-6 months which showed no effect, all remaining periods showed a tendency of protecting against abdominal obesity, however not significantly also after adjustment.

Exclusive breastfeeding for all periods besides >9months showed a tendency, but not significant, of protection against child being overfat. Periods up to three months (AOR= 0.66; p=0.28) and 6-9months (AOR=0.82:p=0.68) seemed to protect against child having high fat values but the result was not statistically significant and the remaining two periods showed no effect on high body fat. A detailed description of the results can be found in the Table 7.2 .

Table 7.1 Association of obesity, abdominal obesity and an increased body fat with the total breastfeeding period.

Nutritional status	Total Breastfeeding period (months)	n	OR	95% CI	p value	AOR	95% CI	p value
obesity	<3	30	1.95	0.83-4.57	0.13	1.73	0.73-4.12	0.22
	3-6	18	1.99	0.84-4.71	0.12	1.82	0.76-4.37	0.18
	6-9	12	1.79	0.75-4.29	0.19	1.52	0.63-3.70	0.35
	>9	35	3.03	1.31-6.97	0.01	2.83	1.22-6.60	0.02
	never	10	Ref			Ref		
overweight	<3	50	0.81	0.37-1.77	0.59	0.77	0.34-1.75	0.53
	3-6	43	0.58	0.25-1.35	0.21	0.46	0.19-1.14	0.10
	6-9	38	0.39	0.16-0.97	0.04	0.37	0.14-0.96	0.04
	>9	85	0.87	0.40-1.89	0.73	0.88	0.39-1.97	0.75
	never	7	Ref			Ref		
WHtR > 0.5	<3	62	1.00	0.54-1.87	1.00	0.93	0.47-1.82	0.83
	3-6	41	0.76	0.39-1.45	0.40	0.68	0.34-1.37	0.28
	6-9	32	0.59	0.30-1.16	0.12	0.58	0.28-1.19	0.14
	>9	85	1.15	0.63-2.12	0.64	1.11	0.58-2.13	0.76
	never	17	Ref			Ref		
High fat	<3	42	0.87	0.42-1.81	0.71	0.91	0.42-1.97	0.80
	3-6	33	0.83	0.39-1.78	0.64	0.80	0.36-1.79	0.59
	6-9	22	0.55	0.25-1.21	0.14	0.56	0.24-1.29	0.17
	>9	61	1.11	0.55-2.27	0.77	1.18	0.56-2.52	0.66
	never	12	Ref			Ref		
Overfat	<3	43	0.71	0.36-1.42	0.33	0.59	0.29-1.21	0.15
	3-6	38	0.77	0.38-1.55	0.46	0.73	0.35-1.49	0.39
	6-9	39	0.78	0.39-1.56	0.48	0.66	0.32-1.37	0.27
	>9	60	0.88	0.45-1.71	0.70	0.80	0.40-1.60	0.53
	never	15	Ref			Ref		

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

AOR- Adjuster for gender, age and SES

p values were considered significant below the 0.05 and underlined

Abbreviations: SES- socioeconomic status; WHtR- waist to height ratio; BF - body fat

Table 7.2 Association of the obesity, abdominal obesity and high body fat with exclusive breastfeeding period.

Nutritional status	Exclusive Breastfeeding period	n	OR	95% CI	p value	AOR	95% CI	p value
obesity	<3	35	2.00	0.83-4.80	0.12	1.87	0.78-4.52	0.16
	3-6	43	2.77	1.16-6.61	0.02	2.70	1.12-6.48	0.03
	6-9	12	1.82	0.67-4.96	0.24	1.61	0.57-4.50	0.37
	>9	4	3.42	1.10-10.63	0.03	3.59	1.14-11.36	0.03
	never	10	Ref			Ref		
overweight	<3	83	0.53	0.24-1.14	0.10	0.51	0.23-1.14	0.10
	3-6	105	0.71	0.33-1.51	0.37	0.69	0.31-1.54	0.37
	6-9	16	0.81	0.32-2.05	0.65	0.83	0.32-2.19	0.71
	>9	10	0.82	0.23-2.96	0.76	0.79	0.21-2.96	0.72
	never	6	Ref			Ref		
WHtR > 0.5l	<3	84	0.85	0.45-1.60	0.62	0.77	0.40-1.50	0.45
	3-6	106	1.14	0.61-2.12	0.69	1.01	0.52-1.95	0.98
	6-9	21	0.98	0.46-2.09	0.95	0.86	0.38-1.94	0.72
	>9	6	0.66	0.23-1.89	0.44	0.56	0.19-1.67	0.30
	never	15	Ref			Ref		
High fat	<3	58	0.64	0.31-1.31	0.22	0.66	0.31-1.41	0.28
	3-6	76	0.86	0.42-1.76	0.69	0.95	0.45-2.00	0.89
	6-9	15	0.81	0.34-1.94	0.64	0.82	0.33-2.07	0.68
	>9	6	0.92	0.29-2.85	0.88	0.97	0.30-3.13	0.96
	never	12	Ref			Ref		
Overfat	<3	75	0.66	0.34-1.28	0.22	0.68	0.34-1.35	0.26
	3-6	71	0.65	0.33-1.26	0.20	0.66	0.33-1.32	0.24
	6-9	21	0.91	0.41-2.00	0.81	0.86	0.37-1.98	0.72
	>9	9	1.10	0.40-3.01	0.85	1.08	0.39-3.05	0.88
	never	15	Ref			Ref		

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

AOR- Adjuster for gender, age and SES

p values were considered significant below the 0.05 and underlined

Abbreviations: SES- socioeconomic status; WHtR- waist to height ratio; BF - body fat

7.4.1.5. Maternal smoking during pregnancy

Children of mothers who smoked during the pregnancy had a 26% increased risk of being obese (AOR=1.26; p=0.51) and 33% (AOR=1.33; p=0.36) increased risk of having high body fat; however, the results did not reach the level of significance. There seemed to be a decreased, although not significantly, risk of becoming overweight for the children of mothers who smoked during pregnancy (OR=0.56; p=0.06). No effect was found on abdominal obesity or overfat status. See Table 7.3.

7.4.1.6. Maternal smoking during the first year of the child's life

Maternal smoking during the child's first year of life showed a 36% increased risk for the child being obese (AOR=1.36; p=0.31), 20% increased risk of having abdominal obesity (AOR=1.20; p=0.45) 34% of child being overfat (AOR=1.34; p=0.26) and 45% increased risk of having high body fat (AOR=1.45; p=0.17), but these results were not significant. Similarly to smoking during pregnancy, maternal smoking during the first year of the child's life was revealed to be protective against the child's becoming overweight (AOR=0.71; p=0.21) but the result was not significant (Table 7.3) .

Table 7.3 Association of obesity, abdominal obesity and high body fat with maternal smoking during the pregnancy and the first year of child's life

Nutritional status	Maternal smoking during the pregnancy	n	OR	95% CI	p value	AOR	95% CI	p value
obesity	yes	13	1.26	0.67-2.38	0.48	1.26	0.63-2.54	0.51
	no	91	Ref			Ref		
overweight	yes	13	0.56	0.30-1.03	0.06	0.64	0.33-1.23	0.18
	no	209	Ref			Ref		
WHtR > 0.5	yes	19	0.85	0.50-1.45	0.56	0.95	0.54-1.70	0.88
	no	216	Ref			Ref		
High fat	yes	18	1.22	0.70-2.15	0.48	1.33	0.72-2.46	0.36
	no	150	Ref			Ref		
Overfat	yes	15	0.86	0.47-1.56	0.62	1.01	0.53-1.90	0.98
	no	178	Ref			Ref		
	Maternal smoking during the 1st year of child's life	n	OR	95% CI	p value	AOR	95% CI	p value
obesity	yes	17	1.33	0.76-2.32	0.32	1.36	0.75-2.46	0.31
	no	87	Ref			Ref		
overweight	yes	20	0.67	0.40-1.11	0.12	0.71	0.42-1.21	0.21
	no	202	Ref			Ref		
WHtR > 0.5	yes	30	1.04	0.67-1.61	0.88	1.20	0.75-1.92	0.45
	no	205	Ref			Ref		
High fat	yes	24	1.29	0.78-2.13	0.32	1.45	0.86-2.45	0.17
	no	144	Ref					
Overfat	yes	27	1.27	0.79-2.06	0.32	1.34	0.80-2.24	0.26
	no	164	Ref			Ref		

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

AOR- Adjuster for gender, age and SES

p values were considered significant below the 0.05 and underlined

Abbreviations: SES- socioeconomic status; WHtR- waist to height ratio; BF - body fat

7.4.2. Current exposure

7.4.2.1. Second hand tobacco use at 6-8 years of age

7.4.2.1.1. Maternal tobacco smoking

Current maternal smoking was significantly associated with an increased risk of obesity (AOR=1.83; p=0.02), abdominal obesity OR= 1.83; p<0.01), overfat (OR=1.91; p<0.01) and high body fat (OR= 1.91; p<0.001) and the association further increased after adjustment for covariates.

Moreover, the number of cigarettes that the mother declared herself to be smoking after adjustment had a significant effect on all of the obesity indicators. A mother smoking over 10 cigarettes per day, comparing to non-smoking mother, significantly increased the risk of obesity (AOR=3.59; p<0.01), abdominal obesity (OR=2.33; p<0.01), overfat (AOR=2.42; p<0.001) and high body fat (OR=2.72; p<0.01). In addition, smoking 1-10 cigarettes per day also increased the risk of being overfat (OR=2.42; p<0.001). Smoking 1-10 cigarettes per day increased, although not significantly (apart from overfat), the risk of all obesity indicators. In cases of obesity, abdominal obesity and body fat, there seemed to be a dose-dependent association with higher numbers of cigarettes representing a higher risk of adiposity developing in children (Table 7.4).

Table 7.4 Association of obesity, abdominal obesity and high body fat with current maternal smoking as well as the number of smoked cigarettes she smokes per day.

Nutritional status	Current Maternal Smoking	n	OR	95% CI	p value	AOR	95% CI	p value
Obesity	yes	26	1.63	1.00-2.63	0.05	1.83	1.10-3.04	0.02
	no	78	Ref			Ref		
Overweight	yes	43	1.14	0.77-1.68	0.52	1.31	0.87-1.97	0.19
	no	179	Ref			Ref		
WHtR > 0.5	yes	54	1.50	1.05-2.16	0.03	1.83	1.24-2.68	<0.01
	no	182	Ref			Ref		
High fat	yes	40	1.74	1.14-2.64	0.01	2.12	1.36-3.29	<0.001
	no	130	Ref			Ref		
Overfat	yes	44	1.67	1.11-2.50	0.01	1.91	1.25-2.94	<0.01
	no	149	Ref			Ref		
	Number of cigarettes mother smokes (per day)	n	OR	95% CI	p value	AOR	95% CI	p value
Obesity	1-10	11	1.34	0.85-2.12	0.21	1.57	0.97-2.53	0.06
	>10	15	1.12	0.59-2.16	0.73	1.27	0.64-2.51	0.50
	0	78	Ref			Ref		
Overweight	1-10	30	1.09	0.55-2.16	0.80	1.10	0.53-2.29	0.81
	>10	13	2.85	1.49-5.47	<0.01	3.59	1.83-7.05	<0.01
	0	178	Ref			Ref		
WHtR > 0.5	1-10	32	1.37	0.88-2.14	0.16	1.54	0.96-2.47	0.07
	>10	22	1.70	0.99-2.90	0.054	2.33	1.32-4.12	<0.01
	0	182	Ref			Ref		
High fat	1-10	21	1.48	0.87-2.54	0.15	1.75	0.99-3.10	0.053
	>10	19	2.15	1.19-3.87	0.01	2.72	1.46-5.07	<0.01
	0	130	Ref			Ref		
Overfat	1-10	34	2.11	1.33-3.35	<0.01	2.42	1.48-3.96	<0.001
	>10	11	1.09	0.54-2.20	0.81	1.25	0.59-2.65	0.56
	0	148	Ref			Ref		

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

AOR- Adjuster for gender, age and SES

p values were considered significant below the 0.05 and underlined

Abbreviations: SES- socioeconomic status; WHtR- waist to height ratio; BF - body fat

7.4.2.1.2. Household members smoking

Generally, having anyone smoking at the household increased the risk of all obesity indicators in children. Having anyone smoking in the child's household significantly increased the risk of obesity (OR=1.56; p=0.03), overfat (OR=1.42; p=0.04) and high body fat (OR=1.70; p<0.01). Even after adjustment the results remained significant high body fat (OR=1.84; p<0.001) and overfat (AOR=1.46; p=0.04) (Table 7.5).

Having two or more people smoking at home increased the risk even further, reaching odds ratio levels after adjustments of 2.02 (p=0.02) for overweight, and 2.32 (p<0.01). A table with complete information on the results can be found in the Table 7.5. A dose effect between number of household members smoking and the risk of obesity, abdominal obesity and high fat was observed.

Table 7.5 Association of obesity, abdominal obesity and high body fat with any household members' smoking at home and dose effect by the number of household members smoking.

Nutritional status	Any member of the household smoking	n	OR	95% CI	p value	AOR	95% CI	p value
Obesity	yes	45	1.56	1.04-2.36	0.03	1.52	0.98-2.35	0.06
	no	60	Ref			Ref		
Overweight	yes	80	1.06	0.77-1.45	0.74	1.11	0.80-1.55	0.53
	no	144	Ref			Ref		
WHtR > 0.5	yes	94	1.34	0.99-1.82	0.06	1.36	0.98-1.88	0.07
	no	142	Ref			Ref		
High fat	yes	73	1.70	1.20-2.41	<0.01	1.84	1.27-2.66	<0.01
	no	96	Ref			Ref		
Overfat	yes	75	1.42	1.01-1.99	0.04	1.46	1.03-2.09	0.04
	no	118	Ref			Ref		
	Number of household members smoking	n	OR	95% CI	p value	AOR	95% CI	p value
Obesity	1	26	1.16	0.81-1.67	0.41	1.26	0.86-1.83	0.23
	2 or more	19	1.09	0.66-1.80	0.73	1.09	0.64-1.86	0.74
	none	60	Ref			Ref		
Overweight	1	56	1.31	0.79-2.15	0.29	1.25	0.74-2.13	0.41
	2 or more	24	2.04	1.14-3.64	0.02	2.02	1.10-3.69	0.02
	none	144	Ref			Ref		
WHtR > 0.5	1	61	1.27	0.89-1.79	0.18	1.26	0.87-1.83	0.22
	2 or more	33	1.51	0.97-2.37	0.07	1.57	0.97-2.53	0.07
	none	142	Ref			Ref		
High fat	1	46	1.54	1.03-2.30	0.04	1.62	1.06-2.49	0.03
	2 or more	27	2.06	1.24-3.43	0.01	2.32	1.37-3.95	<0.01
	none	96	Ref			Ref		
Overfat	1	52	1.42	0.97-2.07	0.07	1.48	0.99-2.21	0.06
	2 or more	23	1.43	0.85-2.42	0.18	1.44	0.82-2.51	0.20
	none	118	Ref			Ref		

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

AOR- Adjuster for gender, age and SES

p values were considered significant below the 0.05 and underlined

Abbreviations: SES- socioeconomic status; WHtR- waist to height ratio; BF - body fat

7.4.2.1.3. Diet

The dietary component classified as the base of the diet was shown to be significantly and inversely correlated to the values of the WHtR (r=-0.07; p=0.02) and remained significant after adjustment for SES (r=-0.07; p=0.046). The saturated fats diet pattern was significantly and inversely correlated with the BMI z-score (r=-0.07; p=0.03) and remained so after the adjustment (r=-0.07; p=0.03). No other result turned out to be significant. A Table 7.6 with all the results can be found below.

Table 7.6 Association of between the adhesion to dietary patterns and childhood adiposity measures: BMI z-score, WHtR and %BF.

Dietary Pattern		Crude			Adjusted		
		%BF	WHtR	BMI z-score	%BF	WHtR	BMI z-score
Base of Portuguese diet	r	-0.04	-0.07	-0.02	-0.02	-0.06	-0.02
	p	0.20	0.02	0.49	0.62	0.09	0.63
Mediterranean Diet	r	0.02	-0.02	0.00	0.02	-0.01	0.01
	p	0.62	0.46	0.99	0.61	0.68	0.79
Saturated fats diet	r	-0.04	-0.04	-0.07	-0.05	-0.06	-0.07
	p	0.24	0.26	0.03	0.16	0.08	0.03

Results obtained using the Pearson correlation test and partial correlations for adjustment

Results are presented as r- correlation coefficient and p values

Adjuster for gender, age and SES

p values were considered significant below the 0.05 and underlined

Abbreviations: SES- socioeconomic status; WHtR- waist to height ratio; BF - body fat

7.4.2.1.4. Physical activity

Even though the frequency of vigorous physical activity in children was not significantly associated with the obesity indicators, a tendency was observed toward less frequent activity being related to an increased risk of all obesity indicators. Exercising vigorously less than 3 times per week increased the risk of developing all three obesity indicators. The highest risk of being obese and overweight was observed for the children who never or occasionally practiced vigorous physical exercise, compared to those who practiced at least 3 times a week (AOR=1.16;p=0.69 and AOR=1.53; p=0.10 respectively). Children practicing 1-2 times per week, comparing to those practicing 3 or more times, were also shown to have an increased risk of obesity (OR=1.18; p=0.53) and overweight (OR=1.21 ;p=0.33), however not statistically significant.

For the abdominal obesity indicator, after adjustment the risk was 22% higher for children practicing 1-2 times per week but the result was not significant (AOR=1.22; p=0.31) and no effect was found for those never or occasionally practicing vigorous physical activity.

No effect was found between the frequency of vigorous physical activity and being overfat. Compared to children practicing vigorous physical activity 3 or more times per week, those practicing never or occasionally or 1-2 times per week had a higher risk of having a high body fat (AOR=1.50;p=0.18 , AOR=1.19; p=0.44 respectively), but the result was not statistically significant. Details of the results can be found in the (Table 7.7).

7.4.2.1.5. TV watching

Compared to those who watched TV over three hours a day, children who watched less than one hour, had a strongly decreased risk of being overweight (OR=0.36;p<0.01) and having abdominal obesity (OR=0.57; p=0.02) and having a high body fat (OR=0.58; p=0.04). Obesity was not significantly affected by the time spent watching TV. After adjustment the risk of being overweight (AOR=0.29; p<0.01) and abdominal obesity (AOR=0.56; p=0.02) remained significant while the risk of having high fat levels remained decreased but only borderline significant (OR=0.58; p=0.06). Watching TV between 1-3 hours a day showed no effect on all indicators of obesity except for slightly increased risk of becoming overfat (AOR=1.23; p=0.37).Details of the results can be found in the Table 7.7.

Table 7.7 Association of obesity, abdominal obesity and high body fat with vigorous physical activity and TV viewing.

Nutritional status	Frequency of vigorous physical activity (a week)	n	OR	95% CI	p value	AOR	95% CI	p value
Obesity	never or occasionally	17	1.56	0.79-3.06	0.20	1.16	0.56-2.41	0.69
	1-2	66	1.41	0.86-2.31	0.18	1.18	0.70-2.00	0.53
	≥3	22	Ref			Ref		
Overweight	never or occasionally	39	1.56	0.96-2.54	0.07	1.53	0.92-2.54	0.10
	1-2	133	1.23	0.86-1.76	0.26	1.21	0.83-1.75	0.33
	≥3	53	Ref			Ref		
WHtR > 0.5	never or occasionally	33	1.25	0.76-2.05	0.38	0.97	0.57-1.66	0.91
	1-2	152	1.39	0.98-1.99	0.07	1.22	0.83-1.79	0.31
	≥3	52	Ref			Ref		
High fat	never or occasionally	29	1.59	0.91-2.76	0.10	1.50	0.83-2.71	0.18
	1-2	104	1.29	0.85-1.97	0.23	1.19	0.77-1.84	0.44
	≥3	37	Ref			Ref		
Overfat	never or occasionally	26	0.96	0.56-1.64	0.87	0.93	0.53-1.66	0.82
	1-2	116	0.97	0.67-1.41	0.88	0.95	0.64-1.41	0.80
	≥3	55	Ref			Ref		
	Watching TV (hours/ day)	n	OR	95% CI	p value	AOR	95% CI	p value
Obesity	<1	13	0.91	0.59-1.42	0.69	0.94	0.59-1.50	0.80
	1-3	68	0.88	0.59-1.30	0.52	0.87	0.57-1.31	0.50
	>3	24	Ref			Ref		
Overweight	<1	63	0.36	0.17-0.73	<0.01	0.29	0.13-0.64	<0.01
	1-3	117	0.99	0.60-1.64	0.97	0.93	0.55-1.57	0.77
	>3	47	Ref			Ref		
WHtR > 0.5	<1	48	0.57	0.36-0.88	0.01	0.56	0.35-0.91	0.02
	1-3	135	0.88	0.61-1.28	0.51	0.90	0.60-1.33	0.58
	>3	55	Ref			Ref		
High fat	<1	35	0.58	0.35-0.96	0.04	0.58	0.34-1.01	0.06
	1-3	97	0.94	0.62-1.45	0.79	0.97	0.62-1.52	0.90
	>3	39	Ref			Ref		
Overfat	<1	45	0.78	0.48-1.28	0.33	0.87	0.51-1.46	0.59
	1-3	115	1.18	0.77-1.81	0.45	1.23	0.78-1.93	0.37
	>3	37	Ref			Ref		

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

AOR- Adjuster for gender, age and SES

p values were considered significant below the 0.05 and underlined

Abbreviations: SES- socioeconomic status; WHtR- waist to height ratio; BF - body fat

7.4.2.1.6. Truck traffic frequency

As showed in the Table 7.8 the frequency of heavy truck traffic near the residence of the family was not significantly associated with childhood obesity, although a tendency was shown toward increased risk of obesity and overweight for children living in the areas with heavy truck traffic often during the day or all day (AOR=1.23; p=0.49 and AOR=1.38; p=0.17 respectively). Also, having heavy trucks passing often during the day or all day was shown to have an adverse effect increasing the risk of having high body fat (AOR=1.18; p=0.35), being overfat (AOR=1.44; p=0.11) and against abdominal obesity (AOR=1.44; p=0.11) but these results were not statistically significant.

Table 7.8 Association of obesity, abdominal obesity and high body fat with heavy truck traffic in the residential area.

Nutritional status	Frequency of heavy trucks in the residential area	n	OR	95% CI	p value	AOR	95% CI	p value
Overweight	Often during the day or all day	186	1.26	0.84-1.90	0.27	1.38	0.88-2.16	0.17
	Never or rarely	35	Ref			Ref		
Obesity	Often during the day or all day	86	1.14	0.66-1.97	0.63	1.23	0.68-2.24	0.49
	Never or rarely	18	Ref			Ref		
WHtR > 0.5	Often during the day or all day	196	1.24	0.84-1.83	0.27	1.44	0.92-2.24	0.11
	Never or rarely	39	Ref			Ref		
High fat	Often during the day or all day	139	1.16	0.75-1.79	0.52	1.18	0.75-1.85	0.48
	Never or rarely	31	Ref			Ref		
Overfat	Often during the day or all day	163	1.40	0.91-2.17	0.13	1.44	0.92-2.27	0.11
	Never or rarely	30	Ref			Ref		

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

AOR- Adjuster for gender, age and SES

p values were considered significant below the 0.05 and underlined

Abbreviations: SES- socioeconomic status; WHtR- waist to height ratio; BF - body fat

7.4.3. Degree of urbanization and socioeconomic status

7.4.3.1. Degree of urbanization

When analysing the association of obesity parameters with the places where families live – rural, suburban or urban – living in urban areas showed to increase the risk of all obesity indicators. The highest and significant risk was found for abdominal obesity and high body fat was observed for children living in urban areas in relation to rural areas residents (OR=3.04, p=0.01 and OR=2.47, p= 0.03 respectively). Although nearly twice increased the obesity risk (AOR=1.96; p=0.17) was also observed among urban children, the result did not reach the level of significance.

Children living in suburban areas also showed to have an increased risk compared to rural residents, with 36% higher risk of obesity (AOR=1.36; p=0.57), and 27% increased risk of abdominal obesity (AOR=1.27; p=0.59), 18% of being overfat and 50% of having high body fat (AOR=1.50; p=0.38); however the results were not statistically significant. Results presented in the Table 7.9.

7.4.3.2. Socioeconomic status

As for the SES, there was an 80% higher risk of obesity in families with lower SES compared against those with higher SES and the result was statistically significant (OR=1.80; p=0.01). There was no significant association between being overweight and SES. Moreover, children from families with lower SES had 48% higher risk of developing abdominal obesity, 47% of being overfat and 58% increased risk of having high body fat content, (AOR= 1.48, p<0.01, AOR= 1.47, p=0.03 and AOR= 1.58; p=0.02 respectively). Detailed results can be found in the Table 7.9.

Table 7.9 Association of obesity, abdominal obesity and a high body fat with socioeconomic status and the degree of urbanization of the residential area.

Nutritional status	SES	n	Crude			Adjusted		
			OR	95% CI	p value	AOR[1]	95% CI	p value
Overweight	Lower	114	1.00	0.74-1.36	1.00	1.04	0.75-1.46	0.81
	Higher	104	Ref			Ref		
Obesity	Lower	64	1.83	1.18-2.81	<0.01	1.80	1.14-2.85	0.01
	Higher	34	Ref			Ref		
WHtR > 0.5	Lower	122	1.34	0.99-1.82	0.06	1.48	1.06-2.07	0.02
	Higher	99	Ref			Ref		
High fat	Lower	91	1.48	1.04-2.10	0.03	1.58	1.08-2.31	0.02
	Higher	71	Ref			Ref		
Overfat	Lower	99	1.33	0.95-1.85	0.09	1.47	1.03-2.11	0.03
	Higher	86	Ref			Ref		
	Degree of urbanization	n	OR	95% CI	p value	AOR[2]	95% CI	p value
Overweight	U	126	1.15	0.70-1.89	0.58	1.08	0.59-1.99	0.81
	SU	53	0.80	0.46-1.38	0.42	0.74	0.37-1.49	0.40
	R	25	Ref			Ref		
Obese	U	63	1.85	0.84-4.07	0.13	1.96	0.74-5.18	0.17
	SU	28	1.35	0.58-3.12	0.48	1.36	0.47-3.91	0.57
	R	8	Ref			Ref		
WHtR > 0.5	U	182	2.92	1.37-6.23	0.01	3.04	1.40-6.62	0.01
	SU	25	1.23	0.53-2.88	0.63	1.27	0.53-3.01	0.59
	R	8	Ref			Ref		
High fat	U	122	2.25	1.00-5.09	0.051	2.47	1.07-5.67	0.03
	SU	26	1.57	0.64-3.84	0.33	1.50	0.61-3.73	0.38
	R	7	Ref			Ref		
Overfat	U	135	1.58	0.80-3.13	0.18	1.65	0.82-3.31	0.16
	SU	33	1.26	0.59-2.70	0.54	1.18	0.55-2.54	0.68
	R	11	Ref			Ref		

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

AOR[1]- Adjuster for gender, age and urbanization degree of the residential area; AOR[2]- Adjuster for gender, age and SES

p values were considered significant below the 0.05 and underlined

Abbreviations: SES- socioeconomic status; WHtR- waist to height ratio; BF - body fat; U- urban; SU-suburban; R-rural

7.4.4. Multivariate regression models

7.4.4.1. Nutritional status

In the overall group, statistically significant risk factors for overweight were birth weight (OR=1.57; 0.01), smoking in the home (OR=0.44; p=0.04) and 1 smoker in the household (OR=2.07; p=0.045). Factors related to obesity were birth weight (OR=2.00; p=0.003) and watching TV less than one hour per day (OR=0.31; p=0.004) as opposed to watching TV 3 or more hours per day. Results in the Table 7.10.

Table 7.10 Multivariate regression model including all the variables associated significantly with overweight and obesity in the univariate models (model adjusted for all these factors)

Risk factors		Overweight			Obesity		
		AOR	95% CI	p value	AOR	95% CI	p value
Age (decimal years)		0.97	0.73-1.27	0.81	1.00	0.69-1.44	0.98
Birth weight (kg)		1.57	1.12-2.22	0.01	2.00	1.26-3.17	0.003
Saturated fats		0.87	0.73-1.04	0.12	0.83	0.65-1.05	0.12
Gender	Girls	1.27	0.91-1.78	0.17	1.28	0.81-2.03	0.29
	Boys						
SES	Lower	0.89	0.63-1.25	0.50	1.51	0.94-2.42	0.09
	Higher						
Total Breastfeeding period	<3	0.74	0.08-6.80	0.79	2.70	0.13-55.81	0.52
	3-6	0.72	0.08-6.61	0.77	1.18	0.06-25.33	0.91
	6-9	0.67	0.07-6.14	0.72	0.92	0.04-20.02	0.96
	>9	1.38	0.15-12.46	0.78	1.79	0.08-38.05	0.71
	never						
Exclusive Breastfeeding period	<3	2.05	0.20-20.77	0.54	0.23	0.01-4.88	0.35
	3-6	2.16	0.22-21.61	0.51	0.48	0.02-10.02	0.64
	6-9	1.16	0.11-12.36	0.90	0.55	0.02-12.48	0.71
	>9	1.96	0.17-22.93	0.59	0.57	0.02-15.02	0.74
	never						
Anyone smoking at home	yes	0.44	0.19-0.97	0.04	1.00	0.39-2.59	1.00
	no						
Number of household members smoking	1	2.07	1.02-4.22	0.045	0.97	0.42-2.23	0.94
	≥2	X		X	X		X
	0						
Current Maternal smoking	yes	X		X	0.80	0.30-2.12	0.65
	no						
Number of cigarettes mother smokes (per day)	1-10	X		X	X		X
	>10	X		X	X		X
	0	X		X	X		X
TV watching (hours a day)	<1	0.85	0.51-1.41	0.53	0.31	0.14-0.69	0.004
	1-3	0.89	0.57-1.40	0.62	0.93	0.53-1.62	0.79
	>3						

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

AOR- Odds ratio adjuster all included factors;

p values were considered significant below the 0.05 and underlined

Abbreviations: SES- socioeconomic status

X- Floating point overflow occurred while computing this statistic. Its value is therefore set to system missing.

7.4.4.2. Abdominal obesity

Associated with abdominal obesity in the final fully adjusted model were gender (for girls OR=2.17; p<0.001), living in an urban zone (OR=3.00; p=0.01), and having a mother smoking1-10 cigarettes per day (OR=2.45; p<0.01). Results in the **Error! Not a valid bookmark self-reference.**.

Table 7.11 Multivariate regression model including all the variables associated significantly with increased Waist to Height Ratio in the univariate models (model adjusted for all these factors)

Risk factor		WHtR <0.5		
		AOR	95%CI	p-value
Age (decimal years)		1.08	0.82-1.42	0.60
Gender	Girls	2.17	1.54-3.06	<0.001
	Boys			
SES	Lower	1.38	0.98-1.96	0.07
	Higher			
Degree of urbanization	U	3.00	1.36-6.60	0.01
	SU	1.25	0.52-2.99	0.62
	R			
Number of cigarettes mother smokes (per day)	1-10	1.47	0.89-2.44	0.13
	>10	2.45	1.35-4.47	<0.01
	0			
TV watching (hours/day)	<1	0.65	0.39-1.10	0.11
	1-3	1.01	0.66-1.56	0.96
	>3			

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

AOR- Odds ratio adjuster all included factors

p values were considered significant below the 0.05 and underlined

Abbreviations: SES- socioeconomic status; WHtR- waist to height ratio; U- urban; SU-suburban; R-rural

7.4.4.3. Body fat

The two factors significantly associated in the final model with high body fat were gender (OR=0.67; p=0.045) and birth weight (OR=1.58; 0.02). No factor remained significantly associated with being overfat in the final model. See results in the **Error! Not a valid bookmark self-reference.**.

Table 7.12 Multivariate regression model including all the variables associated significantly with increased body fat percentage in the univariate models (model adjusted for all these factors)

Risk factor		High fat			Overfat		
		AOR	95% CI	p value	AOR	95% CI	p value
Age (decimal years)		0.85	0.62-1.17	0.32	0.88	0.65-1.19	0.41
Gender	Girls	0.67	0.45-0.99	0.045	0.95	0.65-1.37	0.77
	Boys						
Birth weight (kg)		1.56	1.07-2.28	0.02	1.28	0.91-1.82	0.16
SES	Lower	1.32	0.88-1.98	0.18	1.39	0.94-2.04	0.10
	Higher						
Degree of urbanization	U	2.32	1.00-5.39	0.05	1.80	0.86-3.75	0.12
	SU	1.43	0.57-3.59	0.45	1.24	0.55-2.78	0.61
	R						
Number of cigarettes mother smokes per day	1-10	0.87	0.40-1.91	0.73	X		X
	>10	1.67	0.72-3.86	0.23	X		X
	0						
TV watching (hours/day)	<1	0.76	0.42-1.39	0.38	0.91	0.50-1.64	0.75
	1-3	1.14	0.69-1.88	0.61	1.44	0.87-2.36	0.15
	>3						
Current Maternal smoking	yes	1.12	1.12-1.12		X		X
	no						
Anyone smoking at home	yes	2.06	0.91-4.65	0.08	0.62	0.26-1.49	0.28
	no						
Number of household members smoking	1	0.75	0.36-1.53	0.42	1.57	0.74-3.34	0.24
	≥2						
	0						

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

AOR- Odds ratio adjuster all included factors

p values were considered significant below the 0.05 and underlined

Abbreviations: SES- socioeconomic status; WHtR- waist to height ratio; U- urban; SU-suburban; R-rural
X- Floating point overflow occurred while computing this statistic. Its value is therefore set to system missing.

7.5. Discussion

Factors related to a significant increase in obesity risk for 6-8 year-old children living in Coimbra were the following – higher values of birth weight, being a girl, higher consumption of foods containing saturated fat, lower socioeconomic status, never being breastfed and exclusively breastfed, smoking by any household members with higher risk if at least two people smoked, maternal current smoking and higher number of cigarettes smoked by her and watching TV over one hour per day.

Significantly influencing the risk of abdominal obesity in our study were being a girl, having a family with lower SES, living in urban areas, mother smoking larger amounts of cigarettes per day and child watching TV over 3 hours a day.

Increased risk of having a high body fat levels were associated with being a boy, lower SES, urban areas of residence, current maternal smoking and the number of smoked cigarettes by mother per day, anyone smoking at home (with higher risk if at least 2 people smoked) and longer periods spent watching TV.

In the final models, birth weight remained significant for overweight and obesity as well as high fat levels. Gender remained significantly associated with increased abdominal obesity for girls and increased body fat for boys. Having a person smoking at home was significantly associated with overweight status, while watching TV less than an hour a day remained significantly protective against obesity. Living in an urban environment had an effect on abdominal obesity compared to rural residents. Higher number of maternal cigarettes intake remained associated with an increased risk of abdominal obesity in children.

These results suggest that these factors are strong predictors of obesity, abdominal obesity and excess of fat in children even considering the complex interactions between them.

We have shown a strong correlation between birth weight and measured obesity later in childhood, confirming a strong impact of the early life environment on body mass. The effect was observed for obesity defined as the increased body mass, as well as abdominal obesity and fat content, of children; however, the effect was strongest for the BMI-z-score. It is a commonly observed result. The data for 6.0 (± 1.8) year-old children were analysed within the German initiative IDEFICS (Identification and prevention of dietary- and lifestyle-induced health effects in children and infants) and an increase in risk of obesity related to a high birth weight (>90percentile for gestational age) was shown. Odds were 60% higher for girls born with high weight and 70% for boys (Sparano et al., 2013). This has also been previously described for the Portuguese population. A study of 7-9.5 year-old children showed a dose-dependent association

between birth weight and consequent childhood obesity, with the increase of 55% for the birth weight range 2.5-3.0kg, 87% for the range 3.0-3.5 kg, 113% for 3.5-4.0 kg, and 174% for children born at weights over 4 kg, when compared to children born at 2.5kg or less (Padez et al., 2005).

Padez et al. also indicated breastfeeding as another early risk factor associated with childhood obesity. They showed that breastfeeding had a protective effect against obesity, with the 3-6 month period of total breastfeeding having the strongest effect. In our study we have shown that being breastfed shows a tendency to protect against obesity, and compared to children who have never been breastfed, those breastfed for periods of between 6-9 months were characterized by the lowest risk of developing obesity, abdominal obesity, and high body fat. The weakest protection found was for period longer than 9 months, which suggests that not only shorter but also prolonged breastfeeding can contribute to the development of increased adiposity in children and there might be a U-shaped association between the period of breastfeeding and risk of childhood obesity. A similar situation was observed in a Finnish study, by the Helsinki Birth Cohort, where people breastfed for the period shorter than 2 as well as those breastfed longer than 8 months had increased BMI and percentage body fat later in life. These data suggest that prolonged breastfeeding might be linked to obesity risk through the maternal hormones in breast milk resetting the infant's lipid metabolism (O'Tierney et al., 2009).

Not all authors, however, reported the association between breastfeeding duration and obesity. In a cluster-randomized trial performed within the Promotion of Breastfeeding Intervention Trial (PROBIT) a successful increase in the duration of breastfeeding, achieved by intervention, did not bring the expected effect of a decrease in the adiposity measures (Kramer et al., 2007). Similarly, a cross-sectional study from Iran, focusing on 7-year-old children, found no association between the duration of total or exclusive breastfeeding (Vafa et al., 2012). In our sample we found evidence for the role of duration of exclusive breastfeeding in raising the risk of obesity. Never having been exclusively breastfed was the most disadvantageous option in relation to body mass, waist circumference and body fat values while the most beneficial was a period of up to 3 months of exclusive breastfeeding. This is in line with other results from Sweden, where a higher risk of obesity was observed for children exclusively breastfed for under 4 months, but the effect disappeared after correcting for other factors (socioeconomic and parental tobacco use).

We have shown that maternal tobacco smoking during pregnancy and the first year of child's life can affect childhood obesity. This concurs with the evidence available in the literature. An adverse effect of tobacco exposure *in utero* and early life and adiposity has

previously been described. Meta-analysis of 14 studies examined the offspring of mothers who smoked during pregnancy with the age span 3-33 years old at the time of the examination. They found a 50% increased risk if the mother smoked while pregnant, and the results were independent of socio-demographic and behavioural covariates (Oken, Levitan, & Gillman, 2008). A longitudinal study where 292 mothers were followed from early pregnancy until 3 years post-partum found that both maternal active smoking and second-hand exposure of the mother to tobacco caused an increase in the offspring's BMI at the ages of 2 and 3 years (Braun et al., 2010).

One plausible mechanism underlying this association might include the nicotine present in the cigarettes. As summarized in the review by Bruin et al. (Bruin, Gerstein, & Holloway, 2010), nicotine working in the hypothalamus of the foetus could modulate the energy homeostasis, which could lead to an increased appetite and cause a long-lasting metabolic effect predisposing children to obesity. More evidence gathered in the review by Levin confirms the plausible role of nicotine in the regulation of adiposity in offspring, through the deregulation (blunting) of the sympathetic nervous system (E. D. Levin, 2005). This could explain how *in utero* and early life tobacco exposure has such a strong effect on childhood obesity, which was shown by epidemiological studies, including ours, to be independent of socioeconomic status and other lifestyle and behavioural covariates.

Although much less described, post-natal environmental smoking has also been shown to increase the risk of adiposity in children. Indeed, we have found that not only pre-natal and early life exposure but also current second-hand tobacco exposure significantly increases the risk of the child being obese, which relates not only to maternal but also other household members' smoking. A study of 6 year-old children in Germany has shown that maternal smoking in the first year *post-partum* significantly influences the risk of obesity developing in children, with the risk being more than tripled compared to the children of non-smoking mothers (Raum et al., 2011). Moreover, two cohort studies, one from Germany which evaluated children's adiposity at 8 years of age (Florath et al., 2014) and one from Belarus with the evaluation at 6.5 years (Yang, Decker, & Kramer, 2013) have shown that not only maternal but also paternal pre- and post-natal smoking significantly increases the risk of higher adiposity in children. We have found that having 2 or more people smoking in the home further increased the risk. However, another study from Germany, of children within a similar age span (6-7 years old) has shown this risk only in cases of pregnancy and not early post-natal life exposure (Toschke, Koletzko, Slikker, Hermann, & von Kries, 2002).

We have also shown that there is a dose-dependent association between the number of cigarettes the mother smokes when the child is 6-8 years old and adiposity in children at the

same age. This topic has mostly been studied through the perspective of maternal tobacco use during pregnancy and in fact we have not found any study showing an association between the number of cigarettes currently smoked by the mother and offspring obesity. Regarding the dose effect during pregnancy, it was shown in a study in Bavaria, where nutritional status and lifestyle information were obtained from parents or legal guardians of 5-7 year-old children between 1999 and 2000, that the higher the mother's tobacco consumption (in this case during pregnancy) the higher the risk of obesity among children, with 2.2% prevalence of obesity in the group of non-smoking mothers, 5.7% in the group of mothers smoking less than 10 cigarettes per day and 8.5% in the group of mothers smoking over 10 cigarettes per day (von Kries, 2002). Other studies also reported a dose effect relationship between the number of cigarettes the mother smoked during pregnancy and offspring BMI: one of them focused on cohorts from Sweden and Norway and the BMI at 5 years of age (Wideroe, Vik, Jacobsen, & Bakketeig, 2003) and the other was held under the auspices of the Viva Project in Massachusetts with the BMI measured at the age of three (Oken, Huh, Taveras, Rich-Edwards, & Gillman, 2005).

Another factor is the quality of diet, which was shown to be altered by TV viewing time. As shown in the review by Pearson & Biddle (2011) screen time was linked negatively with intake of fruits and vegetables and positively with consumption of energy-dense snacks, drinks, and fast foods, as well as total energy intake This could be due to advertising often targeting the youngest viewers. As pointed out by the Turkish researchers Guran and Bereket, the vast majority (even 90%) of the advertised food products are unhealthy and contain a high fat, sugar or salt content (Guran & Bereket, 2011). Indeed, a longitudinal study performed in the US showed an increased consumption of fast-food and soda drinks among children in response to exposure to TV advertisements for unhealthy foods (Andreyeva, Kelly, & Harris, 2011). Moreover, in another study, it was shown that exposure to light from the electronic devices, especially at night before going to sleep, can disturb sleep duration (Chahal, Fung, Kuhle, & Veugelers, 2013), which disturbance in turn was shown to increase the risk of obesity in children (Padez et al., 2009).

Increased consumption of high-fat foods and sugars and decreased consumption of vegetables and fruits has been proposed as one of the predictors of obesity. The Mediterranean diet, traditional also in Portuguese culture, has been shown to have a protective effect against obesity (Esposito et al., 2011; Silva-del Valle et al., 2013). The health benefits of this diet come from its promoting a high intake of olive oil, vegetables, fruits and fish. Recently, there seems to be a tendency toward replacement of traditional cuisine with highly processed foods, animal fat, and fast foods. A study from Greece showed that only 4.3% of children had an optimal level of adherence to the traditional Mediterranean diet, and the adherence was lower in urban areas, comparing to suburban and rural (Farajian et al., 2011). Moreover, a study from Italy

demonstrated that there was a correlation between lower income and decreased adherence to this diet (Bonaccio et al., 2012). This is especially troubling within the perspective of the economic crisis affecting many European countries, including Portugal. In our study we did not find evidence for the protective role of the Mediterranean diet against obesity in children, nor the harmful effect of the saturated fats based diet. We have found a significant negative correlation between abdominal obesity and the base diet (meat, potatoes, pasta and rice) and a negative correlation between the saturated fats dietary pattern (fast-food, butter and eggs) and BMI in children. These results, although contradictory to what would be expected, can perhaps be explained by the design of the dietary evaluation. First of all, data that is self-reported is always prone to bias. A general inaccuracy in self-reported calories-intake has been noted (Hill & Davies, 2007), with obese individuals having a stronger tendency to underestimate their caloric intake and overestimate the activity levels (Lichtman et al., 1992). This could also apply as a plausible explanation in regard to parent-reported diet, and parents, being aware of their children's weight problems, could (consciously or subconsciously) lower the intake of the foods which they are aware are unhealthy, and elevate the reported amounts of healthy foods. Another explanation could be reversed causality. Some children could already have dietary restrictions implemented due to their overweight or obese status. Finally, another reason could be the design of the question. Observation of Portuguese eating habits allowed us to conclude that typically, there are around 5 meals in the children's daily routine. Breakfast, mid-morning snacks, lunch, afternoon snacks and dinner. That gives 5 opportunities per day to consume any kind of foods listed in our questionnaire. That amounts to 35 regular meals per week. The highest consumption frequency detected by the ISAAC questionnaire is 3 or more times per week, which might not allow for representation of the full variety of dietary intake among the Portuguese population.

Although we found an increased risk of obesity, abdominal obesity and high body fat related to lower frequency of vigorous physical activity, the results did not reach the level of significance. Physical activity as a protective factor against obesity in childhood is one of the most frequently described and well-known predictors (Hills, Okely, & Baur, 2010; Laurson, Lee, Gentile, Walsh, & Eisenmann, 2014; Nemet et al., 2005; Prentice-Dunn & Prentice-Dunn, 2012). Nevertheless, as shown in our study, the association between physical activity and adiposity is not always established. A study which recruited 40 mother and child pairs using objectively measured physical activity levels (activity monitor) showed no difference in activity level between obese and non-obese children (Romanella et al., 1991). Similarly, in a more recent study by Suton et al. (2013), the self-reported level of physical activity was not associated with body fat in 10 year-old children. In Portugal, Mota et al. (2006) studied a group

of adolescents (14.6 years old) and also did not find an association between self-reported physical activity and weight status (Mota & Ribeiro, 2006)

A study of children 3-11 years old from the Portuguese municipality of Lousã in 2013 evaluated the children's levels of physical activity, reported by parents, and also did not show any significant association with the children's nutritional status (Ferreira Pronto, 2013).

Although activity results in energy expenditure and, in consequence, facilitates weight loss and maintenance of healthy body mass, cross-sectional studies, due to their design, might not reflect this process. The link is bidirectional and in our study, we could only observe the current state of activity-obesity interaction. This means that an increase in the frequency of practicing vigorous physical activity is not only a factor contributing to decreased adiposity levels, but also is related to obesity as a consequence of the decision to introduce a weight-loss intervention. In fact, during our data collection, many overweight and obese children, being aware of their condition and understanding the purpose of our measurements, admitted to having started practicing more sports and were already losing some weight (despite still being above recommended levels).

Our results show that watching TV less than an hour per day as compared to watching over 3 hours a day very significantly decreases the risk of obesity, high fat percentage and abdominal obesity. As we can observe, the effect of sedentary behaviours, such as time spent on television viewing, has an even more pronounced effect than physical activity level. This study demonstrated the same effect as was previously reported in Portuguese studies. In 2005 Padez et al. found that compared to children watching TV less than 2 hours a day, those who watched between 2 and 3 hours had a 50% increased risk of obesity, those who watched 3-4 hours had a 72% increased risk, and those viewing over 4 hours a 63% increased risk. These results were reproduced later in a national sample of 3-10 year-old Portuguese children and again TV viewing for over one hour per day was found to significantly increase the odds of obesity (Bingham et al., 2013). The association we found is strong, with the effect being over four-fold for children who spent 3-5 hours in front of the screen compared to those watching only amounts of under an hour per day. The observed effect was independent of the socioeconomic status of the family. There are many ways in which TV viewing can influence the risk of adiposity. Above all, it can be a substitute for active playing, and cause a decrease in energy expenditure. An intervention study from England, engaging families in a 10-week active play time programme, showed that active playing decreased sedentary behaviours in children (O'Dwyer, Fairclough, Knowles, & Stratton, 2012).

Further, we studied the traffic in the child's neighbourhood, as road safety could influence children's mobility, alter opportunities for active playing outdoors, and therefore

modulate sedentary behaviours and obesity. In a study performed in Australia on 5-6 and 10-12 year-old children, it was shown that children whose parents perceive the neighbourhood as having heavy road traffic were less likely than other children to walk or cycle in the residential area (Timperio, 2004). In another study of the same research group, based on the same sample, it was shown that negative perceptions about traffic also increase the risk of childhood obesity (Timperio et al., 2005). Our study confirmed this finding, and we observed an increased risk of obesity and overweight as well as abdominal obesity and high fat related to residence placed near the road with high truck traffic.

We observed a greater risk of obesity in urban populations compared to rural ones. Notably, this pattern is more characteristic for developing countries. Nevertheless, this result is in agreement with the national study run in 2008, analysing the children in the same age interval that we did (6-8 years old), where urban children had an over 20% higher risk of being overweight (Rito et al., 2012).

Another study, based on a sample of older individuals (18 year-old men), also confirmed that the prevalence of obesity in Portugal tends to increase with the degree of urbanization, therefore being highest in urban and lowest in rural areas (Padez, 2006).

Altogether, inequalities in the risk of obesity exist within the district, and children from lower socioeconomic status and those living in urban areas are more likely to have the problem of increased body mass. This, in turn, means that they are also at a higher risk for comorbidities related to this disease, which constitutes a serious social and public health problem.

An increased prevalence of obesity among children from lower socioeconomic status was observed, which agrees with the results published from developed countries. In the review by Wang et al. (Wang & Lim, 2012b) it was observed that the association between childhood obesity and socioeconomic status differs between the developing and the developed world. In the developing world, an increased risk of developing obesity is related to higher socioeconomic status, while in the developed world it is related to lower socioeconomic status, so in both cases it affects groups with easier access to energy-dense diets in their environment. For example, in India, a study of 12-18 year-old children reported the lowest prevalence of obesity and overweight among the individuals of lower socioeconomic status compared to middle and high levels, which were shown to have the most unhealthy behaviours, such as high-fat and high-sugar diet and sedentary lifestyle (Goyal et al., 2010).

In Europe, an increase in prevalence of overweight and obesity was shown to correlate directly to inequality among households and these disparities seem to be rising, increasing the

gradient between lower and higher socioeconomic groups (Knai, Lobstein, Darmon, Rutter, & McKee, 2012). This trend was previously observed by Stamatakis et al. (E Stamatakis, Wardle, & Cole, 2010) when they studied 5-10 year-old children in England. They reported a stabilization of obesity rates between 2002/3 and 2006/7, which did not, however, apply to groups of lower socioeconomic status; that again expresses the increase in the socioeconomic gradient. In Portugal, the study run in 2002-2003 demonstrated that in the population of 7-9.5 year-old children, higher parental levels of education was a protector against childhood obesity (Padez et al., 2005).

One of the putative links between socioeconomic status and body mass in Portuguese children was suggested in a study of 8-10 year-old children. It showed that children from lower-middle and higher socioeconomic status families had perceived physical activity as being of greater importance than those from lower SES, and reported enjoying the practice of physical activity more than lower SES children (Seabra et al., 2013).

Such discrepancies may begin early, as was suggested in a study of an English and Welsh birth cohort of twins, recruited in 2007. They showed a graded association between weight gain in infancy and socioeconomic status defined as maternal education and occupation. No association was found for birth weight (Wijlaars, Johnson, van Jaarsveld, & Wardle, 2011).

To summarize, exposure to risk factors related to parental SES together with children's own consciousness and perception of healthy behaviours, influenced by their parents, contribute to an increased risk of obesity among socially deprived groups, which was also confirmed in our study. Our results, together with results from the other studies described above, indicate an existing inequality within populations, with adverse health outputs for underprivileged groups. This underscores the necessity of identifying underlying processes and implementing specific didactic interventions, especially in the current national situation of economic crisis in Portugal, when more and more families face financial difficulties which might in consequence be reflected in children's (and not only children's) health status.

7.6. Conclusion

In this chapter, we have described a variety of predictors related to increased adiposity among children living in the Coimbra District. Factors such as birth weight, breastfeeding, lower socioeconomic status, urban residence, TV viewing for over 3 hours a day, and environmental tobacco smoking were the strongest predictors of childhood obesity. They affected not only total body mass, but also its composition and fat distribution, which can constitute a great risk for health. Together with alarming levels of overweight and obesity existing in the district, as reported in the previous chapter, this chapter's results emphasize the

need for change. It is especially important in view of the current crisis, which might further enhance the social gradient and have adverse consequences on children's health.

There is a large amount of literature available describing the role of environmental, socioeconomic and behavioural factors in the modulation of obesity risk; however, due to multidimensional and changing interactions between the environment, culture, technology and society, new studies are always of great importance. Each population has its sub-populations which might be exposed to different risk factors and require different intervention tools. The same population can also change over time, and risk factors can reduce or augment their effect with time passing. Therefore, to be able to prepare evidence-based intervention and prevention programmes and consequently minimize risk and social discrepancies, there is a need for constant examination and re-examination of the behavioural and environmental factors which can contribute to obesity.

8. Asthma risk factors

8.2. Introduction

As shown in the previous chapter, asthma and rhinitis continue to be serious problems among the children living in Coimbra and there seems to have been an increase in the prevalence of these conditions. As has been suggested, environmental and family factors are most likely contributing significantly to this situation.

Nonetheless, asthma and rhinitis are hereditary diseases, with a proven genetic risk (Ober & Yao, 2011; Paternoster et al., 2012; Ramasamy et al., 2011) and a family history plays a role (Bjerg et al., 2007; Burke et al., 2003) in their development. Environmental and lifestyle factors modulate susceptibility and influence the risk of their occurrence and the severity of allergies (Asher et al., 2010; Pegas et al., 2011). The list of risk factors involved in the development of asthma and rhinitis is growing and there is growing evidence of interaction between genetics and environment in the pathogenesis of these conditions (Ege et al., 2011; Kahr et al., 2014).

Exposure to risk factors begins already in utero (Martino & Prescott, 2011), and some evidence even indicates that conditions in the pre-pregnancy environment, such as obesity, can modify the susceptibility of children to asthma or rhinitis (Kumar et al., 2010). One of the early life factors described in the literature as a predictor of asthma and rhinitis is birth weight, and it has been shown that both low (Liu et al., 2014) and high birth weight (Flaherman & Rutherford, 2006; Sin et al., 2004) can contribute to the development of these diseases.

Another early life factor associated with these chronic respiratory diseases is breastfeeding. Studies have shown that being breastfed protects the child from asthma and rhinitis and the period of total and exclusive breastfeeding can also modulate the protective effect (Bloch, Mimouni, Mimouni, & Gdalevich, 2007; Fredriksson, Jaakkola, & Jaakkola, 2007; Bright I Nwaru et al., 2010; Sonnenschein-van der Voort et al., 2012). Breast milk, including elements such as fatty acids, antibodies such as IgA (Immunoglobulin A), CD14 (Cluster of Differentiation 14), a co-receptor for the detection of bacterial lypopolysacharyde (LPS), cytokines, and others, can provide long-lasting immunity for a child (Calder, Kremmyda, Vlachava, Noakes, & Miles, 2010; Iyengar & Walker, 2012). The WHO, for the general purpose of healthy child development as well as promoting the health and well-being of mothers, recommends exclusive breastfeeding during the first 6 months and a total breastfeeding period (with parallel complementary foods) of up to the age of two or longer (WHO, 2014b).

A strong risk factor for asthma and rhinitis in children is second-hand exposure to tobacco. Maternal smoking in general, but especially during periods of intensive development of the child's immunity, such as pregnancy and the first months of post-natal life, can have an

adverse effect on pulmonary function and increase the child's chance of developing asthma and rhinitis (Lemke, Hartert, Gebretsadik, & Carroll, 2013; Tsai et al., 2010). Furthermore, the presence of other smokers in the household can cause harmful effects as well (Ciaccio & Gentile, 2013; Gonzalez-Barcala et al., 2013; Mitchell, Beasley, Keil, Montefort, & Odhiambo, 2012).

Throughout all of life, lifestyle and behavioural options modulate the risk of asthma and rhinitis; the one factor that seems to have the most impact on risk of asthma is diet (Barros et al., 2008; Ellwood et al., 2001). As described in the chapter about risk factors in obesity, we can observe a certain abandonment of the traditional diet consisting of homemade food, which has an adverse effect on the respiratory (and not only) health of the children (Bach-Faig et al., 2011; Monteiro, Levy, Claro, de Castro, & Cannon, 2011). In particular, low adherence to the Mediterranean diet, rich in polyunsaturated fatty acids, antioxidants and vitamins, and poor in saturated fats, seems to have an effect on inflammatory processes and lead to asthma and rhinitis (Barros et al., 2008; Sexton et al., 2013). On the other hand, a diet containing significant amounts of fast food has become more common and is a risk factor for development and higher severity of these diseases (Bose, Curtin-Brosnan, & Matsui, 2013; Ellwood et al., 2013). Cavicchia et al. (2009) in their paper introduced the Inflammatory Index of the diet, calculated for dietary elements based on the data obtained from the literature. They have shown that the most pro-inflammatory elements were, respectively, carbohydrates, fat, saturated fat, total energy intake, and cholesterol, and the most anti-inflammatory were, among others, magnesium, turmeric (Curcuma longa) β-carotene, genistein (present in beans), vitamin A, tea, alcohol, fibre, quercetin, wine, luteolin (type of flavonoid), vitamin E, omega-3 fatty acids, vitamin C, and vitamin D (Cavicchia et al., 2009). In another study, this index has been shown to be associated with inflammation in asthma, which means that the increased consumption of products with pro-inflammatory and decreased consumption of those with anti-inflammatory effects can lead to development of this disease (Wood, Shivappa, Berthon, Gibson, & Hebert, 2014).

Physical activity is another lifestyle factor that has undergone a change in recent decades and was related to increased prevalence of asthma and rhinitis among children. Physical activity has an overall positive effect on health and is recommended for all children, including asthmatics (Philpott, Houghton, & Luke, 2010; Riner & Sellhorst, 2013); however, children with chronic respiratory conditions, especially if uncontrolled, might avoid it, especially if they experience exercise-induced bronchoconstriction (asthma attacks) (B. Williams, Powell, Hoskins, & Neville, 2008). This tendency could have an opposite effect, as physical activity was shown to actually protect against asthma (Eijkemans, Mommers, Draaisma, Thijs, & Prins, 2012). A decreasing level of physical activity together with an increase in sedentary behaviours

(behaviours that occur whilst sitting or lying down and that require very low amounts of energy expenditure) such as watching television, using a computer, or playing video game, is believed to play a significant role in epidemics of childhood asthma (Matricardi & Bonini, 2008; Platts-Mills, 2005). Studies have found that physical activity and limited time spent watching television have a protective effect against asthma (Corbo et al., 2008; Eijkemans et al., 2012). There seems to be no pronounced effect on rhinitis (Mitchell et al.., 2013; Vlaski, Stavric, Seckova, Kimovska, & Isjanovska, 2008).

Children's mobility depends on many factors, such as neighbourhood safety. Various features of safety and parental perceptions of safety such as 'stranger danger' and road safety among others have been found to be related to children's activity (Carver et al., 2008; Ferrão et al., 2013; Timperio et al., 2005). Lack of physical activity per se, and a consequent increase in body mass can lead to a higher risk of asthma (Corbo et al., 2008). Heavy truck traffic in the residential area can heighten the risk of asthma not only through limiting children's activity, but also through low air quality (McConnell, Islam, & Shankardass, 2010). Many centres worldwide involved in the ISAAC phase III have shown a higher risk of asthma and rhinitis among children exposed to this factor (Brunekreef et al., 2009).

As for the degree of urbanization, generally, rural areas, in comparison with urbanized areas, correlate with worse housing conditions, fewer health facilities, families with lower resources and lower education, among many other factors. According to the WHO report, in 2010 as large a figure as 70% out of 1.4 billion people living in extreme poverty occupy rural areas in developing countries. These regions are still severely disadvantaged and suffer from health inequalities (WHO Regional Office for Europe, 2010). As the residential area and the degree of urbanization are strong health determinants, and asthma is associated with higher degree of urbanizations, we would expect the differences in risk between rural and urban areas.

Asthma and allergies are described as diseases of affluence: urbanization and wealth of the population are believed to increase their prevalence (von Hertzen & Haahtela, 2004).This suggests that we could expect different levels of risk for these diseases among groups with varying levels of socio-economic status and from different residential areas. We should remember, however, that area-based indicators of socioeconomic status can have a different influence than individual socioeconomic levels in relation to asthma and rhinitis risk. This means that although we observe an increase associated with higher wealth of populations when comparing population levels of larger structures, such as countries, the contrary is usually the case when comparing socioeconomic status among individuals or families, where wealth tends to be protective. Therefore, the socioeconomic status of a family or a person might be a stronger

predictor of asthma and rhinitis than area-related indexes (Cesaroni, Farchi, Davoli, Forastiere, & Perucci, 2003).

As described in the previous chapter, the prevalence of asthma and rhinitis has reached a troubling level in our studied population and recognizing the risk factors that could have led to this situation is of great importance. Therefore, this chapter analyses the role of environmental and socioeconomic factors associated with asthma, rhinitis, and their severity among 6-8 year-old children living in Coimbra.

8.3. Aims and Objectives

The aim of this study was to study environmental and socioeconomic risk factors modulating the risk of asthma and rhinitis development and the severity of both conditions among children 6-8 years old living in the Coimbra District.

8.4. Methodology

Asthma, rhinitis and their symptoms were defined using the ISAAC tools, as described in the general methodology chapter. We have analysed the effect of each putative risk factor on the development of these diseases and their symptoms. The size of the sample did not allow reliable analyses of asthma and rhinitis severity (number of wheezing attacks per week, number of waking-up episodes, speech disturbances caused by wheezing and disturbance to daily activities caused by nose symptoms), so we decided to focus only on an analysis of the presence of lifetime and current symptoms. For the same reason, we excluded the hay-fever variable from further statistical treatment.

Family history of asthma and rhinitis were analysed in relation to presence of childhood asthma and rhinitis episodes at least once in child's life. Odds of the child's experiencing symptoms were analysed depending on whether anyone had the diseases in the family and the presence of the diseases in particular family members: mother, father, siblings and other family members. For this particular analysis, the Binary Logistic Regression was applied.

Further, early life factors were studied in relation to asthma and rhinitis, such as birth weight, breastfeeding, and total and exclusive breastfeeding periods. Both high (Flaherman & Rutherford, 2006) and low (Liu et al., 2014) birth weights were shown to increase the risk of asthma and rhinitis; we therefore categorized that variable using the following cut-off points, as applied previously in studies, as shown in the review by Yu at al 2011 (Yu et al., 2011):

Low birth weight <2500g

Normal birth weight 2500-4000g

High birth weight >4000g

Multiple logistic regressions were used to test risk size related to low and high birth weight and odds ratios were calculated: both crude and adjusted for child's age, gender, SES and gestational age (continuous variable).

For breastfeeding (whether the child was ever breastfed, period of total and exclusive breastfeeding), multiple logistic regression tests were used to estimate the risk size. The "Never being breastfed" option was used as the reference response for both periods. Odds ratios were calculated: both crude and adjusted for gender, age and SES.

Risk related to environmental tobacco exposure was also investigated. We checked the effect of maternal smoking at the time of data collection, the number of cigarettes the mother

smoked, whether she smoked during pregnancy and during the 1st year of the child's life, whether anyone smoked in the household and if so, how many members smoked. Binary or multiple logistic regression tests were used where applicable to estimate risk size. Odds ratios were calculated: both crude and adjusted for gender, age and SES.

Dietary patterns were analysed depending on the status of respiratory symptoms, and means of the dietary pattern scores were compared using the Student's t-test for binary respiratory variables. Significant results were adjusted for gender, age and SES using the ANCOVA analyses of covariance test.

Sedentary lifestyle indicators, namely vigorous physical activity and TV watching time, were also included in this study. Engaging in a vigorous activity 3 or more times per week and watching TV less than 1 hour per day were chosen as the references. Multiple logistic regression tests were used to estimate the risk size. Odds ratios were calculated: both crude and adjusted for gender, age and SES.

We studied the effect of a heavy level of truck traffic in the residential area on children's respiratory health and a binary logistic regression was used with the reference response being: heavy truck traffic never or rarely passing in the residential area of the child. Odds ratios were calculated: both crude and adjusted for gender, age, SES and residential area.

We also analysed the effect of the degree of urbanization of residential areas (U- urban area; SU- suburban area; R- rural area) and socioeconomic status (Higher SES and Lower SES) on asthma and rhinitis and their severity. The definitions used for each classification are described in detail in the chapter on general methodology. Multiple logistic regression tests were used where applicable to estimate the risk size. SES associations with respiratory variables were adjusted for degree of urbanization and vice versa, and they were both adjusted for each child's gender and age.

Finally, we built a multivariate model including all factors that were shown to be significantly associated with each variable describing asthma and rhinitis in the univariate analyses. All tests were adjusted for family history of asthma and rhinitis, as well as the child's gender and age.

P-valued below 0.05 were considered significant.

8.5. Results

8.5.1. Family History of asthma and rhinitis

At least one family member (anybody) having rhinitis in the family very significantly increased the risk of this disease in the children studied, and the risk was more than twice as big as for children without a positive family history of rhinitis (OR=2.34; p<0.001). A similar effect was found for maternal rhinitis, being over twice as big and also strongly significant (OR=2.38; p<0.001). However, a significantly lower effect was observed for paternal rhinitis, with the risk being increased by 59% (OR=1.59; p=0.03). A 59% increased risk was also observed if a sibling had rhinitis (OR=1.59; p>0.05); it was, however, non-significant.

The effect of the family history was even stronger for asthma. Having a sibling with asthma had the most effect, with the risk over 4 times higher than for children with no asthmatic sibling (OR=4.44; p<0.001). The second strongest association found was with maternal asthma, with a similar effect of the risk being over 4 times higher (OR=4.35; p<0.001) compared to children of non-asthmatic mothers. Paternal asthma also significantly increased the risk of this disease in the child with the risk being over twice as high than in case of non-asthmatic fathers (OR=2.37; p=0.005). Anyone in the family having had asthma resulted in the odds ratio of 3.82 and also had a strongly significant effect on children's asthma (OR=3.82; p<0.001). Detailed results of these analyses can be found in the Table 8.1.

Table 8.1 Association of the positive family history asthma and rhinitis with children's asthma and rhinitis.

Family history of asthma	Child's Asthma ever			
	n (yes)	OR	95% CI	p value
Anyone in the family	74	3.82	2.39-5.66	<0.001
Mother	22	4.35	2.57-7.38	<0.001
Father	17	2.37	1.29-4.34	0.005
Siblings	24	4.44	2.61-7.53	<0.001
Family history of rhinitis	Child's Rhinitis ever			
Anyone in the family	136	2.34	1.74-3.17	<0.001
Mother	81	2.38	1.71-3.30	<0.001
Father	39	1.59	1.05-2.42	0.03
Siblings	22	1.59	0.95-2.67	0.078

Results are presented as crude Odds Ratios (OR) with the 95% Confidence Interval (CI).
Results obtained using the binary logistic regression test with no family history of the diseases set as reference
p values were considered significant below the 0.05 and underlined

8.5.2. Early Life Factors

8.5.2.1. Birth weight

A high birth weight was found to increase the risk of having asthma and its symptoms, especially wheezing, as shown in the Table 8.2. High birth weight (compared to normal birth weight) increased by 81% the risk of wheeze ever (OR=1.81; $p<0.05$) and more than doubled the risk of having had an attack within the past 12 months of child's life (OR=2.32; $p<0.05$). These results became even stronger and the risk further increased after adjustment for SES and gestational age. Although not statistically significant, other symptoms were also shown to be increased by a high birth weight, with 66% increased risk of asthma ever (AOR=1.66; p=0.28), over 2.5 times increased risk of exercise-induced asthma (AOR=2.62; p=0.06). Low birth weight showed a tendency toward increasing the risk of asthma and wheezing symptoms, however not statistically significant, which suggests a U-shaped association between birth weight and the risk of developing asthma symptoms.

A high birth weight was also found to increase the risk of having rhinitis ever (OR=1.62; p=0.10) and in the past year (OR=1.71; p=0.10) and the former became significant after adjustment for SES and gestational age (AOR=1.96; $p<0.05$). On the contrary, low birth weight seemed to have a weak protective effect on rhinitis in children, although the results were not significant. Unlike in the case of asthma, there was no U-shaped association observed. The complete results can be found in the Table 8.2.

Table 8.2 Association of asthma and rhinitis with child's birth weight.

Symptom	Birth weight	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	low	30	1.23	0.76-1.99	0.39	1.01	0.55-1.85	0.98
	high	24	1.81	1.02-3.23	0.04	2.03	1.08-3.80	0.03
	normal	299	Ref.			Ref.		
Wheeze 12m	low	11	1.36	0.69-2.66	0.37	1.13	0.46-2.74	0.79
	high	11	2.32	1.15-4.70	0.02	2.62	1.22-5.64	0.01
	normal	96	Ref.			Ref.		
Asthma ever	low	10	1.33	0.66-2.69	0.42	0.79	0.30-2.04	0.62
	high	7	1.56	0.68-3.58	0.30	1.66	0.67-4.15	0.28
	normal	90	Ref.			Ref.		
Exercise-induced asthma 12m	low	7	1.53	0.67-3.50	0.31	0.93	0.29-3.00	0.90
	high	5	1.76	0.67-4.62	0.25	2.62	0.95-7.21	0.06
	normal	54	Ref.			Ref.		
Night cough 12m	low	19	1.03	0.60-1.78	0.91	0.92	0.47-1.81	0.81
	high	12	1.03	0.53-2.02	0.92	1.20	0.58-2.45	0.62
	normal	213	Ref.			Ref.		
Rhinitis ever	low	13	0.68	0.37-1.26	0.22	0.52	0.24-1.16	0.11
	high	16	1.62	0.88-3.01	0.12	1.73	0.89-3.34	0.10
	normal	200	Ref.			Ref.		
Rhinitis 12m	low	13	0.84	0.45-1.56	0.58	0.67	0.30-1.50	0.33
	high	14	1.71	0.90-3.25	0.10	1.96	1.00-3.84	0.05
	normal	169	Ref..			Ref.		
Itchy and watery eyes	low	8	1.10	0.51-2.37	0.81	0.93	0.34-2.51	0.88
	high	5	1.06	0.41-2.75	0.90	1.27	0.48-3.36	0.63
	normal	84	Ref..			Ref.		

OR- crude Odds Ratio; AOR- Adjusted for gender, age, gestational age and SES

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

8.5.2.2. Breastfeeding

Having been breastfed was shown to play a protective role against all asthma and rhinitis symptoms. The results for asthma reached the level of significance, and remained significant after adjustment (AOR- adjusted Odds Ratio) for most symptoms, namely for wheezing in the past 12 months (AOR=0.46; p=0.01), Exercise-induced asthma (AOR=0.40; p=0.04) and Night cough (AOR=0.51; p=0.01). Wheeze ever did not reach the level of significance, either crude (OR=0.77; p=0.27) or after adjustment (OR=0.75; p=0.26); neither did asthma ever, crude (OR=0.55; p=0.06) or after adjustment (OR=0.54; p=0.07). Rhinitis both ever and in the past year, which were significant when crude (OR=0.60; p=0.04 and OR=0.57; p=0.04 respectively), became not statistically significant after adjustment for covariates (AOR=0.63; p=0.08 and AOR=0.61; p=0.07 respectively) and only tearing and itchy eyes remained significant after adjustments (OR=0.51; p=0.04). See Table 8.3.

Table 8.3 Association of asthma, rhinitis and their symptoms with breastfeeding.

Symptom	Breastfed	n	OR	95% CI	p	AOR	95% CI	p value
Wheeze ever	Yes	327	0.77	0.48-1.23	0.27	0.75	0.46-1.24	0.26
	No	32	Ref.			Ref.		
Wheeze 12m	Yes	105	0.48	0.27-0.87	0.02	0.46	0.25-0.86	0.01
	No	16	Ref.			Ref.		
Asthma ever	Yes	95	0.55	0.29-1.04	0.06	0.54	0.28-1.05	0.07
	No	13	Ref.			Ref.		
Exercise-induced asthma 12m	Yes	57	0.44	0.21-0.89	0.02	0.4	0.19-0.87	0.02
	No	10	Ref.			Ref.		
Night cough 12m	Yes	222	0.58	0.35-0.94	0.03	0.51	0.30-0.84	0.01
	No	27	Ref.			Ref.		
Rhinitis ever	Yes	209	0.6	0.36-0.99	0.04	0.63	0.37-1.06	0.08
	No	25	Ref.			Ref.		
Rhinitis 12m	Yes	177	0.57	0.34-0.97	0.04	0.61	0.35-1.05	0.07
	No	22	Ref.			Ref.		
Itchy and watery eyes 12m	Yes	85	0.49	0.26-0.93	0.03	0.51	0.26-0.98	0.04
	No	13	Ref.			Ref.		

AOR- Adjuster for gender, age and SES

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

8.5.2.3. Total breastfeeding period

Our study showed that children being breastfed for any period, by comparison with those never breastfed, were generally protected against asthma and rhinitis, although only two associations reached the level of significance. Children were protected against tearing and itchy eyes if they were breastfed for a period longer than 9 months (OR=0.43; p=0.03) which became not statistically significant after adjustment for covariates (AOR=0.50; p=0.09). In addition, although not significant when crude (OR=0.58; p=0.07), being breastfed for periods of longer than 9 months protected against Night cough in the past year after adjustment (AOR=0.52; p=0.04).

Generally, a tendency toward a dose-dependent effect could also be observed, with a higher period of breastfeeding representing a higher level of protection against these diseases. Being breastfed for periods of 9 months or more showed the most protective effect (even if mostly not significant) against all the studied symptoms of asthma and rhinitis in children. Results presented in Table 8.4.

Table 8.4 Association of asthma, rhinitis and their symptoms with total breastfeeding period.

Symptom	Total breastfeeding period (months)	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	<3	93	0.96	0.55-1.68	0.89	0.96	0.53-1.72	0.89
	3-6	73	0.85	0.48-1.51	0.58	0.86	0.47-1.56	0.62
	6-9	74	1.00	0.56-1.77	1.00	1.05	0.57-1.91	0.88
	>9	91	0.67	0.39-1.17	0.16	0.69	0.38-1.22	0.20
	never	26	Ref.			Ref.		
Wheeze 12m	<3	34	0.81	0.39-1.71	0.59	0.80	0.36-1.76	0.58
	3-6	22	0.60	0.27-1.32	0.20	0.58	0.25-1.33	0.20
	6-9	23	0.69	0.32-1.50	0.35	0.68	0.30-1.56	0.36
	>9	31	0.58	0.27-1.22	0.15	0.65	0.30-1.43	0.29
	never	11	Ref.			Ref.		
Asthma ever	<3	34	1.15	0.51-2.63	0.73	1.22	0.51-2.95	0.65
	3-6	22	0.86	0.36-2.03	0.72	0.81	0.32-2.05	0.65
	6-9	24	1.04	0.44-2.45	0.92	1.09	0.44-2.71	0.85
	>9	19	0.48	0.20-1.15	0.10	0.56	0.22-1.41	0.22
	never	8	Ref.			Ref.		
Exercise-induced asthma 12m	<3	19	0.71	0.28-1.76	0.45	0.69	0.25-1.85	0.46
	3-6	11	0.47	0.18-1.27	0.14	0.41	0.13-1.22	0.11
	6-9	13	0.63	0.24-1.65	0.35	0.68	0.24-1.92	0.47
	>9	17	0.51	0.20-1.28	0.15	0.55	0.21-1.49	0.24
	never	7	Ref.			Ref.		
Night cough 12m	<3	71	0.87	0.48-1.56	0.64	0.80	0.43-1.47	0.47
	3-6	46	0.62	0.33-1.14	0.12	0.53	0.28-1.01	0.05
	6-9	47	0.71	0.38-1.31	0.27	0.66	0.35-1.24	0.20
	>9	64	0.58	0.32-1.04	0.07	0.52	0.28-0.96	0.04
	never	21	Ref.			Ref.		
Rhinitis ever	<3	66	0.98	0.53-1.80	0.94	0.92	0.49-1.75	0.81
	3-6	51	0.87	0.46-1.62	0.65	0.85	0.45-1.64	0.63
	6-9	46	0.86	0.45-1.62	0.64	0.93	0.48-1.79	0.83
	>9	52	0.56	0.30-1.04	0.07	0.60	0.31-1.13	0.11
	never	18	Ref.			Ref.		
Rhinitis12m	<3	62	1.25	0.65-2.41	0.51	1.21	0.61-2.40	0.60
	3-6	42	0.93	0.47-1.83	0.83	0.92	0.45-1.87	0.81
	6-9	37	0.89	0.44-1.77	0.73	0.98	0.48-2.00	0.95
	>9	44	0.62	0.32-1.22	0.17	0.68	0.34-1.37	0.28
	never	14	Ref.			Ref.		
Itchy and watery eyes 12m	<3	27	0.62	0.29-1.33	0.22	0.60	0.27-1.35	0.22
	3-6	20	0.53	0.24-1.18	0.12	0.54	0.24-1.25	0.15
	6-9	16	0.46	0.20-1.06	0.07	0.51	0.22-1.20	0.13
	>9	24	0.43	0.20-0.94	0.03	0.50	0.22-1.10	0.09
	never	11	Ref.			Ref.		

AOR- OR Adjuster for gender, age and SES

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

8.5.2.4. Exclusive breastfeeding

A significant association was found between lifetime wheezing and duration of exclusive breastfeeding, with being exclusively breastfed for over 9 months protecting the child from the Wheeze ever (OR=0.33; p=0.03), and the result remained significant after adjustment (AOR=0.35; p=0.046). In addition, after adjustment, the protective role of 6-9 months of exclusive breastfeeding against Night cough in the past year became significant (AOR=0.40; p=0.02).

For rhinitis, being breastfed for a period of 6-9 months was shown to protect significantly against the child experiencing tearing and itchy eyes (OR=0.28; p=0.04), which, however, became only borderline significant after adjustments (AOR=0.30; p=0.053).

Generally, for asthma, we could again observe that the period of 9 or more months of exclusive breastfeeding was the most protective against its symptoms, while for rhinitis, the most beneficial amount seemed to be a period of 6-9 months, suggesting a slight U-shaped association between exclusive breastfeeding and rhinitis symptoms.

Details of these results can be found in the Table 8.5.

Table 8.5 Association of asthma, rhinitis and their symptoms with exclusive breastfeeding period.

Symptom	Exclusive Breastfeeding period (months)	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	<3	152	0.99	0.57-1.72	0.98	0.94	0.53-1.67	0.83
	3-6	143	0.86	0.50-1.50	0.60	0.85	0.48-1.50	0.57
	6-9	29	0.75	0.38-1.48	0.41	0.78	0.39-1.58	0.50
	>9	6	0.33	0.12-0.91	0.03	0.35	0.12-0.98	0.046
	never	24	Ref.			Ref.		
Wheeze 12m	<3	54	0.82	0.39-1.71	0.60	0.71	0.34-1.52	0.38
	3-6	43	0.62	0.29-1.30	0.20	0.58	0.27-1.25	0.17
	6-9	8	0.51	0.19-1.37	0.18	0.52	0.19-1.42	0.20
	>9	3	0.49	0.12-1.91	0.30	0.52	0.13-2.05	0.35
	never	10	Ref.			Ref.		
Asthma ever	<3	48	0.91	0.41-2.03	0.82	0.82	0.36-1.84	0.62
	3-6	41	0.74	0.33-1.67	0.47	0.68	0.30-1.56	0.36
	6-9	6	0.47	0.16-1.44	0.19	0.48	0.16-1.48	0.20
	>9	2	0.4	0.08-2.01	0.27	0.41	0.08-2.07	0.28
	never	8	Ref.			Ref.		
Exercise-induced asthma 12m	<3	28	0.59	0.25-1.42	0.24	0.48	0.20-1.18	0.11
	3-6	25	0.52	0.21-1.25	0.14	0.45	0.18-1.12	0.09
	6-9	3	0.27	0.07-1.09	0.07	0.26	0.06-1.06	0.06
	>9	1	0.24	0.03-2.02	0.19	0.23	0.03-1.97	0.18
	never	7	Ref.			Ref.		
Night cough 12m	<3	106	0.75	0.42-1.34	0.34	0.64	0.35-1.15	0.13
	3-6	97	0.66	0.37-1.17	0.16	0.56	0.31-1.02	0.06
	6-9	17	0.49	0.23-1.04	0.06	0.4	0.18-0.88	0.02
	>9	6	0.43	0.16-1.21	0.11	0.4	0.14-1.12	0.08
	never	20	Ref.			Ref.		
Rhinitis ever	<3	101	0.98	0.53-1.80	0.95	0.88	0.47-1.64	0.68
	3-6	92	0.86	0.47-1.59	0.64	0.82	0.44-1.53	0.54
	6-9	13	0.5	0.22-1.14	0.10	0.5	0.22-1.16	0.11
	>9	7	0.73	0.27-2.00	0.55	0.7	0.25-1.94	0.49
	never	16	Ref.			Ref.		
Rhinitis12m	<3	92	1.12	0.58-2.16	0.73	1.01	0.52-1.96	0.98
	3-6	76	0.87	0.45-1.68	0.67	0.82	0.42-1.61	0.57
	6-9	9	0.42	0.17-1.07	0.07	0.43	0.17-1.09	0.08
	>9	5	0.63	0.20-1.94	0.42	0.61	0.19-1.89	0.39
	never	13	Ref.			Ref.		
Itchy and watery eyes 12m	<3	43	0.72	0.33-1.56	0.4	0.62	0.28-1.37	0.24
	3-6	38	0.62	0.28-1.35	0.23	0.61	0.28-1.35	0.22
	6-9	4	0.28	0.08-0.96	0.04	0.3	0.09-1.02	0.05
	>9	2	0.36	0.07-1.79	0.21	0.38	0.08-1.87	0.23
	never	9	Ref.			Ref.		

OR-Crude ; AOR- Adjuster for gender, age and SES

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

8.5.3. Second-hand tobacco exposure

8.5.3.1. Pregnancy smoking

Smoking during pregnancy showed a general strong adverse effect on asthma and rhinitis symptoms in the children studied. Maternal smoking during pregnancy significantly increased the risk of asthma ever (OR=1.83; p=0.047), exercise-induced wheezing/asthma attack (OR=2.13; p=0.03), rhinitis ever (OR=1.74; p=0.02) or in the past 12 months (OR=2.05; p=0.003). Apart from asthma ever, the results remained significant after adjustment (AOR=2.32; p=0.03 for Exercise-induced asthma, AOR=1.83; p=0.02 for rhinitis ever and AOR=2.20; p=0.003).See Table 8.6.

Table 8.6 Association of asthma, rhinitis and their symptoms with maternal smoking during the pregnancy.

Symptom	Pregnancy maternal smoking	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	yes	37	1.40	0.89-2.18	0.14	1.47	0.90-2.41	0.13
	no	315	Ref.			Ref.		
Wheeze 12m	yes	14	1.44	0.78-2.64	0.24	1.43	0.72-2.84	0.30
	no	106	Ref.			Ref.		
Asthma ever	yes	15	1.83	1.01-3.32	0.047	1.62	0.82-3.22	0.17
	no	92	Ref.			Ref.		
Exercise-induced asthma 12m	yes	11	2.13	1.07-4.23	0.03	2.32	1.08-4.98	0.03
	no	56	Ref.			Ref.		
Night cough 12m	yes	29	1.53	0.96-2.44	0.08	1.45	0.87-2.45	0.16
	no	217	Ref.			Ref.		
Rhinitis ever	yes	30	1.74	1.09-2.76	0.02	1.83	1.10-3.03	0.02
	no	199	Ref.			Ref.		
Rhinitis 12m	yes	29	2.05	1.28-3.28	0.003	2.2	1.31-3.67	0.003
	no	167	Ref.			Ref.		
Itchy and watery eyes 12m	yes	12	1.44	0.75-2.75	0.27	1.33	0.63-2.77	0.45
	no	86	Ref.			Ref.		

Adjuster for gender, age and SES

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

8.5.3.2. 1st year of child's life maternal smoking

Maternal smoking in the first year of child's life showed even more consistent results than pregnancy amoking and apart from wheeze ever and itchy and tearing eyes, all the associations were significant. Maternal smoking in the first year of the child's life resulted in a greatly and significantly increased risk of wheezing in the past 12 months (OR=1.88; p=0.01), asthma ever (OR=2.01; p=0.01), exercise-induced asthma attack (OR=2.65; p=0.001), and rhinitis episode in the past 12 months (OR=1.78; p=0.01). Results remained significant after adjustment for exercise-induced asthma (AOR=2.18; p=0.02) and rhinitis in the past year (AOR=1.67; p=0.03) Exercise-induced asthma was the symptom that increased most with maternal smoking in the first year of a child's life. Results presented in **Error! Not a valid bookmark self-reference.**.

Table 8.7 Association of asthma, rhinitis and their symptoms with maternal smoking period during the first year of child's post-natal life.

Symptom	1st year of child's life maternal smoking	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	yes	52	1.46	0.99-2.15	0.06	1.42	0.93-2.16	0.10
	no	300	Ref.			Ref.		
Wheeze 12m	yes	23	1.88	1.14-3.11	0.01	1.70	0.97-2.98	0.06
	no	97	Ref.			Ref.		
Asthma ever	yes	22	2.01	1.21-3.36	0.01	1.64	0.92-2.94	0.10
	no	86	Ref.			Ref.		
Exercise-induced asthma 12m	yes	17	2.65	1.47-4.76	0.001	2.18	1.10-4.28	0.02
	no	50	Ref.			Ref.		
Night cough 12m	yes	38	1.45	0.96-2.19	0.08	1.35	0.86-2.12	0.19
	no	207	Ref.			Ref.		
Rhinitis ever	yes	38	1.55	1.02-2.34	0.04	1.44	0.92-2.25	0.11
	no	191	Ref.			Ref.		
Rhinitis 12m	yes	36	1.78	1.17-2.72	0.01	1.67	1.05-2.64	0.03
	no	160	Ref.			Ref.		
Itchy and watery eyes 12m	yes	15	1.29	0.72-2.31	0.40	1.07	0.55-2.08	0.85
	no	83	Ref.			Ref.		

Adjuster for gender, age and SES

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

8.5.3.2. Second-hand smoking at 6-8 years of age- Maternal smoking

Maternal smoking when the child was 6-8 years old was shown to significantly increase the risk of exercise-induced asthma attacks in the past 12 months (OR=1.94; p=0.02), however it turned not statistically significant after adjustment for covariates (AOR=1.52;p=0.19). Generally, we can observe a tendency of increased risk of asthma symptoms related to maternal tobacco use in the child's 6th to 8th year of life; however, it was mostly not statistically significant. The effect was much weaker on rhinitis symptoms, with only rhinitis in the past year having a 24% increased risk due to current maternal smoking, though not significant (OR=1.24;p=0.28), and there was no effect on lifetime rhinitis, nor was there tearing or itchy eyes. See Table 8.8.

As for the number of cigarettes that the mother smoked, children of mothers smoking 1-10 cigarettes per day, compared to those of non-smoking mothers, had a two times higher risk of experiencing exercise-induced wheezing attacks in the past year (OR=2.05;p=0.03) which however became not statistically significant after adjustment (AOR=1.59;p=0.23). No other significant association was found between the number of cigarettes smoked by the mother and the child's respiratory symptoms. We can, however, notice that there is a certain dose effect with mothers that had a smoking habit of over than 10 cigarettes per day; in those cases children were at a higher risk of asthma, rhinitis and associated symptoms thereof than children whose mothers usually smoked 1-10 cigarettes. For more details see Table 8.9.

Table 8.8 Association between asthma, rhinitis and their symptoms and the maternal smoking at 6-8 years of child's age.

Symptom	Maternal smoking (6-8years of child's age)	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	yes	70	1.15	0.83-1.60	0.41	1.15	0.81-1.63	0.44
	no	282	Ref.			Ref.		
Wheeze 12m	yes	30	1.54	0.99-2.41	0.06	1.47	0.90-2.39	0.12
	no	90	Ref.			Ref.		
Asthma ever	yes	24	1.29	0.79-2.09	0.30	1.15	0.68-1.97	0.60
	no	83	Ref.			Ref.		
Exercise-induced asthma 12m	yes	20	1.94	1.12-3.36	0.02	1.52	0.81-2.86	0.19
	no	47	Ref.			Ref.		
Night cough 12m	yes	49	1.11	0.77-1.59	0.59	1.03	0.70-1.52	0.89
	no	197	Ref.			Ref.		
Rhinitis ever	yes	46	1.07	0.74-1.54	0.73	1.00	0.68-1.49	0.99
	no	185	Ref.			Ref.		
Rhinitis 12m	yes	43	1.24	0.84-1.81	0.28	1.17	0.78-1.76	0.46
	no	154	Ref.			Ref.		
Itchy and watery eyes 12m	yes	18	0.94	0.55-1.61	0.83	0.89	0.50-1.59	0.69
	no	80	Ref.			Ref.		

Adjuster for gender, age and SES

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

Table 8.9 Association between asthma, rhinitis and their symptoms and the number of cigarettes mother smoked (at 6-8 years of child's age).

Symptom	Number of cigarettes mother smoked per day	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	1-10	41	1.00	0.67-1.49	0.99	1.02	0.66-1.57	0.93
	>10	30	1.54	0.93-2.54	0.09	1.48	0.86-2.55	0.15
	none	281	Ref.			Ref.		
Wheeze 12m	1-10	19	1.53	0.90-2.63	0.12	1.49	0.83-2.68	0.18
	>10	12	1.75	0.90-3.39	0.10	1.64	0.79-3.37	0.18
	none	89	Ref.			Ref.		
Asthma ever	1-10	13	1.10	0.59-2.05	0.76	0.96	0.48-1.93	0.91
	>10	12	1.81	0.94-3.51	0.08	1.71	0.83-3.50	0.15
	none	82	Ref.			Ref.		
Exercise-induced asthma 12m	1-10	13	2.05	1.07-3.93	0.03	1.59	0.75-3.37	0.23
	>10	8	2.13	0.96-4.70	0.06	1.80	0.73-4.44	0.20
	none	46	Ref.			Ref.		
Night cough 12m	1-10	28	0.98	0.62-1.54	0.92	0.98	0.61-1.58	0.93
	>10	22	1.42	0.84-2.42	0.19	1.20	0.67-2.14	0.54
	none	196	Ref.			Ref.		
Rhinitis ever	1-10	28	1.01	0.64-1.59	0.96	0.98	0.61-1.59	0.94
	>10	19	1.25	0.72-2.17	0.42	1.13	0.62-2.05	0.68
	none	184	Ref.			Ref.		
Rhinitis12m	1-10	24	1.06	0.65-1.71	0.82	1.02	0.61-1.70	0.94
	>10	20	1.69	0.98-2.92	0.06	1.57	0.87-2.82	0.13
	none	153	Ref.			Ref.		
Itchy and watery eyes 12m	1-10	11	0.90	0.46-1.74	0.75	0.84	0.41-1.72	0.63
	>10	7	1.00	0.44-2.26	1.00	0.96	0.40-2.31	0.93
	none	80	Ref.			Ref.		

Adjuster for gender, age and SES

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

8.5.3.3. Second-hand smoking at 6-8 years of age- household members smoking

Having any member of the household currently smoking did not significantly change the risk of asthma and rhinitis symptoms, but we were able to understand that it increased the risk of wheeze ever (AOR=1.27; p=0.11), asthma ever (AOR=1.24; p=0.34), and exercise-induced asthma attacks (AOR=1.36; p=0.28). There was almost no effect observed on rhinitis. See Table 8.10.

Considering the number of household members smoking, having 2 or more people currently smoking, when compared to no one smoking at home, significantly increased the child's risk of having one episode of asthma at least once in his or her lifetime (OR=1.94; p=0.02) and at least one exercise-induced asthma attack in the past year (OR=2.36; p=0.01), which became not statistically significant after adjustment (AOR=1.72; p=0.08 and AOR=1.78; p=0.13 respectively). See Table 8.11.

Table 8.10 Association between asthma, rhinitis and their symptoms and the household members smoking.

Symptom	Anyone smoking at home	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	yes	135	1.23	0.94-1.61	0.13	1.27	0.95-1.69	0.11
	no	217	Ref.			Ref.		
Wheeze 12m	yes	41	0.96	0.64-1.43	0.82	0.91	0.59-1.41	0.68
	no	78	Ref.			Ref.		
Asthma ever	yes	44	1.30	0.86-1.96	0.21	1.24	0.80-1.92	0.34
	no	63	Ref.			Ref.		
Exercise-induced asthma 12m	yes	30	1.56	0.95-2.59	0.08	1.36	0.78-2.36	0.28
	no	36	Ref.			Ref.		
Night cough 12m	yes	89	1.05	0.78-1.42	0.75	0.95	0.69-1.31	0.78
	no	156	Ref.			Ref.		
Rhinitis ever	yes	84	1.04	0.76-1.41	0.81	1.03	0.75-1.42	0.87
	no	146	Ref.			Ref.		
Rhinitis 12m	yes	74	1.10	0.80-1.52	0.56	1.09	0.78-1.54	0.60
	no	122	Ref.			Ref.		
Itchy and watery eyes 12m	yes	31	0.82	0.52-1.28	0.38	0.80	0.50-1.29	0.37
	no	66	Ref.			Ref.		

Adjuster for gender, age and SES

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

Table 8.11 Association between asthma, rhinitis and their symptoms and the number of household members smoking.

Symptom	Number of household members smoking	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	1	93	1.28	0.94-1.74	0.12	1.37	0.99-1.90	0.06
	≥2	42	1.14	0.75-1.72	0.54	Ref.	0.68-1.66	0.78
	0	217	Ref.					
Wheeze 12m	1	24	0.81	0.50-1.32	0.41	0.79	0.47-1.34	0.39
	≥2	17	1.27	0.72-2.23	0.42	1.16	0.62-2.17	0.64
	0	78	Ref.			Ref.		
Asthma ever	1	24	1.02	0.62-1.67	0.94	1.02	0.60-1.74	0.93
	≥2	20	1.94	1.12-3.36	0.02	1.72	0.94-3.14	0.08
	0	63	Ref.			Ref.		
Exercise-induced asthma 12m	1	16	1.21	0.66-2.22	0.54	1.15	0.59-2.23	0.68
	≥2	14	2.36	1.23-4.52	0.01	1.78	0.84-3.77	0.13
	0	36	Ref.			Ref.		
Night cough 12m	1	54	0.91	0.64-1.30	0.61	0.83	0.57-1.21	0.33
	≥2	35	1.37	0.88-2.11	0.16	1.24	0.78-1.98	0.36
	0	156	Ref.			Ref.		
Rhinitis ever	1	59	1.10	0.78-1.55	0.60	1.10	0.76-1.58	0.62
	≥2	25	0.92	0.57-1.49	0.73	0.90	0.54-1.48	0.67
	0	146	Ref.			Ref.		
Rhinitis12m	1	52	1.16	0.81-1.67	0.42	1.16	0.79-1.70	0.45
	≥2	22	0.98	0.59-1.62	0.93	0.97	0.57-1.65	0.90
	0	122	Ref.			Ref.		
Itchy and watery eyes 12m	1	21	0.82	0.49-1.38	0.46	0.79	0.46-1.38	0.41
	≥2	10	0.81	0.40-1.62	0.55	0.82	0.39-1.72	0.60
	0	66	Ref.			Ref.		

Adjuster for gender, age and SES

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

8.5.4. Diet

8.5.4.1. Base of Portuguese diet

First component extracted from data was what we called the Base of Portuguese Diet and clustered together the consumption of meat, potatoes, rice and pasta. We have found a significantly higher mean consumption of the Base of Diet component among children reporting wheezing at least once in their lives (difference of consumption score of 0.14; p=0.03) and exercise-induced asthma attacks in the past 12 months (difference of consumption score of 0.26; p=0.04) compared with children not having these symptoms. These associations lost significance after adjustment for covariates (p=0.11 and p=0.09 respectively). No other association reached the level of significance. Nevertheless, some tendencies could be observed. Consequently, higher consumption of Base of Diet component was also observed among children having asthma ever as well as those experiencing wheezing attacks in the past 12 months, exercise-induced asthma attacks, and night cough. On the contrary, lower consumption of this component was observed among children reporting rhinitis ever and in the past 12 months, as well as reporting tearing and itchy eyes, compared to those not experiencing these symptoms. See **Error! Reference source not found.** and Figure 8.2.

8.5.4.2. Mediterranean diet

The second component extracted from the data was what we called the Mediterranean Diet and clustered together consumption of fish, fruits, vegetables, and legumes. Although none of the associations between Mediterranean diet and respiratory symptoms among children was significant, we were able to observe some tendencies. Higher consumption of the Mediterranean diet component was perceived among children reporting at least one wheezing attack in a lifetime as well as in the past year, those reporting asthma ever and exercise-induced asthma attacks in the past year. On the contrary, it was lower among children reporting a night cough in the past year when compared to those not experiencing this symptom. In the case of rhinitis, no observable difference was found for rhinitis ever or in the past 12 months, nor was one found for tearing and itchy eyes. See **Error! Reference source not found.** and Figure 8.2.

8.5.4.3. Saturated fat diet

The third component extracted from data was the Saturated fat diet and clustered together the consumption of fast food, eggs, butter. No significant association was found for this component and asthma or rhinitis symptoms. However, lower consumption of the Saturated fat diet component was found for children reporting wheezing and asthma ever compared to those who did not report these symptoms. On the contrary, it was higher for those experiencing symptoms in the past year, such as wheezing, exercise-induced asthma, and night cough,

compared to children not experiencing these symptoms. Children having a rhinitis episode at least once in a lifetime and in the past year reported higher consumption of saturated fat diet than those who did not report the presence of the disease. Children reporting tearing and itchy eyes had lower consumption of this component than those who did not. No clear differences were observed for the remaining symptoms. Below we can see the figures illustrating the mean consumption of the three components in relation to all the symptoms studied. See **Error! eference source not found.** and Figure 8.2.

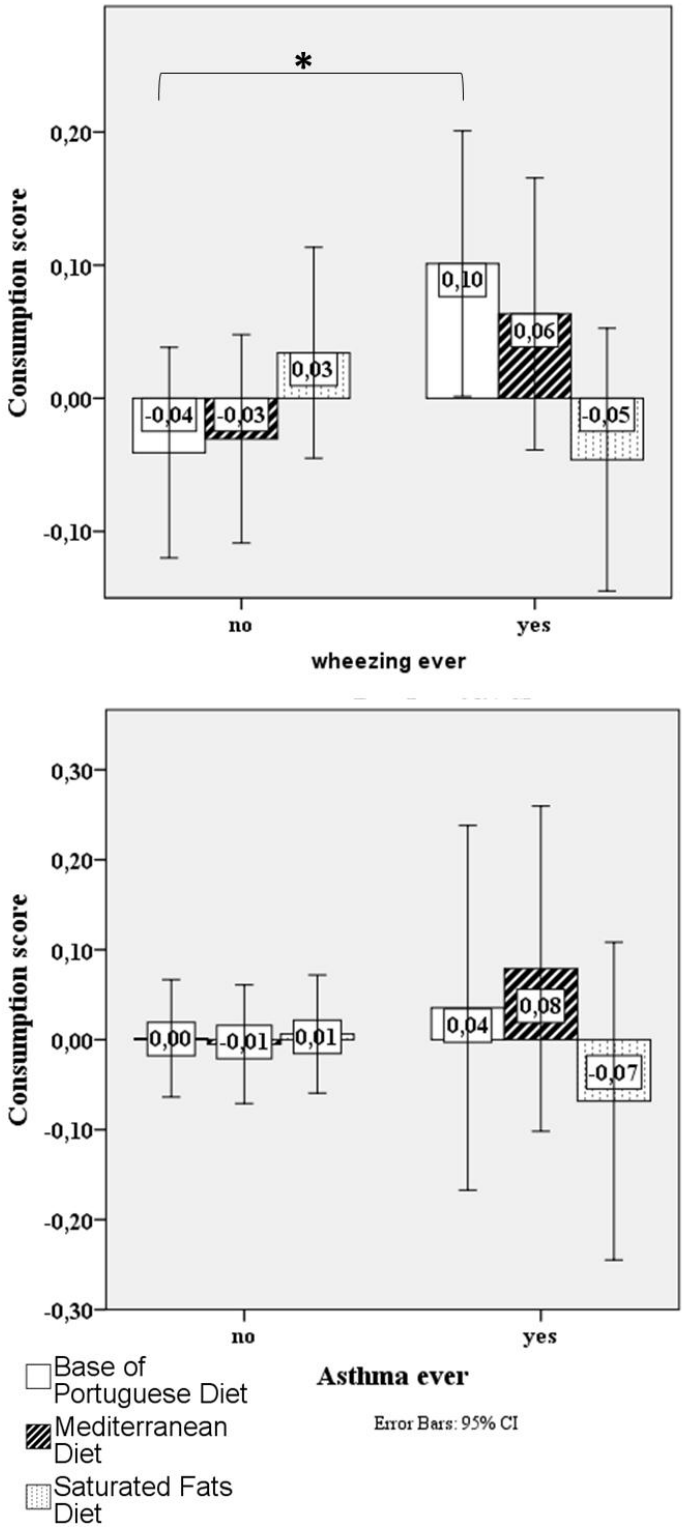


Figure 8.1 Association between the consumption of each dietary component and lifetime asthma and wheeze.

Results are presented as means of adherence to each dietary component (95% Confidence Interval). Differences of means were tested using Student's t-test. Significant results (p>0.05) were marked with *.

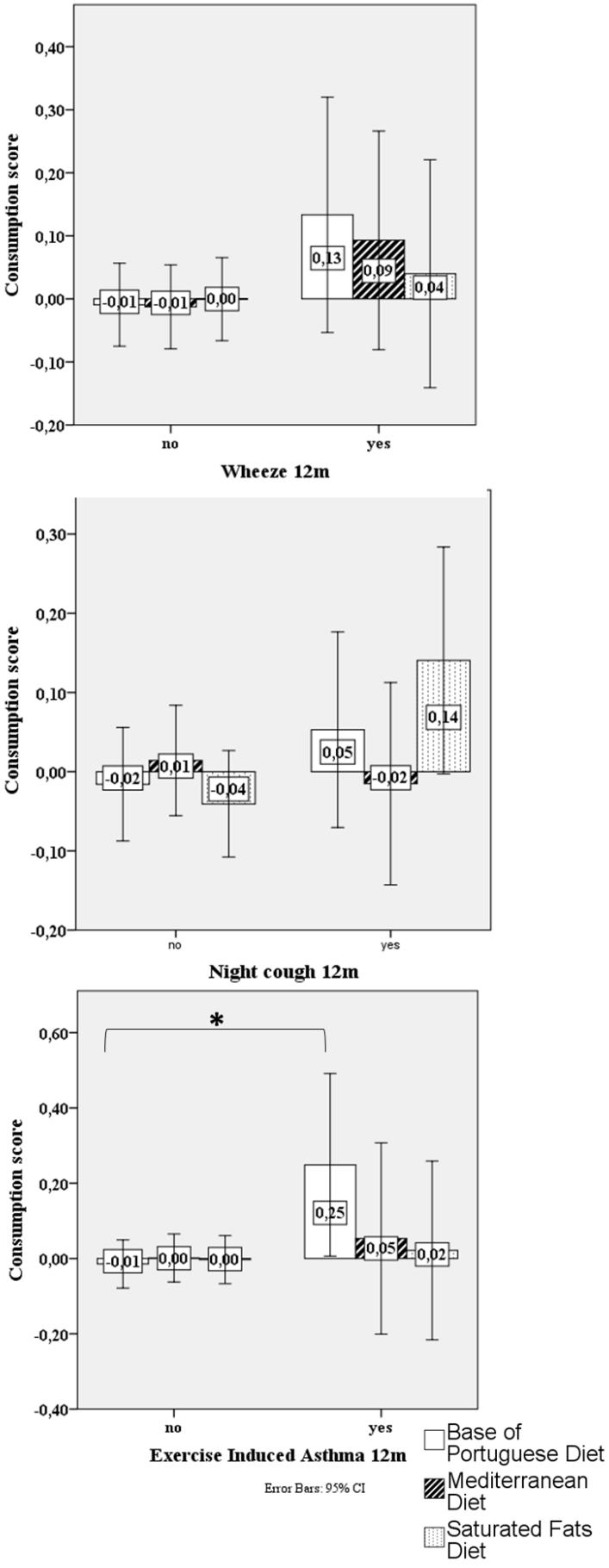


Figure 8.2 Association between the consumption of each dietary component and current asthma symptoms.

Results are presented as means of adherence to each dietary component (95% Confidence Interval). Differences of means were tested using Student's t-test. Significant results (p>0.05) were marked with *.

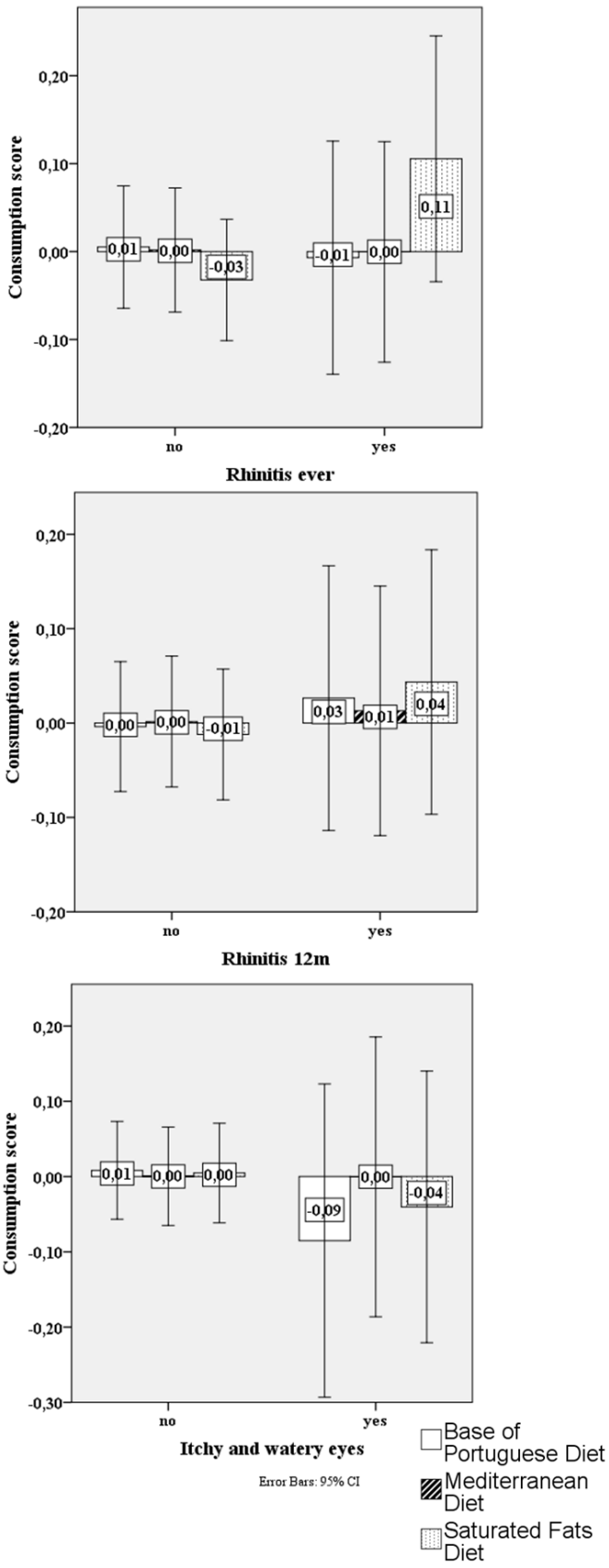


Figure 8.3 Association between consumption of each dietary component and rhinitis.

Results are presented as means of adherence to each dietary component (95% Confidence Interval). Differences of means were tested using Student's t-test. Significant results (p>0.05) were marked with *.

8.5.5. Physical activity

After adjustment those children who never or occasionally engage in vigorous physical activity had significantly higher risk of experiencing wheezing in the past year (AOR=2.12; p=0.02). For children never engaging in vigorous exercise there was also a not statistically significant tendency of increased risk of asthma ever (AOR=1.68; p=0.13), exercise-induced asthma attack (AOR=2.10; p=0.10) and asthmatic night cough (AOR=1.24; p=0.39). No clear tendency was found for 1-2 times weekly exercise practice and asthma symptoms. No significant correlation between vigorous exercise frequency and rhinitis in children was found, whether crude or after adjustment, but there was a slight protective effect from vigorous physical activity 1-2 times weekly compared to 3 or more times per week. A full list of the results can be found in the Table 8.12.

Table 8.12 Association of asthma, rhinitis and their symptoms with vigorous physical activity.

Symptom	Vigorous physical activity (times/week)	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	never or occasionally	46	0.93	0.60-1.44	0.74	1.12	0.71-1.79	0.62
	1-2	217	1.07	0.79-1.45	0.67	1.25	0.91-1.73	0.17
	≥3	91	Ref.			Ref.		
Wheeze 12m	never or occasionally	23	1.67	0.92-3.03	0.09	2.12	1.11-4.02	0.02
	1-2	67	1.06	0.66-1.69	0.81	1.21	0.73-1.98	0.46
	≥3	28	Ref.			Ref.		
Asthma ever	never or occasionally	19	1.31	0.70-2.44	0.40	1.68	0.86-3.28	0.13
	1-2	57	0.87	0.54-1.41	0.58	0.97	0.58-1.63	0.92
	≥3	28	Ref.			Ref.		
Exercise-induced asthma 12m	never or occasionally	13	1.69	0.78-3.67	0.18	2.10	0.88-5.04	0.10
	1-2	37	1.08	0.58-2.01	0.80	1.34	0.67-2.67	0.41
	≥3	15	Ref.			Ref.		
Night cough 12m	never or occasionally	40	1.21	0.76-1.92	0.41	1.24	0.76-2.02	0.39
	1-2	137	0.88	0.63-1.23	0.46	0.87	0.61-1.24	0.44
	≥3	66	Ref.			Ref.		
Rhinitis ever	never or occasionally	34	0.97	0.60-1.56	0.91	1.10	0.67-1.82	0.70
	1-2	128	0.82	0.58-1.15	0.25	0.85	0.59-1.22	0.38
	≥3	66	Ref.			Ref.		
Rhinitis12m	never or occasionally	31	1.10	0.67-1.80	0.72	1.29	0.76-2.19	0.34
	1-2	110	0.87	0.61-1.25	0.46	0.93	0.63-1.37	0.72
	≥3	54	Ref.			Ref.		
Itchy and watery eyes 12m	never or occasionally	13	0.97	0.48-1.96	0.93	1.25	0.60-2.58	0.55
	1-2	56	0.98	0.60-1.61	0.94	1.03	0.61-1.74	0.91
	≥3	25	Ref.			Ref.		

Adjuster for gender, age and SES
Results obtained using the binary logistic regression test crude and adjusted for covariates
Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.
p values were considered significant below the 0.05 and underlined

8.5.6. Television watching

Watching television is an experience shared by the vast majority of children; however, no significant association was observed between the time that children spend watching television and asthma symptoms. There was not a significantly increased risk of all symptoms for children who watched 3 or more hours of TV a day or 1 to 3 hours a day compared to those who only watched under an hour a day.

With rhinitis, the results were different: after the adjustments, children watching television for over 3 hours a day, compared to those watching under an hour a day, had a higher risk of lifetime rhinitis (AOR=1.60; p=0.046) and rhinitis in the past year (AOR=1.72; p=0.03), and higher, although not significantly, risk of tearing and itchy eyes (AOR=1.84; p=0.09) for those who watched TV for over 3 hours a day and for those who watched TV for 1-3 hours (AOR=1.57; p=0.18). See Table 8.13

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Table 8.13 Association of asthma, rhinitis and their symptoms with the time spent watching TV.

Symptom	TV watching (hrs/day)	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	≥3	91	1.02	0.69-1.50	0.92	0.95	0.63-1.43	0.79
	1-3	201	1.22	0.87-1.72	0.25	1.18	0.82-1.69	0.37
	<1	66	Ref.			Ref.		
Wheeze 12m	≥3	37	1.51	0.84-2.71	0.17	1.42	0.75-2.70	0.29
	1-3	64	1.3	0.76-2.22	0.35	1.34	0.75-2.40	0.33
	<1	19	Ref.			Ref.		
Asthma ever	≥3	32	1.21	0.67-2.18	0.54	1.14	0.60-2.19	0.68
	1-3	55	1.02	0.60-1.76	0.93	1.11	0.62-1.98	0.72
	<1	20	Ref.			Ref.		
Exercise-induced asthma 12m	≥3	22	1.53	0.72-3.22	0.27	1.42	0.62-3.27	0.41
	1-3	34	1.16	0.58-2.33	0.68	1.12	0.52-2.41	0.78
	<1	11	Ref.			Ref.		
Night cough 12m	≥3	70	1.22	0.79-1.87	0.37	1.05	0.66-1.66	0.84
	1-3	134	1.15	0.78-1.69	0.48	1.13	0.75-1.68	0.56
	<1	45	Ref.			Ref.		
Rhinitis ever	≥3	73	1.4	0.91-2.16	0.13	1.6	1.01-2.53	0.046
	1-3	116	1.06	0.71-1.58	0.77	1.15	0.76-1.74	0.52
	<1	42	Ref.			Ref.		
Rhinitis12m	≥3	63	1.49	0.94-2.37	0.09	1.72	1.04-2.82	0.03
	1-3	100	1.14	0.74-1.74	0.56	1.26	0.80-1.98	0.32
	<1	34	Ref.			Ref.		
Itchy and watery eyes 12m	≥3	30	1.68	0.86-3.25	0.13	1.84	0.90-3.77	0.09
	1-3	52	1.46	0.79-2.69	0.23	1.57	0.82-3.04	0.18
	<1	14	Ref.			Ref.		

Adjuster for gender, age and SES

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

8.5.7. Truck traffic in residential area

There was no significant effect of heavy truck traffic on asthma symptoms; however, children living in neighbourhoods with heavy trucks passing often during the day or all day seemed to be protected from asthma ever and wheezing in the past 12 months. There was no clear effect on the remaining asthma symptoms.

In the case of rhinitis, children whose parents reported heavy truck traffic in the residential area often during the day or all day were significantly protected from having rhinitis in the past 12 months (OR=0.66; p=0.03) and tearing and itchy eyes (OR=0.57; p=0.02) compared to children living in the areas with trucks passing rarely or never, and these results remained significant after adjustment (AOR=0.66; p=0.04 and AOR=0.55; p=0.02 respectively). Detailed presentation of the results can be found in the Table 8.14

Table 8.14 Association of asthma, rhinitis and their symptoms with the frequency of heavy truck traffic in the residential area.

Symptom	Heavy truck traffic near residence	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	often during the day or all day	284	0.97	0.70-1.34	0.84	1.01	0.71-1.44	0.96
	never or rarely	71	Ref.			Ref.		
Wheeze 12m	often during the day or all day	92	0.78	0.49-1.22	0.27	0.74	0.45-1.20	0.22
	never or rarely	28	Ref.			Ref.		
Asthma ever	often during the day or all day	84	0.84	0.52-1.36	0.47	0.87	0.51-1.48	0.61
	never or rarely	24	Ref.			Ref.		
Exercise-induced asthma 12m	often during the day or all day	53	0.91	0.49-1.67	0.76	0.96	0.48-1.92	0.91
	never or rarely	14	Ref.			Ref.		
Night cough 12m	often during the day or all day	190	0.77	0.54-1.09	0.14	0.76	0.52-1.11	0.16
	never or rarely	56	Ref.			Ref.		
rhinitis ever	often during the day or all day	175	0.70	0.50-1.00	0.05	0.75	0.51-1.09	0.13
	never or rarely	56	Ref.			Ref.		
Rhinitis 12m	often during the day or all day	148	0.66	0.46-0.95	0.03	0.66	0.44-0.98	0.04
	never or rarely	50	Ref.			Ref.		
Itchy and watery eyes 12m	often during the day or all day	70	0.57	0.36-0.91	0.02	0.55	0.33-0.91	0.02
	never or rarely	28	Ref.			Ref.		

Adjuster for gender, age, SES and residential area

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

8.5.8. Degree of urbanization of the residential area

An increased risk of most symptoms of asthma, namely lifetime wheezing and asthma, exercise-induced wheezing attacks, and night cough, were found for urban and suburban residents, although none of the results had reached a significant level. The strongest effect was observed for the wheeze ever variable, with a 60% increase in the risk in the case of urban (AOR=1.60; p=0.10) and 23% in the case of suburban children (AOR=1.23;p=0.51), relative to rural children. Urban children were at highest risk for wheeze ever (as above), exercise-induced asthma (AOR=1.52; p=0.50) and night cough (AOR=1.22; p=0.52).

In the case of rhinitis, although again no result was significant, all the Odds Ratios for urban and suburban populations were above 1 (rural=1 as reference) meaning that as was the case with asthma, suburban and urban children seem to be at higher risk for developing rhinitis compared to rural children. The only symptom that suburban children seemed to be protected from was tearing and itchy eyes (AOR=0.57; p=0.28), although these results were not significant. Detailed results are presented in the Table 8.15.

Table 8.15 Association of asthma and rhinitis symptoms with degree of urbanization of the residential area.

Symptom	Residential area	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	U	254	1.70	0.98-2.93	0.06	1.60	0.91-2.80	0.10
	SU	61	1.35	0.74-2.48	0.33	1.23	0.67-2.29	0.51
	R	19	Ref.			Ref.		
Wheeze 12m	U	83	0.98	0.47-2.05	0.96	0.81	0.38-1.72	0.58
	SU	22	0.93	0.41-2.14	0.87	0.77	0.33-1.80	0.54
	R	9	Ref.			Ref.		
Asthma ever	U	74	1.15	0.51-2.59	0.74	1.08	0.47-2.49	0.86
	SU	21	1.18	0.48-2.91	0.72	1.05	0.42-2.62	0.92
	R	7	Ref.			Ref.		
Exercise-induced asthma 12m	U	47	1.28	0.45-3.67	0.64	1.52	0.45-5.11	0.50
	SU	12	1.19	0.37-3.82	0.77	1.17	0.31-4.42	0.82
	R	4	Ref.			Ref.		
Night cough 12m	U	173	1.32	0.73-2.39	0.36	1.22	0.66-2.24	0.52
	SU	43	1.16	0.60-2.25	0.66	1.08	0.55-2.12	0.81
	R	15	Ref.			Ref.		
Rhinitis ever	U	155	1.03	0.58-1.85	0.91	1.10	0.60-2.00	0.76
	SU	45	1.12	0.58-2.14	0.74	1.05	0.54-2.03	0.89
	R	16	Ref.			Ref.		
Rhinitis 12m	U	135	1.12	0.60-2.11	0.72	1.17	0.61-2.22	0.63
	SU	39	1.22	0.61-2.45	0.57	1.14	0.56-2.32	0.72
	R	13	Ref.			Ref.		
Itchy and watery eyes 12m	U	71	1.07	0.47-2.42	0.88	1.05	0.45-2.41	0.92
	SU	13	0.69	0.26-1.80	0.44	0.57	0.21-1.56	0.28
	R	7	Ref.			Ref.		

Abbreviations: U-urban; SU- suburban; R- rural

Results obtained using the binary logistic regression test crude and adjusted for covariates

OR- crude; AOR- Adjusted for gender, age and SES

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

8.5.9. Socioeconomic status

As we can see in the Table 8.16, generally, a family's higher socioeconomic status was associated with a tendency toward higher risk of asthma and wheezing although the results were not statistically significant. Only after adjusting for covariates was the risk of an attack of wheezing in the past 12 months significantly higher for higher SES compared to lower SES (AOR=1.61; p=0.03 and AOR=1.70; p=0.04 respectively). There was increased but not significantly risk of wheeze ever (OR=1.30; p=0.054), asthma ever (OR=1.14; p=0.55), and exercise-induced asthma (OR=1.16; p=0.58) related to a higher SES but the effect decreased after adjustment (AOR=1.20; p=0.21; AOR=1.11; p=0.63 and AOR=1.08; p=0.79).

In the case of rhinitis the effect of SES was not strong and was not statistically significant. There was a small and not significant tendency toward protection against rhinitis ever and in the past year related to a higher SES (OR=0.85; p=0.50 and OR=0.90; p=0.52). Results presented inTable 8.16.

Table 8.16 Association of asthma and rhinitis symptoms with family SES.

Symptom	SES	n	OR	95% CI	p value	AOR	95% CI	p value
Wheeze ever	Higher	153	1.30	1.00-1.70	0.054	1.20	0.90-1.60	0.21
	Lower	188	Ref.			Ref.		
Wheeze 12m	Higher	46	1.45	0.97-2.16	0.07	1.61	1.05-2.48	0.03
	Lower	66	Ref.			Ref.		
Asthma ever	Higher	46	1.14	0.75-1.72	0.55	1.11	0.72-1.73	0.63
	Lower	53	Ref.			Ref.		
Exercise Induced Asthma 12m	Higher	27	1.16	0.68-1.97	0.58	1.08	0.61-1.89	0.79
	Lower	32	Ref.			Ref.		
Night cough 12m	Higher	115	1.01	0.75-1.35	0.97	1.05	0.77-1.44	0.75
	Lower	119	Ref.			Ref.		
Rhinitis ever	Higher	116	0.85	0.63-1.15	0.30	0.86	0.62-1.18	0.35
	Lower	107	Ref.			Ref.		
Rhinitis 12m	Higher	96	0.90	0.65-1.24	0.52	0.91	0.65-1.27	0.58
	Lower	92	Ref.			Ref.		
Itchy and watery eyes 12m	Higher	42	1.16	0.75-1.79	0.50	1.20	0.76-1.89	0.44
	Lower	50	Ref.			Ref.		

Abbreviations: SES- Socioeconomic Status;

Results obtained using the binary logistic regression test crude and adjusted for covariates

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

OR- crude; AOR- Adjusted for gender, age and degree of urbanization

p values were considered significant below the 0.05 and underlined

8.5.10. Multivariate regression models

Multivariate analyses show us which factors continue to have a significant influence on risk of asthma and rhinitis symptoms even adjusted for all other risk factors shown to be associated with these symptoms in our studied population of children.

In the univariate analyses significant risk factors for developing wheeze ever were SES, high birth weight and there was a significant protective effect of being breastfed for the period of at least 9 months. In the models which had undergone the final adjustment, in the overall group the only factor remaining statistically significant was high birth weight (AOR=1.93; p=0.047). See Table 8.17;

Table 8.17 Multivariate regression model including all the variables associated significantly with lifetime wheeze in the univariate models.

Risk of wheeze ever		AOR	95% CI	p value
Base of Portuguese Diet		1.13	0.97-1.31	0.11
SES	Higher	1.02	0.76-1.37	0.89
	Lower	Ref.		
Birth weight	Low	1.21	0.69-2.10	0.51
	High	1.93	1.01-3.69	0.047
	Normal	Ref.		
Exclusive Breastfeeding period	<3	0.85	0.47-1.54	0.59
	3-6	0.81	0.45-1.47	0.49
	6-9	0.78	0.37-1.61	0.5
	>9	0.36	0.13-1.06	0.06
	never	Ref.		

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.
p values were considered significant below the 0.05 and underlined
Model additionally adjusted for gender, age and family history of asthma and rhinitis.

In the univariate analyses significant risk factors for developing wheeze in the past 12 months were high birth weight, not being breastfed, mother smoking in the first year of child's life and never or occasionally practicing vigorous physical activity. In the models which had undergone the final adjustment, in the overall group the factors remaining statistically significant were high birth weight (AOR=2.86; p=0.01), maternal smoking in the first year of child's life (AOR=2.29; p=0.003) and never or occasionally engaging in vigorous physical activity (AOR=1.93; p=0.049) See **Error! Not a valid bookmark self-reference.**.

Table 8.18 Multivariate regression model including all the variables associated significantly with wheeze in the past 12 months in the univariate models.

Risk of Wheeze 12m		AOR	95% CI	p value
Birth weight	Low	1.13	0.52-2.47	0.75
	High	2.86	1.31-6.21	0.01
	Normal	Ref.		
Breastfed	yes	0.6	0.30-1.20	0.15
	no	Ref.		
1st year of life maternal smoking	yes	2.29	1.32-3.99	0.003
	no	Ref.		
Vigorous Physical activity	never or occasionally	1.93	1.00-3.72	0.0495
	1-2	1.09	0.65-1.80	0.75
	≥3	Ref.		

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

Model additionally adjusted for gender, age and family history of asthma and rhinitis.

p values were considered significant below the 0.05 and underlined

In the univariate analyses significant risk factors for developing asthma ever was maternal smoking during the pregnancy, first year of child's life and having two or more people smoking at home. In the models which had undergone the final adjustment no factor remained significantly associated with lifetime asthma. See **Error! Not a valid bookmark self-reference.**.

Table 8.19 Multivariate regression model including all the variables associated significantly with lifetime asthma in the univariate models.

Risk of asthma ever		AOR	95% CI	p value
Pregnancy maternal smoking	yes	1.32	0.53-3.30	0.55
	no	Ref.		
1st year of life maternal smoking	yes	1.81	0.79-4.17	0.16
	no	Ref.		
Anyone smoking at home	1	0.83	0.48-1.45	0.52
	≥2	1.28	0.64-2.59	0.49
	0	Ref.		

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

Model additionally adjusted for gender, age and family history of asthma and rhinitis.

p values were considered significant below the 0.05 and underlined

In the univariate analyses significant risk factors for developing exercise induced asthma attack in the past year were never being breastfed, current maternal smoking and mother smoking over 10 cigarettes per day, maternal smoking during the pregnancy and during the first year of child's life and having two or more people smoking in the household. In the models which had undergone the final adjustment being breastfed continued to have a significantly protective role against exercise-induced asthma attacks (AOR=0.38; p=0.01). For more details see **Error! Not a valid bookmark self-reference.**.

Table 8.20 Multivariate regression model including all the variables associated significantly with Exercise-induced wheeze in the univariate models.

Risk of Exercise-induced asthma 12m		AOR	95% CI	p value
Base of Portuguese Diet		1.27	0.95-1.70	0.1
Breastfed	yes	0.38	0.18-0.81	0.01
	no	Ref.		
current maternal smoking	yes	X	X	X
	no	Ref.		
Number of cigarettes mother smokes per day	1-10	X	X	X
	>10	X	X	X
	none	Ref.		
Pregnancy maternal smoking	yes	1	0.32-3.12	1
	no	Ref.		
1st year of life maternal smoking	yes	2.38	0.85-6.67	0.1
	no	Ref.		
Number of Family members smoking	1	1.02	0.47-2.21	0.96
	≥2	1.51	0.49-4.69	0.47
	0	Ref.		

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.
p values were considered significant below the 0.05 and underlined
Model additionally adjusted for gender, age and family history of asthma and rhinitis.
X Insufficient n for calculation.

In the univariate analyses factors significantly protecting against night cough in the past year was being breastfed, being breastfed for over 9 months, and being exclusively breastfed for 6-9 or over 9 months. In the models which had undergone the final adjustment no factor remained significantly associated with night cough. See Table.

Table 8.21 Multivariate regression model including all the variables associated significantly with Night cough in the univariate models.

Risk of Night cough 12m		AOR	95% CI	p value
Breastfed	yes	0.33	0.11-1.03	0.06
	no	Ref.		
Breastfeeding period	<3	2.30	0.31-17.31	0.42
	3-6	1.78	0.23-14.00	0.59
	6-9	1.96	0.25-15.49	0.53
	>9	1.70	0.21-13.40	0.62
	never	Ref.		
Exclusive Breastfeeding period	<3	0.98	0.14-6.71	0.98
	3-6	1.01	0.15-7.01	0.99
	6-9	0.88	0.12-6.53	0.90
	>9	0.80	0.09-6.89	0.84
	never	Ref.		

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.
p values were considered significant below the 0.05 and underlined
Model additionally adjusted for gender, age and family history of asthma and rhinitis.

In the univariate analyses significant risk factors for developing rhinitis ever was never being breastfed, maternal smoking during the pregnancy and the first year of child's life and child watching TV over three hours a day. No factor remained significantly associated with lifetime rhinitis in the final, fully adjusted model. See **Error! Not a valid bookmark self-reference.**.

Table 8.22 Multivariate regression model including all the variables associated significantly with lifetime rhinitis in the univariate models.

Risk of rhinitis ever		AOR	95% CI	p value
Breastfed	yes	0.62	0.36-1.06	0.08
	no	Ref.		
Pregnancy maternal smoking	yes	1.49	0.75-2.98	0.26
	no	Ref.		
1st year of life maternal smoking	yes	1.46	0.79-2.70	0.23
	no	Ref.		
TV watching	≥3	1.53	0.95-2.45	0.08
	1-3	1.15	0.75-1.77	0.51
	< 1	Ref.		

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.
p values were considered significant below the 0.05 and underlined
Model additionally adjusted for gender, age and family history of asthma and rhinitis.

In the univariate analyses significant risk factors for developing rhinitis ever were high birth weight, never being breastfed, pregnancy and the first year or child's life maternal smoking, child watching TV over 3 hours per day and never or rarely heavy trucks passing in the residential area. The factors which after the final adjustment continued to significantly modulate the risk of rhinitis in the past year were: being breastfed (AOR=0.56; p=0.048), watching TV 3 or more hours per day (AOR=1.73; p=0.04) and having heavy trucks passing often during the day or all day near the place of residence (AOR=0.65; p=0.03). See **Error! Not a valid bookmark self-reference.**.

Table 8.23 Multivariate regression model including all the variables associated significantly with rhinitis in the past 12 months in the univariate models.

Risk of Rhinitis 12m		AOR	95% CI	p value
Birth weight	Low	0.83	0.43-1.60	0.58
	High	1.97	0.99-3.94	0.055
	Normal	Ref.		
Breastfed	yes	0.56	0.32-0.99	0.048
	no	Ref.		
Pregnancy maternal smoking	yes	1.68	0.81-3.49	0.16
	no	Ref.		
1st year of life maternal smoking	yes	1.66	0.86-3.20	0.13
	no	Ref.		
TV watching	≥3	1.73	1.03-2.92	0.04
	1-3	1.28	0.79-2.07	0.31
	< 1	Ref.		
Heavy trucks traffic	often during the day or all day	0.65	0.44-0.96	0.03
	never or rarely	Ref.		

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.
p values were considered significant below the 0.05 and underlined
Model additionally adjusted for gender, age and family history of asthma and rhinitis.

In the univariate analyses significant risk factors for developing rhinitis ever were never being breastfed, Heavy truck traffic also remained significantly associated with tearing and itchy eyes (AOR=0.54; p=0.01). See **Error! Not a valid bookmark self-reference.**.

Table 8.24 Multivariate regression model including all the variables associated significantly with tearing and itchy eyes in the univariate models.

Risk of Itchy and watery eyes 12m		AOR	95% CI	p value
Breastfed	yes	0.70	0.15-3.24	0.65
	no	Ref.		
Breastfeeding period	<3	0.33	0.03-3.64	0.37
	3-6	0.25	0.02-2.94	0.27
	6-9	0.22	0.02-2.59	0.23
	>9	0.27	0.02-3.17	0.30
	never	Ref.		
Exclusive Breastfeeding period	<3	3.00	0.31-28.54	0.34
	3-6	3.19	0.34-30.19	0.31
	6-9	1.41	0.13-15.97	0.78
	>9	1.80	0.12-26.61	0.67
	never	Ref.		
Heavy trucks traffic	often during the day or all day	0.54	0.33-0.88	0.01
	never or rarely	Ref.		

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.
p values were considered significant below the 0.05 and underlined
Model additionally adjusted for gender, age and family history of asthma and rhinitis.

8.6. Discussion

This study allowed us to verify that the risk factors increasing the probability of asthma symptoms were: positive family history of asthma, higher socioeconomic status, high birth weight, not being breastfed, shorter periods of total and exclusive breastfeeding, maternal smoking of over 10 cigarettes per day, maternal smoking during pregnancy and during the 1st year of the child's life, 2 or more people smoking in the household, and the child never or occasionally practicing vigorous physical activity.

Factors increasing the risk of rhinitis and its symptoms were: positive family history of rhinitis, high birth weight, not being breastfed or being breastfed in total and exclusively for shorter period, maternal smoking during pregnancy and during the 1st year of the child's life, watching television for 3 or more hours per day, and living in an area with frequent heavy truck traffic.

The symptoms most strongly associated with asthma, even after adjustment for all the remaining risk factors, were high birth weight, not being breastfed, never or occasionally engaging in vigorous physical activity, and maternal smoking in the first year of the child's life. As with rhinitis, higher and more consistent risk was associated with the absence of breastfeeding, watching TV 3 or more hours per day, and heavy trucks passing through the residential area often during the day or all day.

Family history of asthma was found to have a strongly significant effect on childhood asthma and its symptoms. Similarly, a significant association was observed between family history of rhinitis and the development of this disease and its symptoms in children, although the effect was smaller than for asthma. The strong impact of a family history of asthma and rhinitis on the development of these diseases in offspring is very well-known and much described in the literature (Bjerg et al., 2007; Burke et al., 2003; Los, Postmus, & Boomsma, 2012; Sly, 2011). We know that a part of this association is due to genetic predisposition and the list of genes related to asthma and rhinitis is growing (Bønnelykke et al., 2013; C Ober & Hoffjan, 2006). A study analysing the data of over 14 000 individuals registered at the Netherlands Twin Register showed a broad heritability of asthma estimated at 75% (defined as "The broad-sense heritability is the ratio of total genetic variance to total phenotypic variance." (McClean, 1997)) (Willemsen, van Beijsterveldt, van Baal, Postma, & Boomsma, 2008).

One of the early life predictors of asthma and rhinitis is birth weight. We have found that both high and low birth weight can increase the chance of developing asthma in childhood and while the risk of rhinitis was also increased by high birth weight, it was decreased by low birth weight. This U-shaped association has already been observed and described in the

literature. The ISAAC study from Germany, including 5-7 year-old children, also found U-shaped associations (although not significant) between birth weight and the prevalence of asthma and current wheezing (Bolte et al., 2004). Also, in another study of the Finnish birth cohort born in 1966, it was demonstrated that the adult atopy had a U-shaped association with Ponderal index at birth (Xu, Pekkanen, Laitinen, & Järvelin, 2002).

A large study of 5,656,507 children born in Sweden during 1973-2004, in Finland during 1987-2004, and in Denmark during 1979-2005 showed that there is a significantly higher risk of hospitalisation in childhood due to asthma for children with lower birth weight where a 1000g decrease in birth weight resulted in a relative risk of 1.17 (Liu et al., 2014). On the other hand, a meta-analysis of 12 studies on birth weight showed a relative risk of 1.2 for children born with higher weight (Flaherman & Rutherford, 2006). However, another study by Sin et al. (2004) in Canada, observing children during the first 10 years of life, found an increased risk of emergency room visits for asthma related to high but not low birth weight. Moreover, contrary to what we found, Project Viva from Boston, US, found no association between a high (≥4,000 g) birth weight and the chance of developing asthma and wheezing by the age of 2 (Taveras et al., 2006).

We have shown that a high birth weight seemed to increase, although not significantly, the risk of rhinitis, while low birth weight decreased it. Literature relating birth weight to rhinitis is relatively scarce. A cohort study from Denmark in which 9,722 women took part found no association between birth weight and allergic rhinitis (Bager, Melbye, Rostgaard, Stabell Benn, & Westergaard, 2003). Another study, from Taipei, of children aged 6 to 13 years old, found an increased, though not significant, risk of allergic rhinitis for children born with low birth weight (<2500 grams). The study did not make a distinction as to high birth weight, though (Hsu, Lin, Tan, Lee, & Huang, 2009). A recent study in Belarus found no evidence for any association between birth weight and wheezing, asthma, or rhinitis prevalence; however, in that study, children born weighing under 2500g were excluded beforehand (Anderson et al., 2013).

Breastfeeding was one of the factors found to be most strongly influencing the risk of developing asthma and rhinitis in children in our study. We found that breastfed children had significantly lower risk of these two diseases than children who had never been breastfed. Indeed, the results obtained through the ISAAC phase II study showed that breastfeeding was associated with lower risk of wheezing both in affluent and non-affluent countries. Closer analysis has revealed that this association only existed in cases of non-atopic wheeze in non-affluent countries (Nagel et al., 2009).

We also discovered a tendency, although not significant, toward dose effect in the association between breastfeeding duration and the risk of asthma and rhinitis, with shorter periods being related to higher risk. A study from Finland, analysing data of 7-14 year-old children, found a U-shaped association between breastfeeding and the risk of asthma, emphasising that the optimal duration was 4 to 6 months (Fredriksson et al., 2007). An adverse effect of prolonged breast-feeding on atopic dermatitis has also been found in the children 5 years old or younger included in the study (Hong et al., 2014). Similarly, in another study from Finland, prolonged exclusive breastfeeding for over 9 months was associated with increased childhood atopic dermatitis at the age of 5 and food hypersensitivity symptoms at the age of 11 (Pesonen, Kallio, Ranki, & Siimes, 2006). Furthermore, a study from Finland found that late introduction of solid foods increased the risk of allergic sensitization to food and inhalant allergens at the age of 5 years (Bright I Nwaru et al., 2010). We observed a certain U-shaped association in cases of exclusive breastfeeding, with periods of 9 months being less protective than periods of 6-9 months against the studied diseases. A study conducted in Lisbon, based on a sample of 5-11 year-old children, did not find evidence for a protective role of breastfeeding against respiratory diseases (Pegas et al., 2011). A meta-analysis of the studies on rhinitis and breastfeeding has found a protective role of exclusive breastfeeding during the first 3 months against allergic rhinitis in children (Bloch et al., 2007).

Second-hand tobacco smoke exposure, especially in utero and in early post-natal life but also across the entire lifespan, affects various aspects of health, including metabolic, cardiovascular, and neurobehavioral health, as well as childhood cancers, fertility, and respiratory health (Bruin et al., 2010). In this chapter, what concerns us is chronic respiratory health.

As shown by Horak et al. (2007), second-hand smoking during pregnancy causes an increased risk of asthma and wheezing in children, which agrees with our findings. In our study, maternal smoking during pregnancy and the first year of life significantly increased the risk of both asthma and rhinitis in the studied population, independently of socioeconomic status. These two factors were among those found to have the strongest impact on respiratory health of children studied by us.

The effect on asthma and rhinitis of maternal smoking in the 1st year of the child's life has also been observed previously. In the ISAAC phase III study, which included data from 32 countries, it was shown that although current maternal smoking did indeed increase the risk of childhood asthma, when considered together with exposure to tobacco in the 1st year of the child's life, the effect of current second-hand smoking was due to early life exposure to tobacco (Mitchell et al., 2012). The effect of maternal smoking in the 1st year of the child's life on

children's asthma and rhinitis has also previously been observed. It was shown in the ISAAC phase III study, which included data from 32 countries, that current maternal smoking increased the risk of childhood asthma. However, after adjustment for exposure to tobacco in the 1st year of the child's life, the effect of current second-hand smoking turned out to be observed as confound explained by early life exposure to tobacco (Mitchell et al., 2012).

Second-hand exposure to tobacco later in life, and not only during the pregnancy and the first months of post-natal life, was, however, shown to have a significant role in asthma development. This includes not only maternal smoking, but smoking by any members of the household. In a study in Spain, using ISAAC methodology, it was found that second-hand tobacco smoke was associated with a higher prevalence of asthma. In addition, the risk was higher if it was the mother who smoked and if both parents smoked as compared to only paternal smoking. This result was observed for both the 6-7 and the 13-14 year-old age groups (Gonzalez-Barcala et al., 2013). Yet another project, carried out by the Taiwan Children Health Study, obtained similar results and also showed a significant effect on early- but not late-onset asthma (Tsai et al., 2010). Although we did not have the relevant information on paternal smoking, we found that any 2 or more people smoking at home further increased the risk of asthma and wheezing but not rhinitis. In addition, there was a dose response to the number of household members smoking, and a higher number of smokers increased the risk of asthma and Exercise-induced asthma 12m.

We have shown that later in a child's life, exposure to tobacco has an adverse effect on respiratory health. In our study, maternal smoking when the child was 6-8 years old had a tendency to increase the risk of asthma symptoms in children, with the highest and only significant effect observed on exercise-induced wheezing attacks. Risk, however, decreased after adjustment for socioeconomic status of the family, suggesting that this factor can explain some part of the association. There was no clear effect of current maternal smoking on rhinitis symptoms. The results of the ISAAC study of 6-7-year-old children from 32 countries showed that both maternal and paternal smoking increased the risk of asthma and, to a lesser extent, rhinitis symptoms as well. Moreover, maternal smoking had a stronger effect than paternal, with an additional dose relationship of risk increasing with higher numbers of cigarettes smoked by the mother.

There seems to be a difference in the response to tobacco smoke depending on the family history of atopy and in a study from US the length of the hospitalisation stay was significantly related to second-hand smoking only for children with familial atopy (Lemke et al., 2013). This may have to do with a genetic predisposition, as it has recently been shown that

there is a gene-environment interaction involved in the link between in utero and early-life tobacco exposure and asthma (Scholtens et al., 2014).

Although early life factors are strong predictors for asthma and rhinitis, events and lifestyle later in a child's life continue to influence predisposition to these diseases and their course. It was previously reported in Portugal that adherence to the Mediterranean diet brings health benefits. In the sample of asthmatic adults, higher consumption of this dietary pattern increased asthma control (Barros et al., 2008). Another study of 7-18 year-old children and adolescents from Greece confirmed the benefits of elements such as fruits, vegetables and nuts in the traditional Mediterranean diet toward protection against both asthma and rhinitis (Chatzi et al., 2007). Also in the ISAAC study phase III, results from the global survey showed that the consumption of fruits at least 3 times per week had a protective effect against severe asthma, whilst the consumption of fast food three or more times per week increased the risk of severe asthma and severe rhinitis among children and adolescents (Ellwood et al., 2013). In addition, it has been shown that the Mediterranean diet protects against wheezing independently of other lifestyle factors such as obesity and physical activity. (Castro-Rodriguez, Garcia-Marcos, Alfonseda Rojas, Valverde-Molina, & Sanchez-Solis, 2008). In a study made in Baltimore, US, focusing on 5-12 year-old children, it was shown that fast food increased the prevalence and severity of wheezing, as well as the medication used by children. Interestingly, consumption of this food did not significantly increase the BMI, so the effect appears to occur independently from obesity (Bose et al., 2013).

We have not found a significant association between the Mediterranean diet or saturated fat diet and asthma or rhinitis. However, higher consumption of the saturated fat diet and lower consumption of the Mediterranean component was observed for children reporting a night cough in the past year. In addition, children with wheezing and rhinitis also seemed to eat more of the saturated fat diet component than the others.

We have also found that consumption of the component including meat, potatoes, rice, and pasta was significantly higher among children with a lifetime history of wheezing and exercise-induced asthma attacks reported in the past year. This could be due to the general increase in energy consumption related to this component. As described in the introduction, total energy intake is on the top on the list of most pro-inflammatory dietary elements. In addition, this component's elements are rich in other nutrients promoting inflammation, such as carbohydrates, fat (especially saturated fat), and cholesterol (Cavicchia et al., 2009).

Yet another lifestyle factor modulating the risk of asthma and rhinitis in children is physical activity. In our study we have confirmed that lack of physical activity increases the risk of asthma and wheezing in children, but no effect was observed for rhinitis.

On the contrary, we did not find that time spent watching television affected the risk of asthma, though it did affect the risk of rhinitis. Some studies have shown that greater participation in sports and other physical activity and lesser participation in sedentary behaviours is conducive to protection against asthma and rhinitis and is recommended in order to obtain better control of those diseases. Eijkemans et al. (2012) in their review summarize the findings as indicating that there is an important role played by physical activity in the prevention of asthma development.

Physical exercise can be double-edged for children affected with chronic respiratory diseases. On the one hand, it is recommended and has been shown to protect against the development of asthma; on the other hand, especially in uncontrolled asthma, it might lead to attacks and worsening of symptoms, and cause lower participation in activities by those children. An example of physical activity having a negative effect on respiratory health can be found in a study performed in Macedonia, where they used ISAAC tools and analysed a population of 13-14 year-old adolescents. They have found that vigorous physical activity increased risk of current wheezing, speech-limiting wheezing, and exercise-induced wheezing, as well as the risk of rhinitis. The risk of current and exercise-induced wheezing attacks was also increased by sedentary behaviour such as TV watching (Vlaski et al., 2008) In phase II of ISAAC, the results pooled from all the centres worldwide showed that vigorous physical activity increased the risk of asthma and rhinitis in 13-14 year-old adolescents, but not in 6-7 year-old children. Watching TV for five or more hours per day was positively associated with asthma and rhinitis symptoms: with an increased risk of asthma symptoms in children and adolescents and of rhinitis in adolescents only (Mitchell et al.., 2013).

The negative association between physical activities and asthma can be bidirectional. For instance, we know that exercise per se can worsen some patients' situation and lead to lower activity levels for those children. Some asthmatics might experience wheezing attacks induced by exercise, which might discourage them from continuing. A cross-sectional observational study from the United Kingdom, focused on 7-14 year-old children in hospital, showed that asthma was considered a serious barrier to physical activity in children, by both the patients themselves and their parents. It was also reflected in a significantly lower level of physical activity and increased BMI (Glazebrook et al., 2006). A study of five year-old children participating in the Copenhagen Prospective Studies on Asthma in Childhood showed that in fact children with higher bronchial responsiveness have lower levels of physical activity, but this difference was not perceived by the parents, and was only observable using accelerometers (Brasholt, Baty, & Bisgaard, 2010). Following this example, asthma would precede and lead to physical inactivity. On the other hand, children who practice less could be at higher risk for asthma, and their inactivity would therefore lead to asthma (Eijkemans et al., 2012).

Nevertheless, the association between sedentary lifestyle and asthma or rhinitis is not always confirmed. In a study of 6-7 year-old children from Italy, wheezing and asthma were not found to be associated with sports activities, but only with watching television for over 5 hours a day (Corbo et al., 2008). A lack of association between physical activity levels and wheezing at 3 and 4 years of age was also shown in an article describing Generation R from Netherlands (Driessen et al., 2014).

Although it has been shown in many studies, as described above, that a sedentary life style increases the risk of asthma, in our sample we found that time spent watching TV did not have any significant impact on this disease. This might be due to the fact that we did not include other sedentary behaviours such as time spent using computer, consoles, etc., which might constitute a larger part of children's sedentary activities than watching TV (Christakis, Ebel, Rivara, & Zimmerman, 2004).

Phase III of the ISAAC study of both 13-14 and 6-7 year old groups found an association between heavy truck traffic in the residential area of the children and their respiratory health. The higher the reported traffic was, the higher the risk of asthma, wheezing, and rhinitis (Brunekreef et al., 2009). Similarly, a recently published study from Macedonia of 13-14 year old adolescents, also conducted within the ISAAC initiative, showed an increase in the risk of asthma related to traffic (Vlaski, Stavric, Seckova, Kimovska Hristova, & Isjanovska, 2013). A study from an industrial region of Poland likewise suggested that even in generally polluted areas, the proximity to roads with high vehicle traffic can modulate children's chance of developing asthma and, to a lesser extent, rhinitis also (Skrzypek, Zejda, Kowalska, & Czech, 2013).

Although we found a slight tendency toward an increase in asthma risk for children living in areas with heavy trucks passing often during the day or all day, these results were only significant for rhinitis. There was a significantly increased risk of rhinitis related to higher traffic, and the results were independent of socioeconomic status and degree of urbanization. Studies have suggested that this could be due in large part to an increased concentration of air pollutants affecting respiratory tracts of children (Bernstein, 2012a, 2012b; Ryan et al., 2009). Moreover, as was described in the chapter on obesity risk factors, heavy road traffic could decrease outdoor physical activity and encourage sedentary behaviours such as watching television (Vlaski et al., 2008), which not only have been shown to be independent risk factors for asthma (Konstantaki et al., 2013; Mitchell et al.., 2013) but could also act as links between asthma and obesity (Carver et al., 2008; Jerrett et al., 2010; Oluyomi et al., 2014; Timperio et al., 2005).

Due to heavy traffic, but not only that, we would expect that the risk of developing asthma and rhinitis would be higher for urban areas, and their severity lower in rural areas. In our study, we observed a significantly higher number of reported wheezing episodes (at least once in the child's life) in urban areas, compared to suburban and rural areas. Urban and suburban populations revealed higher risk levels of asthma and wheezing compared to rural populations. In the case of rhinitis, the association was even weaker; however there was again a slight increase in the risk of lifetime and current rhinitis for urban and suburban children. Urban and suburban residents, compared to rural residents, were also characterised by higher risk of experiencing disturbances to daily activities caused by rhinitis. These results were, however, not very consistent or strong; we can therefore only talk about some tendencies and the weak effect of the area of residence on these chronic respiratory diseases. We suggest that there is a modest protective effect of rural regions against asthma and rhinitis among children. These results are in agreement with the information we find in the epidemiological literature. In a review by Wong and Chow (2008) analysing the literature, describing rural and urban populations, the authors confirm that rural environments are characterised by lower asthma risk. There are many putative reasons for this health inequality. Oliveira et al. (2010) showed in their study that there is a difference between rural and urban areas in the concentration of potentially allergenic fungal spores in the air. Higher concentration of these elements in rural areas would increase the risk of allergies and comorbidities. Similarly, Sousa et al. (2011) found that higher ozone pollution in rural areas increased the risk of asthmatic diseases. This would, however, indicate that rural environments represent higher risk for asthma and allergies, which is contrary to what we saw in our sample of children living in Coimbra.

Generally, apart from the prevalence of asthma and allergies being lower in rural areas, this type of area is characterised by higher asthma severity and hospitalizations (Pesek et al., 2010). Our results did not allow us to study the severity of these diseases, as that would require a larger sample.

In one study performed in France, it was observed that indoor pollution increases the risk of asthma and indoor air quality is different in rural compared to urban houses. Pollution components, such as nitrogen dioxide, fine particles, and volatile organic compounds (formaldehyde, acetaldehyde, benzene, toluene, ethylbenzene, and xylenes) were studied, and pollution levels were found to be doubled in urban homes (Hulin, Caillaud, & Annesi-Maesano, 2010). This, together with behavioural differences, could in part explain the higher risk related to urban areas.

Despite certain tendencies, the differences were not strong. There are many possible reasons for that. To start with, it has been suggested, that area of residence is not an independent

indicator of risk, but rather simply exacerbates existing socioeconomic disparities (Smith, Humphreys, & Wilson, 2008). To study those, a more detailed study of the socioeconomic status groups within each residential area would be necessary, which could not be done in our study, due to insufficient sample size.

We have observed a tendency toward higher risk of asthma and its symptoms related to higher socioeconomic status and we have not observed any consistent association between SES and rhinitis.

Socioeconomic status is a strong modulator of health risk, as it is related to unequal financial resources, access to information, consciousness of risk factors and their health consequences, and more. Lower SES can limit prevention and treatment capacities through the inability to afford such elements of a healthy lifestyle as appropriate housing conditions, diet, and extracurricular activities, among several other factors. Moreover, it can contribute through the lack of essential knowledge of what is considered healthy and protective, which even with economic capacity can increase susceptibility and, in consequence, lead to the development of various conditions, especially diseases of affluence.

A study performed in UK concerning children born within one week in April 1970 and their wheezing outputs at 5 year of age have shown that the risk of wheezing increased together with decreasing social status of parents, but the persistence of wheezing in the same children at the age of 16 was associated with higher socioeconomic status (Lewis, Richards, Bynner, Butler, & Britton, 1995). Another study of 5-11 year-old children from England and Scotland found a higher risk of persistent wheezing to be associated with the areas with higher poverty (Duran-Tauleria & Rona, 1999). A Generation R study from the Netherlands analysing the effect of socio-demographic factors on childhood asthma showed that 6 year-old children from families experiencing financial difficulties had higher risk of wheezing and those with parental unemployment or lower levels of education had higher risk of asthma (Hafkamp-de Groen et al., 2013). Some authors also reported weak or no association of asthma prevalence with socioeconomic status (Hancox et al., 2004; Violato, Petrou, & Gray, 2009). Our study found rather the opposite tendency, and it was the group of children from families with higher SES that seemed to be at higher risk of asthma and wheezing. Although poor health is generally associated with lower SES, which is not always the case when analysing westernized diseases. As epidemics of these diseases are linked to increased wealth in societies, the situation can be the opposite. In a prospective cohort study from New Zealand, atopy measured at 13 years of age using skin-prick test and Immunoglobulin E concentration in blood was higher among the group with higher SES in childhood, and the same SES variable showed no association with asthma at 9 years (Hancox et al., 2004).

The situation is clearer when it comes to severity, hospitalizations, and mortality related to asthma and allergic diseases, and these factors have generally been described as being more frequent in lower socioeconomic groups (Cesaroni et al., 2003; Eisner, Katz, Yelin, Shiboski, & Blanc, 2001; Grant, Lyttle, & Weiss, 2000; Roberts, Lowndes, Milne, & Wong, 2012). In our study, however, we did not study this pattern, for the reasons mentioned above.

The objective assessment and comparison of the effect of socioeconomic status and type of residential area is not an easy task. To start with, the definition of both variables differs between studies, and different elements are used to constitute them. Moreover, the impact of these factors is indirect, usually through lifestyle, behavioural patterns, financial capacities, and quality of life. Such elements as income or education might have different modulating effects on these factors, depending, for example, on the area-based socioeconomic level, local health system and insurance, employment availability, and many more. Consequences of living in an area with a lower degree of urbanization will differ depending on transportation availability, socioeconomic level, housing conditions, car ownership, geographical structure, etc. This may be the origin of inconsistencies existing in reporting the effect of SES and type of residential area on health, including asthma and rhinitis.

8.7. Conclusion

This chapter has shown that the elevated prevalence of asthma, rhinitis, and their symptoms among children living in Coimbra is most likely an effect of epidemiological dynamics, with altering environmental and lifestyle factors. Unlike genetic predisposition, environmental exposures can be consciously controlled and the alarming situation observed with regard to the rates of asthma and rhinitis could be combated by changes in lifestyle. We have to remember that rather than working individually, these risk factors often cluster, and risky and unhealthy behaviours can accumulate, further increasing the chance of the child ending up with severe and uncontrolled asthma or rhinitis (Chiolero, Wietlisbach, Ruffieux, Paccaud, & Cornuz, 2006; Héroux et al., 2012). These results once again underline the necessity of interventions and prevention programmes. Especially now, in view of the economic and social situation Portugal is currently facing, an effort should be made to eliminate these inequalities and improve the health conditions of the disadvantaged social and demographic groups. As we can see, many of the same factors that change the risk of obesity also influence the development of asthma and rhinitis. This led to the hypothesis of the environmental and socio-demographic link between them. The next chapters are designed to test this hypothesis and have as their objective to determine the answer to the question: to what extent and how do these factors modulate the association of obesity with asthma and rhinitis in children?

9. Association between asthma and obesity- role of the common risk factors

9.2. Introduction

The parallel rise in the prevalence of obesity and respiratory diseases such as asthma and rhinitis registered in the last few decades has led to increased interest in a plausible link between these conditions. Indeed, numerous epidemiological studies have shown that there is an association between these conditions among all age groups, although the mechanism behind that remains undetermined (Black et al., 2012; Jeong et al., 2010; Okabe et al., 2012; Papoutsakis et al., 2013; Taveras et al., 2008).

An increased risk of developing asthma has been widely observed among obese individuals, including adolescents and children, and a childhood obesity-related asthma phenotype has also been proposed (Jensen, Collins, Gibson, & Wood, 2011). A recent review by Papoutsakis et al., (2013) confirms that most studies concerning this topic corroborate the existing significant association between an obesity and asthma risk in the paediatric population. Indeed, we can find evidence of this association in various cross-sectional (Black et al., 2012; Okabe et al., 2012) and longitudinal studies (Jeong et al., 2010; Taveras et al., 2008).

Obesity-induced asthma has been proposed as one of many distinctive asthma phenotypes (Farzan, 2013; Jensen et al., 2011; Lang et al., 2011; Sutherland et al., 2012). This particular type of asthma seems to be more common among adult women, is more likely to be non-atopic, and is characterized by a later onset (Farzan, 2013). In fact, obesity has been identified as one of the most important determinants of the asthma phenotype, stronger even than asthma severity, control and age of onset. Obesity-related asthma or, as it is often called, the "obese asthma phenotype," is also described as one of the phenotypes of asthma in children. Classification of obesity-related asthma as a distinct phenotype means that this group of asthmatics have a distinct clinical and immunological profile that differs from other phenotypes. They are generally characterised by primary and predominantly atopic asthma and the severity of asthma in this phenotype is increased by the presence of obesity (Rasmussen & Hancox, 2014). Moreover, obese asthmatic children were shown to have a Th1 polarization rather than the typical atopic Th2 immunological profile (Rastogi et al., 2012). Interestingly, it has been shown that obese children might respond differently to environmental triggers and traffic exposure to PAH is more likely to cause asthma in obese children than those with normal weight (Jung et al., 2014).

Nevertheless, even within the obesity-related asthma phenotype, heterogeneity can be observed in the clinical characteristics of patients, and corresponding differences in their treatment approach (Sutherland et al., 2012).

Regarding gender differences in the predisposition to this type of asthma (asthma-related obesity), there are some discrepancies in the literature, such that it looks like this phenotype is more commonly observed in adulthood among women, (Y. Chen et al., 2002), while in childhood reports show inconsistent results. Some studies show that this type of asthma is more common among boys (Chen, Dong, Lin, & Lee, 2013; Lang et al, 2013. Suglia, Chambers, Rosario, & Duarte, 2011), while others state otherwise and claim that it is more common among girls (Murray et al., 2011; Wang et al., 2014; Willeboordse et al., 2013). Others have found no clear gender influence in this area (Yao et al., 2011).

Obese patients with asthma are characterized by higher asthma severity, lower disease control compared to normal weight patients, and, therefore, a strong focus was placed on describing the clinical profile of these individuals. It has even been suggested that obesity has even more effect on lung function for children than it has for adults (Lang et al., 2011). As in the case of adults, among children too, obesity is more closely related to non-atopic asthma (Visness et al., 2010). Similarly, it has also been observed that obese children have lower response to treatment with inhaled steroids and are at a higher risk for emergency hospitalizations than asthmatics with normal weight (Forno et al., 2011). Obese children also tend to have lower disease control, higher severity of symptoms, and more exacerbations (Quinto et al., 2011).

Lately there has been a focus on the effect of the weight loss in asthmatic children. Studies performing a weight loss intervention on asthmatic obese children have found that with decreased weight there is a significant improvement in asthma control, lung function, asthma-related quality of life (Luna-Pech et al., 2014; van Leeuwen, Hoogstrate, Duiverman, & Thio, 2013), and some report decrease in systemic and airways inflammation (Abd El-Kader, Al-Jiffri, & Ashmawy, 2013), while others did not find this association (Jensen, Gibson, Collins, Hilton, & Wood, 2013).

The pathophysiologic mechanism that links asthma with obesity in children is still not completely understood. Although it has been suggested that some genes play a role (Melén et al., 2010), that does not explain the full variation of this asthma phenotype.

A mechanical restriction of the chest due to an increased thoracic and abdominal fat mass has been proposed as one of the confounders contributing to overestimation of asthma severity among obese children. It has been suggested that increased obesity is more related to a non-specific (self-reported and not specific to one disease only) asthma symptoms such as dyspnoea or nocturnal awakenings and could lead to the impression of lower asthma control, unrelated to severity of inflammation (Sah et al., 2013).

Moreover, a reverse causation has also been proposed as a putative mechanism contributing to increased weight among asthmatic children. It has been shown that inhaled steroids, a commonly prescribed medication for asthma, might have a positive dose effect on children's weight and therefore increased medication use would cause obesity, rather than the other way around (Jani et al., 2005). It seems, however, more plausible, and there is growing evidence indicating, that obesity precedes asthma or at least its manifestation (Papoutsakis et al., 2013).

The hormones produced by fat tissue play an important role in the pathogenesis of asthma induced by obesity. As described in the general introduction, these hormones called adipokines secreted by adipose tissue are by far the strongest link found, with growing evidence showing that this endocrine function of the adipocytes can lead to systemic and airways inflammation. The pro-inflammatory effect of the imbalance of such cytokines such as leptin, resistin, ghrelin and adiponectin has been described for adults (Muc et al., 2013) and children (K. W. Kim et al., 2008; Gabriele Nagel et al., 2009; Yuksel, Sogut, Yilmaz, Onur, & Dinc, 2012).

The link between asthma and rhinitis among children has been studied much less. To give a clearer idea, a search on PubMed (), after requesting publications on "obesity asthma children" be shown returned 755 articles, compared to only 64 when we requested "rhinitis obesity children" (data from 31.05.2014). Some evidence on the association between increased body weight and rhinitis has also been described (Cervoni, 2011; Ciprandi et al., 2011; Musaad et al., 2009) although many authors have not found such an association (Ekström et al., 2014; Sidell, Shapiro, & Bhattacharyya, 2013; Sybilski et al., 2014; Tanaka, Miyake, Arakawa, Sasaki, & Ohya, 2011).

Despite only weak evidence linking rhinitis with obesity, adipokines imbalance has been observed to have a relationship to increased weight and especially allergic rhinitis in adults, with the highest levels reported for active allergic rhinitis, suggesting that the serum concentration of these cytokines could be unregulated during allergen exposure, independently of obesity (Giorgio Ciprandi, De Amici, Tosca, & Marseglia, 2009, 2010a, 2010b; Unal, Eskandari, Muşlu, Pata, & Akbaş, 2006). We found only two publications studying the role of adipokines in rhinitis in children, and one of them showed a significant association between serum leptin and adiponectin levels and allergic rhinitis and nasal symptoms score (Hsueh, Lin, Lin, & Lin, 2010), while the second, examining the leptin concentration, found only a significant result for asthma and not for rhinitis (Quek et al., 2010).

As has been widely described, and as the results of this study appear to confirm, childhood asthma, rhinitis, and obesity share some common risk factors, such as high birth

weight, lack or shorter periods of total and exclusive breastfeeding, diet, sedentary life style with low level of physical activity, and second-hand exposure to tobacco, among others. This has led to a theory that these lifestyle factors could not only lead to an increase in the prevalence of asthma, rhinitis and obesity each taken independently, but also could explain the frequent coexistence of these diseases.

Studies have been conducted worldwide examining the role of these factors in childhood obesity, related especially to asthma. In their review, Litonjua & Gold (2008) emphasize the role of early exposure (prenatal and early life) including quality of the mother's diet during pregnancy (especially Vitamin D, C, E and Polyunsaturated Fatty Acids deficiency), microfloral colonization of the gastrointestinal tract, and unbalanced adipokines levels, in the development of asthma and obesity and the putative link between them.

Birth weight is one of the most important factors linking asthma with obesity, not only because it is strongly associated with these diseases, but also because it shows how early in life we can observe an indication of children's increased chances of developing these diseases, i.e., already from birth. In a longitudinal study, it has been shown that neonatal size can already predispose infants to the development of childhood asthma(Sevelsted & Bisgaard, 2012). That clearly underscores the necessity of studying pre-natal environmental and behavioural risk factors that might be responsible for an increase in the global prevalence of obesity and asthma as well as the obesity-related asthma phenotype among children.

Another important early life factor is breastfeeding, which, as was described in the previous chapters, plays an important role in the modulation of obesity, asthma and rhinitis in children. The possibility of its playing a role in contributing to obesity-induced asthma has also been suggested (Oddy et al., 2004; Papoutsakis et al., 2013; Rzehak et al., 2013).

In the previous chapters, we described how physical activity and sedentary lifestyle, including watching TV and playing computer games, can increase the risk of obesity, as well as asthma and rhinitis; in consequence, the impact of this lifestyle has been studied as a putative link between these chronic diseases in childhood, suggesting that decreased activity and increased sedentary behaviours, through an increase in obesity and abdominal obesity, can predispose people towards the development of asthma (Chen et al., 2014; Corbo et al., 2008; Garcia-Marcos et al., 2007; Mitchell et al.., 2013; Violante et al., 2005).

Similarly, a diet lacking in balance, with high caloric value and low intake of essential nutrients, could be associated with obesity-induced asthma, not only indirectly, through increased weight, but also through the pro-inflammatory character of particular foods as described in previous chapters (Corbo et al., 2008; Lawson, Rennie, Dosman, Cammer,

&Senthilselvan, 2013; Luna-Pech et al., 2014; Myers & Allen, 2011; Pinheiro, 2009; Violante et al., 2005).

Although there are fewer results available, second-hand exposure to tobacco has also previously been studied as a plausible covariate in the association between childhood obesity and asthma (Hancox et al., 2004; Michelson, Williams, Benjamin, & Barnato, 2009; Schachter, Peat, & Salome, 2003; Suglia, Chambers, Rosario, & Duarte, 2011).

Finally, family socioeconomic status and geographic factors play an important role in the asthma-obesity link in childhood as well, as they are strong modulators of health in societies. As was explained in previous chapters, asthma, rhinitis and obesity are diseases of affluence (Chen et al., 2011; Ezzati et al., 2005; von Hertzen & Haahtela, 2004), and their highest rates are observed in regions with higher levels of urbanization, and variations are observed between groups with different socioeconomic levels, which indicates that these two factors could be potential confounders in the association between asthma and obesity or rhinitis and obesity.

Most likely, the association between increased obesity among children and chronic respiratory diseases such as asthma and rhinitis is multifactorial. Surely, some part of the link can be explained by overestimation due to fat mass on the thoracic chest mimicking asthma symptoms (Sah et al., 2013); part of the weight increase may also be due to medication or decreased activity caused by exercise-induced wheezing attacks, resulting in reverse causation (Jani et al., 2005). There is no doubt that the endocrine role of adipose tissue (adipokines) is a strong physiological link and very plausibly could be a mechanism in causing a chain of disruption leading to inflammation and narrowing of airways (K. W. Kim et al., 2008; Loureiro et al., 2012; Muc et al., 2013; Yuksel et al., 2012).

Likewise, westernized lifestyle and subsequent changes increased exposure to risk factors common to these conditions, and contributed in large measure to the increase in obese children's development of asthma and rhinitis symptoms and experiencing them more severely and with less success in treatment (Brisbon, Plumb, Brawer, & Paxman, 2005; Chen et al., 2014; Litonjua & Gold, 2008; Oddy et al., 2004; Rasmussen & Hancox, 2014; Suglia et al., 2011). The link constituted by common environmental, lifestyle and socioeconomic risk factors, will be studied as a potential modulator of the association between obesity and asthma and obesity and rhinitis among children.

9.3. Objectives

The aim of this chapter was to examine the role played by environmental, socioeconomic, and early life factors in fostering the association between childhood obesity and asthma as well as obesity and rhinitis in children.

The objectives were:

To study whether the three indicators of increased weight in children, BMI z-score derived obesity measure, abdominal obesity defined as WHtR>0.5, and body composition (overfat and high fat) caused an increased risk of asthma and rhinitis and their prevalence in the studied population.

Further, the plan was to study whether the association was different according to children's gender.

Next, to select the significant associations and examine how the common risk factors (SES, residential area degree of urbanization, birth weight, breastfeeding, second-hand tobacco exposure, physical activity, TV watching and heavy truck traffic in the residential area) modulated the risk between the obesity indicators and respiratory symptoms.

9.4. Methodology

9.4.1. Obesity definition

Three indicators of obesity were selected to study our hypothesis and the following variables were categorized.

Obesity and overweight- variable based on BMI measure. The variable was categorized using WHO methodology, with overweight and obesity defined as BMI z-score >+1SD<+2SD and BMI z-score >2+SD respectively.

Abdominal obesity – defined as the WHtR above 0.5 (Browning et al., 2010). This is a measure of fat distribution.

High body fat - body fat percentage was applied as another weight indicator. We have used cut-off points proposed by the McCarthy et al. (McCarthy et al., 2006). Obesity defined by this measure was classified as:

Normal: $<85^{th}$ age and gender-specific percentile

Overfat: $\geq 85^{th} > 95^{th}$ age and gender-specific percentile

High fat: $\geq 95^{th}$ age and gender-specific percentile

This indicator describes body composition.

9.4.2. Asthma and rhinitis symptoms

Due to numerous symptoms and their frequency in the evaluation, in order to avoid an excessive number of tests, for this part of the study we pre-selected seven variables describing children's respiratory status, giving priority to those representing the prevalence rather than the severity of the disease. We decided to study the obesity related risk of wheeze ever and wheeze in the past 12 months, asthma ever, night cough and exercise-induced asthma in the past year and finally rhinitis ever and in the past 12 months of life.

9.4.3. Environmental and socioeconomic factors

The objective of this study was to investigate the role of risk factors that are common for obesity as well as asthma and rhinitis in fostering the association between these diseases. Therefore, we selected environmental, lifestyle and family factors described in the literature as modulating the risk of these diseases. We planned to observe changes in the risk of

asthma/rhinitis symptoms related to obesity when including these covariates in the models. It would allow us to study whether these covariates can explain the association between obesity and asthma and rhinitis in children or whether the association exists independently of these factors.

The selected factors were grouped in five clusters:

The "socio-demographic factors" cluster consisted of the SES and zone of residence. Both variables were used as categorical.

The "diet and sedentary lifestyle" cluster consisted of the components for three types of alimentary patterns: base diet, Mediterranean diet, and fast food (continuous variables), as well as time spent on watching TV and physical activity (both categorized).

The "tobacco exposure" cluster gathered the data on the tobacco used in the child's household (if the mother was currently smoking, if she had been smoking during pregnancy, during the first year of the child's life, and whether any member of the family was currently smoking). All variables were dichotomized based on yes/no answers in the questionnaire.

The cluster labelled as **"early life factors"** consisted of the birth weight, length, gestational age (all three used as continuous), breastfeeding ever, and the period of total and exclusive breastfeeding.

The last covariate included in the analyses was "**heavy truck traffic"** in theresidential area (categorical).

9.4.4. Statistical analyses

First, we planned to check whether there was a difference in distribution between obese and normal weight children with respiratory health problems. In order to do that, we compared the proportion of normal-weight healthy children, normal-weight children with respiratory symptoms (asthma or rhinitis), obese/overweight (we here joined overweight and obese children; BMI z-score based) with respiratory symptoms, obese/overweight children without any respiratory symptoms of different SES groups, degree of urbanization groups, and genders, and children with and without family history of asthma and rhinitis. A chi-square test was performed to test the difference between the groups.

Next, a multinominal logistic regression was used to assess the risk of developing asthma and rhinitis symptoms depending on nutritional status (Model A- unadjusted). As we expected the effect to differ between genders, we repeated the test for girls and boys separately.

In order to investigate the influence of each of the behavioural and lifestyle covariates on the association between weight and respiratory symptoms, five models were created (Models B-F). Only the tests that showed significant results in the crude associations were chosen for further modelling.

Multivariate analysis was run using Multinominal Logistic Regression for models created adding in sequence following variables or groups of variables:

Model A= unadjusted;

Model B= adjusted for socio-demographic factors (SES and Zone of residence);

Model C= adjusted for all of the above as well as diet and sedentary lifestyle (consumption of Portuguese base diet elements, Mediterranean diet, Saturated fats diet);

Model D= adjusted for all of the above and tobacco exposure (current maternal smoking, maternal smoking in 1st year of child's life, maternal pregnancy smoking, presence of family members who smoke)

Model E= adjusted for all of the above and early life factors (birth weight, birth length, gestational age, breastfeeding (ever breastfed or not; total and exclusive period of breastfeeding)

Model F = adjusted for all of the above and heavy truck traffic in the residential area.

Variations in odds ratios' values in each model were observed in order to examine the role of the covariates in the risk of asthma/rhinitis dependent on obesity.

Moreover, to calculate the frequency of children's asthma and rhinitis symptoms related to overweight/obesity, we created groups based on nutritional status and the presence (+) or absence of symptoms of asthma and rhinitis. We chose a definition of obesity and overweight based on BMI z-score. For this part of the analysis, due to relatively small sample size, we merged the groups of obese and overweight children (abbreviated as "O"). The following abbreviations were used in connection with asthma and rhinitis:

A - Asthma ever,

EIA- Exercise-induced asthma

NC- Night cough

W- Wheeze ever

W12- Wheezing in the past year

R- Rhinitis ever

R12- Rhinitis in the past year

For each asthma and rhinitis symptom, four groups were created based on the presence or absence of both the symptom and overweight (including obesity). Asthmatic overweight children were therefore assigned to the A+O+ group, with asthmatic children with normal weight designated as A+O-, overweight non-asthmatic children as A-O+, and non-asthmatics with normal weight as A-O-, and so on for each asthma/rhinitis symptom.

More details concerning our methodology can be found in the general methodology section.

P-values were considered significant below the level of 0.05. As there is a high level of ns correlation within obesity measures as well as respiratory symptoms, tests were not corrected for multiple testing to avoid type 2 errors.

9.5. Results

Demographics and a detailed description of the studied population (including respiratory and nutritional status) can be found in the previous chapters.

We tested the prevalence in the four groups created for each symptom of asthma and rhinitis based on the presence or absence of this symptom and presence or absence of overweight status. Among all the children tested, 4.1% both had asthma and were overweight (A+O+), 2.5% were overweight and experienced exercise- induced asthma attacks in the past year (EIA+O+), 9.5% were overweight and reported a night cough in the past year (NC+O+), 12.8% were overweight and had a lifetime history of wheezing (W+O+), and 5.4% were overweight and had had wheezing attacks in the past year (W12+O+). As for rhinitis, some lifetime history of this disease and of overweight was reported for 8.5% of the children (R+O+) and 7.4% were overweight and had had a rhinitis episode in the past year (R12+O+). Details can be found in the Figure 9.1 .

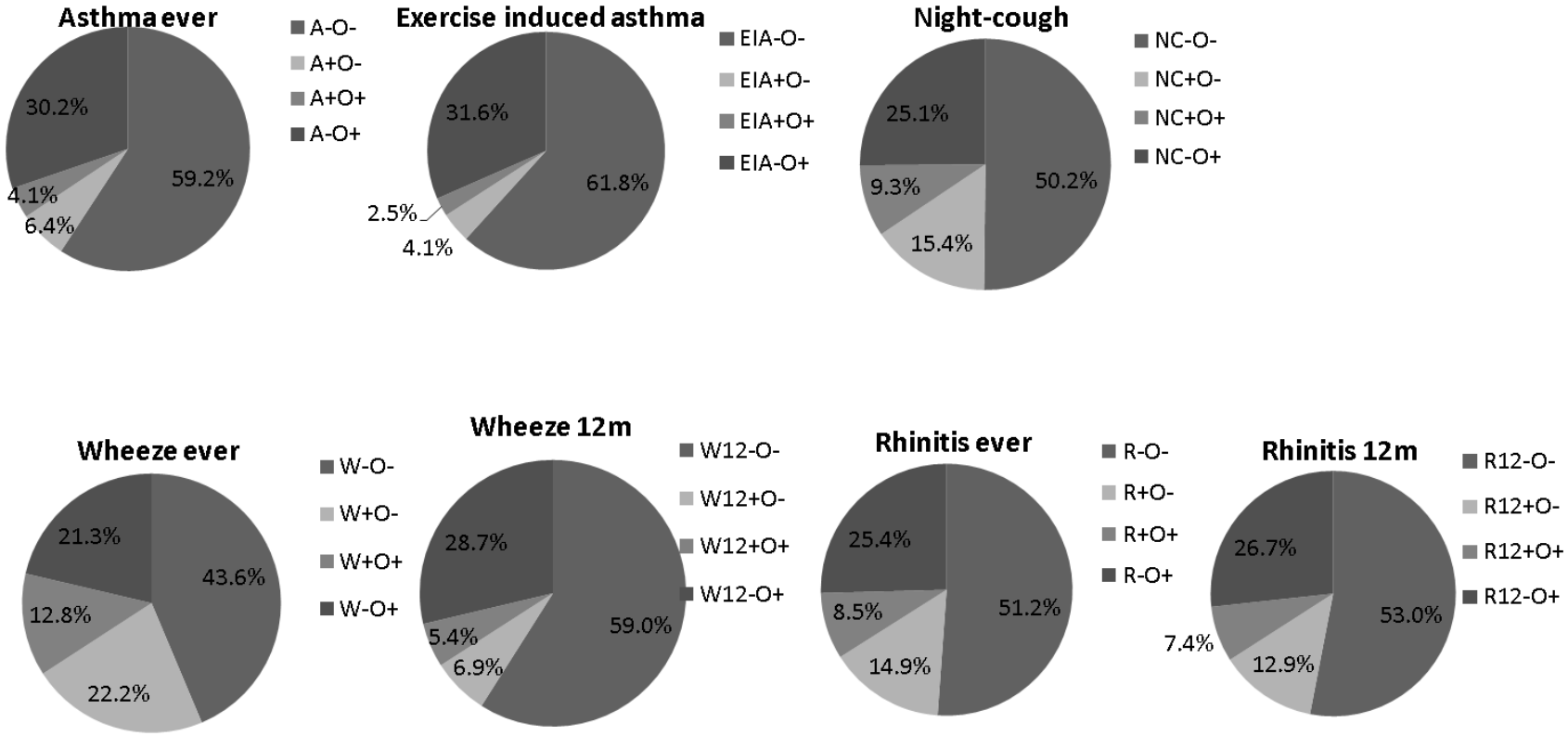


Figure 9.1 Frequencies of children with or without each asthma and rhinitis symptom in combination of presence or absence of overweight status.

9.5.1. Association of asthma and rhinitis with adiposity and the differences between genders

9.5.1.1. Obesity

Considering nutritional status defined by BMI, there was a general and consistent tendency, for the entire population and in each gender, of increased risk among overweight and obese children of having had any of the studied respiratory symptoms; nevertheless, only one result was statistically significant, with increased risk of having experienced wheezing in the past 12 months for overweight children (OR=1.79, p<0.01) for total sample.

An increased risk related to being obese was observed for the total sample for all asthma symptoms and all rhinitis symptoms. The situation was similar with regard to overweight status: the risk for all symptoms of asthma and rhinitis increased, but this association was not statistically significant apart from current wheezing (as above). A certain tendency toward dose effect could be observed in the case of asthma ever (OR=1.35:p=0.34), exercise-induced asthma (OR=1.94:p=0.07), night cough (OR=1.44:p=0.11), and rhinitis ever (OR=1.25:p=0.34) the risk was higher for obese than for overweight children suggesting a dose effect.

Despite the lack of significance, we could observe a very consistent tendency of increased risk of asthma and rhinitis symptoms for obese girls with increased risk of wheeze ever (OR=1.54:p=0.14), wheezing in the past year (OR=1.56; p=0.32), asthma ever (OR=1.79; p=0.18), exercise-induced asthma attacks (OR=2.60; p=0.06), night cough (OR=1.55; p=0.16), rhinitis ever (OR=1.25; p=0.50), and rhinitis in the past year (OR=1.17; p=0.66). Being overweight increased the risk of wheeze ever (OR=1.36:p=0.17), wheezing in the past year (OR=1.86; p=0.06), exercise-induced asthma attacks (OR=1.88; p=0.14), night cough (OR=1.19; p=0.46) and rhinitis in the past year (OR=1.18; p=0.54); however, these results were not statistically significant.

As for boys, being obese increased (though the result was not statistically significant) their risk of wheezing in the past year (OR=1.57; p=0.27), exercise-induced asthma attacks (OR=1.48; p=0.45), night cough (OR=1.32; p=0.40), and rhinitis ever (OR=1.26; p=0.49) and in the past year (OR=1.11; p=0.78). By contrast, being obese seemed to have a protective effect against wheeze ever (OR=0.78; p=0.42) although not statistically significant. Being overweight showed a tendency (although not statistically significant) to increase the risk of wheeze ever (OR=1.20; p=0.41), wheezing in the past year (OR=1.77; p=0.06), exercise-induced asthma attacks (OR=1.13; p=0.78), and rhinitis ever (OR=1.23; p=0.42) and in the past year (OR=1.20; p=0.49). Detailed results can be found in the Table 9.1 .

Table 9.1 Association of overweight and obesity status with asthma and rhinitis symptoms presented for the total population and per gender.

Symptom	Nutritional status	TOTAL				GIRLS				BOYS			
		n	OR	95% CI	p-value	n	OR	95% CI	p-value	n	OR	95% CI	p-value
Wheeze ever	Obesity	40	1.10	0.72-1.68	0.65	23	1.54	0.86-2.76	0.14	17	0.78	0.42-1.44	0.42
	Overweight	92	1.27	0.93-1.73	0.13	47	1.36	0.88-2.09	0.17	45	1.20	0.77-1.88	0.41
	Normal		Ref.				Ref.				Ref.		
Wheeze 12m	Obesity	16	1.56	0.86-2.82	0.14	7	1.56	0.64-3.79	0.32	9	1.57	0.71-3.49	0.27
	Overweight	38	1.79	1.15-2.76	0.01	18	1.86	0.98-3.53	0.06	20	1.77	0.97-3.21	0.06
	Normal		Ref.				Ref.				Ref.		
Asthma ever	Obesity	14	1.35	0.73-2.51	0.34	8	1.79	0.77-4.17	0.18	6	1.01	0.40-2.54	0.98
	Overweight	26	1.16	0.71-1.88	0.55	10	0.94	0.44-2.01	0.88	16	1.38	0.73-2.61	0.33
	Normal		Ref.				Ref.				Ref.		
Exercise-induced asthma 12m	Obesity	11	1.94	0.95-3.96	0.07	6	2.60	0.95-7.07	0.06	5	1.48	0.53-4.14	0.45
	Overweight	18	1.44	0.80-2.61	0.23	10	1.88	0.81-4.36	0.14	8	1.13	0.48-2.64	0.78
	Normal		Ref.				Ref.				Ref.		
Night cough 12m	Obesity	34	1.44	0.93-2.25	0.11	19	1.55	0.85-2.85	0.16	15	1.32	0.69-2.54	0.40
	Overweight	61	1.13	0.80-1.60	0.48	35	1.19	0.75-1.90	0.46	26	1.05	0.63-1.76	0.84
	Normal		Ref.				Ref.				Ref.		
Rhinitis ever	Obesity	29	1.25	0.79-1.99	0.34	14	1.25	0.65-2.43	0.50	15	1.26	0.66-2.41	0.49
	Overweight	55	1.10	0.77-1.56	0.62	25	0.98	0.59-1.65	0.95	30	1.23	0.75-2.01	0.42
	Normal		Ref.				Ref.				Ref.		
Rhinitis 12months	Obesity	23	1.13	0.69-1.87	0.62	11	1.17	0.57-2.42	0.66	12	1.11	0.55-2.22	0.78
	Overweight	50	1.18	0.81-1.71	0.38	24	1.18	0.69-2.02	0.54	26	1.20	0.71-2.01	0.49
	Normal		Ref.				Ref.				Ref.		

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

9.5.1.2. Body composition

Results were slightly more consistent for body composition measured with body fat levels. Generally, having high fat levels increased the risk of all studied asthma and rhinitis symptoms for the total population and for girls. For boys, we observed increased risk of most symptoms, except for lifetime asthma and lifetime wheezing history, in relation to high fat levels with OR values close to one.

Significant results were found for high fat levels, significantly increasing the risk of having at least one episode of an exercise-induced asthma attack in the past year for the total population (OR=2.06, $p<0.05$), but after the split by gender, the result only remained significant for girls (OR=2.93, $p<0.05$), not for boys (OR=1.51; $p>0.05$). In the case of rhinitis symptoms, the presence of lifetime rhinitis was significantly related to high fat levels in the total population (OR=1.57, $p<0.05$) but, when comparing genders, it remained significant only for boys (OR=1.73, $p<0.05$) but lost significance for girls (OR=1.28, $p>0.05$).

For the total sample, being overfat showed a statistically not significant tendency of increasing the risk of developing wheeze ever (OR=1.31; p=0.11), wheezing in the past year (OR=1.21; p=0.45), and exercise-induced asthma attacks (OR=1.55; p=0.18), as well as lifetime (OR=1.13; p=0.53) and past-year rhinitis (OR=1.12; p=0.58). Moreover, it seemed to protect against night cough in the past year (OR=0.89; p=0.56), but the result was not statistically significant. For the girls, being overfat showed a tendency although not statistically significant toward increasing the risk of having asthma ever (OR=1.30; p=0.50) and exercise-induced asthma attacks (OR=1.97; p=0.14), and showed a protective effect against wheezing in the past year (OR=0.87; p=0.71) and night cough in the past year (OR=0.68; p=0.16). For boys, being overfat showed a significant association with the higher risk of lifetime wheezing (OR=1.63; $p<0.05$) and not significant but increased the risk of wheezing in the past year (OR=1.55; p=0.19), exercise-induced asthma attacks (OR=1.23; p=0.66), night cough (OR=1.21; p=0.50) and lifetime rhinitis. The tendency of protection against lifetime asthma from being overfat was observed (OR=0.84; p=0.65), although the result was not statistically significant. See Table 9.2.

Table 9.2 Association of children's body fat level with asthma and rhinitis symptoms presented for total population and per gender.

Symptom	Body fat	Total				GIRLS				BOYS			
		n	OR	95%CI	p value	n	OR	95%CI	p value	n	OR	95%CI	p value
Wheeze ever	High fat	64	1.22	0.86-1.74	0.27	29	1.52	0.89-2.58	0.12	35	1.01	0.63-1.64	0.95
	Overfat	77	1.31	0.94-1.83	0.11	33	1.04	0.65-1.68	0.87	44	1.63	1.02-2.62	0.04
	Normal	200		Ref		103		Ref		97		Ref	
Wheeze 12months	High fat	23	1.29	0.78-2.15	0.32	9	1.31	0.59-2.87	0.51	14	1.25	0.63-2.45	0.52
	Overfat	25	1.21	0.74-1.98	0.45	9	0.87	0.40-1.88	0.71	16	1.55	0.81-2.97	0.19
	Normal	65		Ref		33		Ref		32		Ref	
Asthma ever	High fat	21	1.30	0.76-2.20	0.34	9	1.77	0.79-3.96	0.17	12	0.97	0.48-1.97	0.94
	Overfat	20	1.04	0.61-1.78	0.88	10	1.30	0.60-2.80	0.50	10	0.84	0.40-1.77	0.65
	Normal	60		Ref		26		Ref		34		Ref	
Exercise-induced asthma	High fat	17	2.06	1.11-3.82	0.02	8	2.93	1.18-7.29	0.02	9	1.51	0.65-3.50	0.34
	Overfat	15	1.55	0.82-2.94	0.18	8	1.97	0.80-4.83	0.14	7	1.23	0.49-3.05	0.66
	Normal	31		Ref		14		Ref		17		Ref	
Night cough 12m	High fat	48	1.19	0.82-1.75	0.36	22	1.24	0.71-2.17	0.45	26	1.24	0.73-2.10	0.43
	Overfat	44	0.89	0.61-1.31	0.56	20	0.68	0.39-1.17	0.16	24	1.21	0.70-2.08	0.50
	Normal	149		Ref		88		Ref		61		Ref	
Rhinitis ever	High fat	50	1.57	1.07-2.30	0.02	17	1.28	0.70-2.36	0.42	33	1.73	1.05-2.87	0.03
	Overfat	45	1.13	0.77-1.66	0.53	20	0.99	0.56-1.73	0.97	25	1.28	0.75-2.19	0.37
	Normal	126		Ref		65		Ref		61		Ref	
Rhinitis12m	High fat	41	1.41	0.94-2.12	0.10	13	1.11	0.57-2.17	0.75	28	1.56	0.92-2.64	0.10
	Overfat	39	1.12	0.75-1.69	0.58	19	1.15	0.64-2.05	0.64	20	1.09	0.61-1.93	0.78
	Normal	109		Ref		54		Ref		55		Ref	

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

9.5.1.3. Abdominal obesity

There was no significant effect of abdominal obesity on the risk of asthma or rhinitis symptoms, but some tendencies could be observed. For the total population, there was a tendency toward an increase in the risk of exercise-induced asthma attacks (OR=1.27; p=0.41) and no other symptom. There was also a tendency toward decreased risk of asthma ever (OR=0.82; p=0.46) and of all rhinitis symptoms. No effect was observed on wheeze ever or in the past year.

For girls, there was a tendency of increased risk of wheezing in the past year (OR=1.29; p=0.41) and exercise-induced asthma attacks (OR=1.58; p=0.24), and decreased risk of asthma ever (OR=0.84; p=0.61), night cough (OR=0.91; p=0.67), rhinitis ever (OR=0.65; p=0.09) and rhinitis in the past year (OR=0.69; p=0.18).

For boys, an increase could be observed for night cough (OR=1.21; p=0.50) and rhinitis, both ever (OR=1.42; p=0.19) and in the past 12 months (OR=1.19; p=0.46), and a slight decrease in the risk of asthma ever (OR=1.34; p=0.29), also not statistically significant. Details of the results can be found in the Table 9.3.

Table 9.3 Association of children's abdominal obesity (WHtR) with asthma and rhinitis symptoms presented for the total population and per gender.

Symptom	WHtR	Total				Girls				Boys			
		n	OR	95%CI	p value	n	OR	95%CI	p value	n	OR	95%CI	p value
Wheeze ever	>0.5	83	1.00	0.74-1.36	0.98	52	1.07	0.72-1.60	0.74	31	0.99	0.61-1.62	0.98
	<0.5	260	Ref.			114	Ref.			146	Ref.		
Wheeze 12m	>0.5	29	1.09	0.69-1.70	0.72	18	1.29	0.70-2.37	0.41	11	1.00	0.50-2.00	0.99
	<0.5	85	Ref.			33	Ref.			52	Ref.		
Asthma ever	>0.5	21	0.82	0.50-1.37	0.46	12	0.84	0.42-1.67	0.61	9	0.90	0.42-1.91	0.78
	<0.5	79	Ref.			33	Ref.			46	Ref.		
Exercise-induced asthma 12m	>0.5	18	1.27	0.72-2.24	0.41	12	1.58	0.74-3.36	0.24	6	1.03	0.41-2.57	0.96
	<0.5	45	Ref.			18	Ref.			27	Ref.		
Night cough 12m	>0.5	60	1.04	0.74-1.46	0.81	38	0.91	0.59-1.41	0.67	22	1.21	0.70-2.07	0.50
	<0.5	181	Ref.			93	Ref.			88	Ref.		
Rhinitis ever	>0.5	50	0.89	0.63-1.27	0.53	24	0.65	0.39-1.08	0.09	26	1.42	0.85-2.38	0.19
	<0.5	172	Ref.			79	Ref.			93	Ref.		
Rhinitis12m	>0.5	43	0.90	0.62-1.31	0.58	21	0.69	0.41-1.18	0.18	22	1.34	0.78-2.31	0.29
	<0.5	147	Ref.			66	Ref.			81	Ref.		

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

p values were considered significant below the 0.05 and underlined

Abbreviations: WHtR - Waist-to-Height-Ratio

9.5.2. Multivariate analyses results

To test the effect of common risk factors on the association between asthma/rhinitis and childhood obesity, the associations that came out significant in the univariate analyses were further subjected to multivariate modelling, applying the models mentioned above.

9.5.2.1. Obesity/overweight effect on wheezing in the past months for the total population

Starting from the initial, unadjusted OR value of 1.79 for experiencing wheezing attacks in the past year for overweight children, we observed changing OR values after applying models to the regression. First, we observed a decreasing OR after adjusting for Socio-demographic data down to 1.66 (Model B), which stayed on approximately the same level in models C (OR=1.66) and D (OR=1.67). The risk increased further when adjusted for early life factors, reaching an even higher level than the unadjusted value, namely OR of 1.95. In the final model F this value decreased slightly, down to 1.89, but was still higher than initially, and remained significant ($p<0.05$).

For obese children, in the initial model A, unadjusted risk was lower than for those who were overweight, and not significant (OR=1.56; p=0.14). For this group of children, the situation was slightly different. The OR value kept increasing consistently, with subsequent adjustments for more covariates in the models introduced. In model B, rather than decreasing, as in the case of overweight children, the risk increased to 1.64 and there remained a sustained increase when adjusting for diet and sedentary life-style in model C (OR=1.71). In model D, with adjustment for tobacco exposure, the OR value underwent only a slight change (OR=1.72). In model E, after adjusting for early life factors, it increased further, to 1.85, and rose to 2.00 after the adjustments in the final model F. Although model F remained not statistically significant, borderline significance could be observed with risk being higher than for overweight children, suggesting a possible dose effect of the BMI on wheezing in children.

The complete table of results and interactions between the covariates can be found in the Table 9.4.

Table 9.4 Multivariate analyses of the effect of common risk factors on association between current wheeze and obesity for total studied sample.

Wheeze 12m x Nutritional Status Total Population													
Covariates	Model A		Model B		Model C		Model D		Model E		Model F		Final p-value
	UOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	
Obesity	1.56	0.86-2.82	1.64	0.87-3.11	1.71	0.88-3.34	1.72	0.88-3.38	1.85	1.09-3.15	2.00	0.99-4.06	0.054
Overweight	1.79	1.15-2.76	1.66	1.03-2.67	1.66	1.02-2.71	1.67	1.01-2.76	1.95	0.96-3.93	1.89	1.11-3.22	0.02
Socio-Demographic Factors													
SES			1.51	0.98-2.34	1.51	0.94-2.41	1.42	0.88-2.29	1.22	0.74-2.01	1.21	0.73-2.01	0.45
Urbanization of the residential area			0.88	0.62-1.23	0.85	0.60-1.21	0.88	0.61-1.28	0.94	0.64-1.39	0.95	0.64-1.40	0.78
Diet and sedentary lifestyle													
Physical activity					0.64	0.45-0.91	0.65	0.46-0.93	0.63	0.43-0.92	0.64	0.44-0.93	0.02
TV watching					0.76	0.57-1.01	0.76	0.57-1.02	0.77	0.57-1.06	0.78	0.57-1.07	0.12
Base of Diet					1.15	0.92-1.45	1.15	0.91-1.45	1.10	0.87-1.39	1.10	0.87-1.39	0.44
Mediterranean Diet					1.08	0.86-1.37	1.07	0.84-1.35	1.03	0.81-1.32	1.02	0.80-1.30	0.86
Saturated Fats Diet					1.12	0.90-1.40	1.13	0.90-1.41	1.10	0.87-1.41	1.10	0.86-1.40	0.45
Tobacco Exposure													
Maternal smoking now							1.96	0.74-5.18	2.10	0.74-5.94	2.12	0.75-6.00	0.16
Pregnancy tobacco use							0.83	0.29-2.43	0.62	0.20-1.93	0.59	0.19-1.87	0.37
1st year of life tobacco use							1.79	0.66-4.83	2.71	0.94-7.81	2.73	0.94-7.89	0.06
Any family members smoking							0.51	0.23-1.10	0.46	0.20-1.05	0.45	0.19-1.03	0.06
Early life factors													
Birth weight									1.63	0.89-3.01	1.66	0.90-3.04	0.10
Birth length									0.94	0.84-1.05	0.94	0.84-1.05	0.28
Gestational age									0.91	0.77-1.07	0.91	0.77-1.07	0.25
Breastfeeding									0.67	0.26-1.74	0.69	0.27-1.78	0.44
Total breastfeeding period									0.93	0.71-1.21	0.92	0.71-1.20	0.55
Exclusive breastfeeding period									1.21	0.80-1.84	1.24	0.81-1.88	0.32
Heavy truck traffic near residence											1.38	0.78-2.42	0.27

UOR=Unadjusted odds ratio; AOR=Adjusted odds ratio; 95%CI=95% Confidence Interval Model A= unadjusted; Model B=adjusted for socio-demographic factors; Model C=adjusted for Diet and sedentary lifestyle ; Model D=Adjusted for Tobacco exposure and Model E= adjusted for early life factors; Model F= adjusted for heavy traffic in the residence

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI.

p values were considered significant below the 0.05 and underlined

9.5.2.2. High body fat and Exercise-induced asthma attack (total population)

Unadjusted model A showed a significant increase in the risk of experiencing exercise-induced asthma attacks in the total sample due to high fat levels with the risk being double compared to children with normal fat levels. In subsequent models B, C, D and E, the risk kept increasing, with ORs of 2.51, 2.94, 2.99 and 3.18 respectively. The value remained on the same level, at 3.18, in model F, and the risk remained significant even after adjustment for all covariates (p=0.002).

Children being overfat in the unadjusted model A were also shown to have an increased risk (though the result was not statistically significant) of exercise-induced asthma attacks in the past year (1.55). The pattern was similar to that among children with high fat, so the risk kept increasing after applying model B (OR=1.76), model C (OR=1.90), and model D (OR=1.92), remained unchanged in model E (OR=1.92) and increased again in the final model F (OR=1.94); however, the result remained not statistically significant. The complete table of results and interactions between the covariates can be found in the Table 9.5.

Table 9.5 Multivariate analyses of the effect of common risk factors on association between exercise-induced asthma and high body fat for total studied sample.

Exercise-induced asthma x Body Fat % Total Population													
Covariates	Model A		Model B		Model C		Model D		Model E		Model F		Final p-value
	UOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	
High Fat	2.06	1.11-3.82	2.51	1.29-4.89	2.94	1.48-5.85	2.99	1.48-6.03	3.18	1.53-6.61	3.18	1.53-6.61	0.002
Overfat	1.55	0.82-2.94	1.76	0.87-3.56	1.90	0.93-3.90	1.92	0.93-3.98	1.92	0.88-4.16	1.94	0.89-4.21	0.10
Socio-Demographic Factors													
SES			1.05	0.59-1.87	1.12	0.60-2.08	1.17	0.62-2.20	0.92	0.47-1.81	0.92	0.47-1.82	0.81
Degree of urbanization			0.89	0.54-1.46	0.97	0.59-1.61	1.01	0.61-1.69	0.88	0.50-1.53	0.88	0.50-1.53	0.65
Diet and sedentary lifestyle													
Physical activity					0.70	0.44-1.12	0.70	0.44-1.13	0.66	0.40-1.08	0.66	0.40-1.09	0.10
TV watching					0.73	0.47-1.14	0.71	0.45-1.11	0.76	0.47-1.23	0.77	0.47-1.25	0.29
Base of Diet					1.28	0.93-1.76	1.27	0.92-1.75	1.25	0.90-1.73	1.24	0.89-1.73	0.20
Mediterranean Diet					1.04	0.77-1.41	1.05	0.77-1.42	1.01	0.74-1.39	1.01	0.74-1.38	0.96
Saturated fats diet					1.09	0.82-1.46	1.09	0.81-1.47	1.05	0.77-1.44	1.04	0.76-1.43	0.80
Tobacco Exposure													
Maternal smoking now							1.29	0.42-4.03	1.05	0.32-3.49	1.04	0.31-3.43	0.95
Pregnancy tobacco use							1.23	0.35-4.33	1.70	0.45-6.45	1.73	0.45-6.63	0.42
1st year of life tobacco use							0.33	0.10-1.08	0.28	0.08-0.96	0.28	0.08-0.97	0.04
Any family members smoking							1.01	0.44-2.33	1.09	0.44-2.67	1.10	0.45-2.71	0.84
Early life factors													
Birth weight									1.78	0.81-3.93	1.79	0.81-3.95	0.15
Birth length									1.02	0.88-1.17	1.02	0.88-1.18	0.82
Gestational age									0.93	0.75-1.16	0.93	0.75-1.17	0.55
Breastfeeding									0.70	0.19-2.55	0.70	0.19-2.55	0.59
Total breastfeeding period									1.01	0.72-1.41	1.01	0.72-1.42	0.95
Exclusive breastfeeding period									0.86	0.53-1.39	0.85	0.52-1.38	0.51
Heavy trucks traffic											1.20	0.56-2.57	0.65

UOR=Unadjusted odds ratio; AOR=Adjusted odds ratio; 95%CI=95% Confidence Interval Model A= unadjusted; Model B=adjusted for socio-demographic factors; Model C=adjusted for Diet and sedentary lifestyle ; Model D=Adjusted for Tobacco exposure and Model E= adjusted for early life factors; Model F= adjusted for heavy traffic in the residence

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI).

9.5.2.3. High body fat and the risk of rhinitis ever in total population

The unadjusted, initial risk of having lifetime rhinitis for children with high fat, relatively to those with normal fat values, was significantly increased (OR=1.57). After applying model B, with adjustment for socio-demographic factors, the risk decreased slightly, down to 1.54. It increased in model C and remained at a similar level in model D (OR=1.88 and 1.87 respectively). The value of OR increased further in model E up to 1.95 and in model F to 1.99 and this final OR value remained strongly significant (p=0.003). The complete table of results and interactions between the covariates can be found in the Table 9.6.

Table 9.6 Multivariate analyses of the effect of common risk factors on association between rhinitis ever and high body fat for total studied sample.

Rhinitis ever x Body Fat % Total Population													
Covariates	Model A		Model B		Model C		Model D		Model E		Model F		Final p-value
	UOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	
High Fat	1.57	1.07-2.30	1.54	1.02-2.34	1.88	1.22-2.89	1.87	1.20-2.91	1.95	1.23-3.09	1.99	1.26-3.16	0.003
Overfat	1.13	0.77-1.66	1.09	0.72-1.66	1.14	0.74-1.76	1.14	0.74-1.77	1.22	0.77-1.93	1.26	0.80-2.00	0.32
Socio-Demographic Factors													
SES			0.82	0.59-1.15	0.77	0.54-1.11	0.80	0.55-1.15	0.80	0.54-1.18	0.82	0.55-1.21	0.32
Degree of urbanization			0.98	0.75-1.29	1.04	0.79-1.38	1.08	0.82-1.43	1.00	0.74-1.35	1.01	0.75-1.36	0.94
Diet and sedentary lifestyle													
Physical activity					1.14	0.86-1.50	1.15	0.87-1.52	1.05	0.78-1.40	1.06	0.79-1.42	0.71
TV watching					0.65	0.50-0.85	0.65	0.50-0.84	0.67	0.50-0.88	0.68	0.52-0.91	0.01
Base of Diet					1.04	0.88-1.23	1.05	0.88-1.24	1.05	0.88-1.25	1.05	0.88-1.26	0.57
Mediterranean Diet					0.94	0.80-1.12	0.96	0.81-1.13	0.96	0.80-1.14	0.94	0.79-1.13	0.53
Saturated fats diet					1.26	1.07-1.49	1.25	1.06-1.48	1.24	1.04-1.47	1.23	1.03-1.47	0.02
Tobacco Exposure													
Maternal smoking now							1.56	0.76-3.19	1.39	0.66-2.92	1.41	0.67-2.99	0.37
Pregnancy tobacco use							0.62	0.26-1.43	0.77	0.31-1.92	0.78	0.31-1.94	0.59
1st year of life tobacco use							0.55	0.25-1.22	0.58	0.24-1.37	0.58	0.24-1.37	0.21
Any family members smoking							1.03	0.64-1.66	1.02	0.62-1.68	1.01	0.61-1.67	0.96
Early life factors													
Birth weight									1.36	0.85-2.18	1.37	0.85-2.19	0.20
Birth length									1.03	0.94-1.13	1.03	0.94-1.12	0.54
Gestational age									0.98	0.86-1.11	0.98	0.86-1.11	0.73
Breastfeeding									0.41	0.19-0.91	0.41	0.19-0.91	0.03
Total breastfeeding period									0.98	0.80-1.19	0.97	0.80-1.18	0.74
Exclusive breastfeeding period									0.84	0.64-1.10	0.84	0.64-1.11	0.22
Heavy trucks traffic											1.39	0.89-2.15	0.15

UOR=Unadjusted odds ratio; AOR=Adjusted odds ratio; 95%CI=95% Confidence Interval Model A= unadjusted; Model B=adjusted for socio-demographic factors; Model C=adjusted for Diet and sedentary lifestyle ; Model D=Adjusted for Tobacco exposure and Model E= adjusted for early life factors; Model F= adjusted for heavy traffic in the residence

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI).

9.5.3.4. High body fat and Exercise-induced asthma in girls

High body fat among girls had the strongest effect on risk of exercise-induced asthma attack in the past year, with the risk nearly three times higher compared to girls with normal fat values (OR=2.93). After adjustment for socio-demographic factors in model B, the risk increased up to 4.52 and increased further in model D, up to OR=7.38. In model E, the OR value increased and reached a level of risk nearly 9 times higher for high fat girls compared to normal fat girls (OR=8.97) and decreased slightly in the last model F, but still remained at the very high level of OR=8.86 and remained strongly significant (p=0.001).

The initial unadjusted model A showed that for girls, being overfat increased the chance of having exercise-induced asthma by nearly twice as much, however the result was not significant (OR=1.97). In model B, the risk increased up to OR=2.72 and then increased even further in model C, up to OR=4.59. It decreased slightly after adjustment for tobacco exposure in model D and again increased to 5.14 in model E after adjustment for early life factors. Although the OR value decreased a bit in model F, down to 5.11, it remained high and turned significant in the final model (p=0.01). This was the most significant and highest risk of asthma symptoms related to obesity encountered in the study. A dose effect of fat on the risk of exercise-induced asthma in girls can be observed. The complete table of results and interactions between the covariates can be found in the Table 9.7.

Table 9.7 Multivariate analyses of the effect of common risk factors on association between exercise-induced asthma and high body fat in girls.

Exercise-induced asthma x Body Fat % Girls													
Covariates	Model A		Model B		Model C		Model D		Model E		Model F		Final p-value
	UOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	
High Fat	2.93	1.18-7.29	4.52	1.66-12.33	7.35	2.42-22.32	7.38	2.28-23.88	8.97	2.46-32.74	8.86	2.43-32.24	0.001
Overfat	1.97	0.80-4.83	2.72	0.98-7.57	4.59	1.50-14.01	4.49	1.44-14.04	5.14	1.47-17.98	5.11	1.46-17.82	0.01
Socio-Demographic Factors													
SES			1.53	0.63-3.70	2.84	0.98-8.18	3.30	1.09-9.95	2.05	0.62-6.75	2.03	0.61-6.74	0.25
Degree of urbanization			1.42	0.70-2.89	1.91	0.88-4.11	1.96	0.89-4.34	1.33	0.53-3.32	1.32	0.53-3.29	0.56
Diet and sedentary lifestyle													
Physical activity					0.60	0.29-1.23	0.56	0.27-1.16	0.42	0.18-0.97	0.42	0.19-0.97	0.04
TV watching					0.60	0.29-1.22	0.62	0.30-1.26	0.61	0.27-1.36	0.62	0.28-1.40	0.25
Base of Diet					0.97	0.64-1.46	0.95	0.63-1.44	0.98	0.61-1.57	0.98	0.61-1.58	0.94
Mediterranean Diet					0.80	0.55-1.17	0.80	0.54-1.17	0.73	0.49-1.09	0.73	0.49-1.09	0.12
Saturated fats diet					1.35	0.91-2.01	1.40	0.93-2.12	1.57	0.95-2.58	1.56	0.95-2.57	0.08
Tobacco Exposure													
Maternal smoking now							0.87	0.17-4.52	0.60	0.10-3.43	0.57	0.09-3.40	0.54
Pregnancy tobacco use							0.63	0.09-4.23	0.76	0.09-6.36	0.79	0.09-6.80	0.83
1st year of life tobacco use							0.35	0.05-2.71	0.38	0.04-3.36	0.39	0.04-3.45	0.40
Any family members smoking							1.35	0.33-5.51	0.94	0.21-4.27	0.97	0.21-4.46	0.97
Early life factors													
Birth weight									2.15	0.46-9.97	2.19	0.47-10.24	0.32
Birth length									1.01	0.78-1.30	1.01	0.78-1.30	0.94
Gestational age									0.89	0.60-1.33	0.90	0.60-1.33	0.58
Breastfeeding									na	na	na	na	na
Total breastfeeding period									1.71	0.98-2.98	1.72	0.98-3.01	0.06
Exclusive breastfeeding period									0.45	0.17-1.17	0.44	0.16-1.18	0.10
Heavy trucks traffic											1.17	0.33-4.14	0.81

UOR=Unadjusted odds ratio; AOR=Adjusted odds ratio; 95%CI=95% Confidence Interval Model A= unadjusted; Model B=adjusted for socio-demographic factors; Model C=adjusted for Diet and sedentary lifestyle ; Model D=Adjusted for Tobacco exposure and Model E= adjusted for early life factors; Model F= adjusted for heavy traffic in the residence

Results obtained using the binary logistic regression test; na- results not available due to small n.

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI).

9.5.3.5. High body fat and risk of lifetime wheeze among boys

Being overfat (OR=1.63) but not having high fat levels (OR=1.01) was initially, in unadjusted model A, found to significantly increase the risk of boys developing wheezing. After applying model B, the OR value went down to 1.56 and kept decreasing in model C (OR=1.46), model D (OR=1.40), and model E (1.28), and remained almost at the same level in the finally adjusted model F (OR=1.29) and was found to be statistically not significant (p=0.40). The effect of high body fat remained statistically not significant, and although it decreased slightly, reaching the lowest value in the model C of 0.83, it went back up with the final OR in model F being nearly one (OR=0.96; p=0.900). It suggests that the effect observed in the unadjusted model can be partly explained by the included covariates with the strongest effect (highest difference in OR values of 0.12) of the early life factors. The complete table of results and interactions between the covariates can be found inTable 8.9.

Table 9.8 Multivariate analyses of the effect of common risk factors on association between wheeze ever and high body fat in boys.

Wheeze ever x Body Fat % Boys													
Covariates	Model A		Model B		Model C		Model D		Model E		Model F		Final p-value
	UOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	
High Fat	1.01	0.63-1.64	0.89	0.52-1.50	0.83	0.48-1.44	0.87	0.50-1.52	0.96	0.53-1.73	0.96	0.53-1.74	0.90
Overfat	1.63	1.02-2.62	1.56	0.93-2.61	1.46	0.87-2.48	1.40	0.81-2.42	1.28	0.72-2.29	1.29	0.72-2.30	0.40
Socio-Demographic Factors													
SES			1.05	0.70-1.59	0.94	0.61-1.45	0.95	0.60-1.49	0.90	0.56-1.45	0.90	0.56-1.45	0.67
Degree of urbanization			0.77	0.55-1.07	0.76	0.54-1.06	0.72	0.51-1.03	0.70	0.48-1.01	0.70	0.49-1.01	0.06
Diet and sedentary lifestyle													
Physical activity					0.71	0.50-1.01	0.72	0.50-1.03	0.72	0.49-1.05	0.72	0.49-1.05	0.09
TV watching					1.02	0.75-1.40	0.94	0.68-1.31	0.93	0.66-1.32	0.93	0.66-1.32	0.70
Base of Diet					1.19	0.95-1.49	1.21	0.96-1.53	1.19	0.93-1.52	1.19	0.93-1.52	0.16
Mediterranean Diet					1.19	0.96-1.49	1.20	0.96-1.51	1.20	0.94-1.53	1.20	0.94-1.52	0.15
Saturated fats diet					0.91	0.73-1.12	0.92	0.74-1.14	0.91	0.72-1.14	0.91	0.72-1.14	0.39
Tobacco Exposure													
Maternal smoking now							1.44	0.57-3.67	1.46	0.55-3.88	1.47	0.55-3.94	0.44
Pregnancy tobacco use							1.23	0.41-3.68	1.54	0.49-4.85	1.53	0.48-4.84	0.47
1st year of life tobacco use							0.56	0.21-1.51	0.42	0.15-1.23	0.42	0.15-1.23	0.11
Any family members smoking							0.73	0.40-1.33	0.76	0.40-1.44	0.76	0.40-1.43	0.39
Early life factors													
Birth weight									1.12	0.64-1.97	1.12	0.64-1.97	0.69
Birth length									0.98	0.89-1.10	0.98	0.88-1.10	0.78
Gestational age									1.04	0.89-1.21	1.04	0.89-1.21	0.66
Breastfeeding									0.63	0.24-1.61	0.63	0.24-1.61	0.33
Total breastfeeding period									0.93	0.73-1.18	0.93	0.73-1.18	0.55
Exclusive breastfeeding period									0.97	0.71-1.34	0.97	0.71-1.34	0.86
Heavy trucks traffic											1.07	0.59-1.93	0.83

UOR=Unadjusted odds ratio; AOR=Adjusted odds ratio; 95%CI=95% Confidence Interval Model A= unadjusted; Model B=adjusted for socio-demographic factors; Model C=adjusted for Diet and sedentary lifestyle ; Model D=Adjusted for Tobacco exposure and Model E= adjusted for early life factors; Model F= adjusted for heavy traffic in the residence

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

9.5.3.6. High body fat and risk of rhinitis ever among boys

In unadjusted model A there was a significantly increased risk of developing rhinitis (at least one attack in a lifetime) related to high body fat among boys (OR=1.73). Applying models B and C further increased the risk with the OR values of 1.88 and 2.40 respectively. This value decreased slightly, down to 2.32, in model D and kept increasing in the last two models, E and F, with OR values of 2.72 and 2.76 respectively, and remained strongly significant after the final adjustments (p=0.002).

A tendency toward increasing (statistically not significant) was observed in model A (unadjusted) related to being overfat for boys (OR=1.28), which did not change in model B and increased up to 1.37 in model D. In model E it decreased back to 1.30; it went back up in the two final models, giving values of 1.41 and 1.47 respectively, but the result remained statistically not significant in the final model (0.29). The complete table of results and interactions between the covariates can be found in the Table 9.9.

Table 9.9 Multivariate analyses of the effect of common risk factors on association between rhinitis ever and high body fat in boys.

Rhinitis ever x Body Fat % Boys													
Covariates	Model A		Model B		Model C		Model D		Model E		Model F		Final p-value
	UOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	AOR	95%CI	
High Fat	1.73	1.05-2.87	1.88	1.09-3.23	2.40	1.35-4.24	2.32	1.29-4.17	2.72	1.45-5.09	2.76	1.47-5.17	0.002
Overfat	1.28	0.75-2.19	1.28	0.72-2.27	1.37	0.75-2.47	1.30	0.71-2.41	1.41	0.73-2.71	1.43	0.74-2.76	0.29
Socio-Demographic Factors													
SES			0.72	0.45-1.13	0.67	0.41-1.10	0.67	0.40-1.11	0.62	0.36-1.07	0.62	0.36-1.06	0.08
Degree of urbanization			1.03	0.72-1.46	1.01	0.69-1.46	1.05	0.72-1.53	0.91	0.60-1.37	0.91	0.60-1.38	0.67
Diet and sedentary lifestyle													
Physical activity					1.04	0.71-1.54	1.09	0.73-1.62	1.04	0.68-1.59	1.03	0.67-1.58	0.88
TV watching					0.67	0.46-0.96	0.64	0.44-0.93	0.61	0.41-0.92	0.61	0.41-0.92	0.02
Base of Diet					0.92	0.72-1.16	0.93	0.73-1.19	0.90	0.69-1.17	0.89	0.68-1.16	0.38
Mediterranean Diet					0.96	0.75-1.22	0.98	0.76-1.25	0.97	0.74-1.27	0.96	0.73-1.25	0.76
Saturated fats diet					1.40	1.12-1.76	1.39	1.10-1.74	1.33	1.04-1.71	1.33	1.03-1.70	0.03
Tobacco Exposure													
Maternal smoking now							0.97	0.34-2.75	1.08	0.36-3.26	1.15	0.38-3.52	0.80
Pregnancy tobacco use							1.23	0.39-3.93	1.97	0.56-6.87	1.94	0.55-6.80	0.30
1st year of life tobacco use							0.49	0.17-1.42	0.38	0.12-1.20	0.38	0.12-1.20	0.10
Any family members smoking							1.02	0.51-2.06	1.04	0.49-2.19	1.00	0.47-2.12	1.00
Early life factors													
Birth weight									0.99	0.52-1.88	1.01	0.53-1.91	0.98
Birth length									1.06	0.94-1.19	1.06	0.94-1.19	0.37
Gestational age									0.98	0.82-1.18	0.98	0.82-1.18	0.87
Breastfeeding									0.27	0.10-0.76	0.27	0.09-0.75	0.01
Total breastfeeding period									0.99	0.75-1.29	0.99	0.76-1.30	0.95
Exclusive breastfeeding period									0.79	0.55-1.14	0.79	0.54-1.13	0.20
Heavy trucks traffic											1.49	0.77-2.87	0.23

UOR=Unadjusted odds ratio; AOR=Adjusted odds ratio; 95%CI=95% Confidence Interval Model A= unadjusted; Model B=adjusted for socio-demographic factors; Model C=adjusted for Diet and sedentary lifestyle ; Model D=Adjusted for Tobacco exposure and Model E= adjusted for early life factors; Model F= adjusted for heavy traffic in the residence

Results obtained using the binary logistic regression test

Results are presented as Odds Ratios (OR) with the 95% Confidence Interval (CI); Ref.- Reference OR=1.

9.6. Discussion

Our study showed increased risk of asthma and rhinitis symptoms to be related to obesity in children, adding to the evidence already existing on the association between atopic diseases and obesity in children. We found that being obese or overweight increased the risk for all asthma and rhinitis symptoms for the total sample, with a significant result for wheezing attack experienced in the past year. Obesity and overweight seemed to have a stronger adverse effect on asthma symptoms for girls than for boys, while the differences were not that pronounced for rhinitis.

Abdominal obesity did not show any significant results; however, there was a visible tendency toward increased risk of exercise-induced asthma attacks and current wheezing for girls and increased risk of rhinitis for boys related to increased fat accumulation in the abdominal area.

Body composition had a stronger modulating effect on the risk of asthma than the remaining two indicators of adiposity. Again, high body fat levels were shown to have a stronger impact on asthma symptoms in girls and on rhinitis symptoms in boys.

For all three indicators, the symptom most strongly associated with obesity in children was presence of exercise-induced asthma attacks, particularly among girls.

The consistent association encountered in our study between obesity and asthma and rhinitis in children fits with the results found in the literature. We used ISAAC tools to define asthma and rhinitis in children. The third phase of the ISAAC study, which included data from 17 countries worldwide, also confirmed the effect of obesity on the development of these diseases. They used the BMI to measure obesity and applied different cut-off points, defined by Cole et al. (2000). Nevertheless, for the group of 6-7 year old children, we reached the same conclusions as they did. They also found an increased risk of asthma, but unlike us, they did not observe an association with rhinitis symptoms. They also reported a dose effect, with the risk being even higher for obese than for overweight children (Mitchell et al.., 2013). A dose effect for the risk of most asthma and rhinitis symptoms can also be observed in our study for the risk related to overweight and obesity, as well as for overfat and high fat children.

We have observed that the effect of obesity was different for each gender, and while it seemed to increase the risk of asthma in girls, the effect was more pronounced for the rhinitis in boys. In the literature, where gender differences are concerned, the results among reported studies are not consistent. In a study from the United States involving children 6-17 years old, the researchers found that obesity only worsens the airflow obstruction in boys, with no effect

on girls, and furthermore, obesity was shown to improve girls' lung function (Lang et al., 2013). Similarly, in another study from the US, in which children from Fragile Families and Child Wellbeing Studies participated, focused on children below the age of 3 years, asthma was only associated with obesity for boys, not for girls (Suglia et al., 2011). Also, in a meta-analysis including 6 studies on the effect of BMI on asthma in children, the authors found that there was indeed a dose-dependent effect of BMI on asthma risk and after splitting by gender, it remained significant only for boys (Chen et al., 2013).

Contrary to these results, a longitudinal study performed in UK, following children from birth with evaluations at 3, 5 and 8 years of age, showed that although an association between obesity and asthma existed at all ages, the gender differences were only significant at 8 years of age and were stronger for girls than for boys (Murray et al., 2011). Another study, from the Netherlands, analysing 6-16 year-old children and adolescents, likewise found that the effect of obesity on asthma was only significant for girls (Willeboordse et al., 2013). Obesity-related asthma was also shown to be more pronounced among girls in a large study from China, including 30,056 children 2-14 years old (Wang et al., 2014). However, no effect of gender was found on the asthma-obesity association in the Taiwanese study using the ISAAC tools, examining children 4-18 years old (Yao et al., 2011).

Notably, all the above mentioned studies used only BMI as the measure of obesity, and none studied the gender differences in body composition (fat to muscle mass ratio) or the effect of abdominal obesity on asthma in children as we did in our study. Using obesity indicators others than BMI, as we did in our study, has many advantages. The BMI measures total body mass, without discrimination between fat and lean mass, while we know from the literature that it is the fat tissue that plays an active role in the pathogenesis of inflammation in asthma and rhinitis (Da Silva et al., 2012; Erel et al., 2007; Jensen, Gibson, Collins, & Wood, 2013; Muc et al., 2013). We now know that fat is not an inactive storage of spare energy, but a very physiologically active tissue, responsible for, among other things, secretion of various adipokines, adipose tissue hormones which not only regulate the appetite but have been proven to be involved in inflammatory processes, including asthmatic inflammation. Including the measure of fat quantity in studies of obesity-related asthma can give a more accurate image of the problem. In fact studies of this association in paediatric populations have shown that abdominal obesity (Chen et al., 2014; Musaad et al., 2009) and body fat percentage (Yiallouros, Lamnisos, Kolokotroni, Moustaki, & Middleton, 2013) might be better predictors for asthma than BMI. Also, BMI does not take into account valuable information about fat distribution (higher deposits of adipose tissue in particular body parts, for example, abdominal obesity). It has been shown that abdominal obesity in children represents a high risk for metabolic comorbidities as well as increased risk of asthma. It was shown in a study performed in Canada

among pupils in grades 1 to 8 at rural schools showed that both BMI and increased waist circumference (an indicator of abdominal obesity) significantly increased the risk of lifetime and current asthma in children (Karunanayake & Pahwa, 2013). In our study, abdominal obesity was the measure least associated with the symptoms of asthma and rhinitis. As suggested by Bekkers et al., (2013) the effect of increased waist circumference on respiratory health might change with age and be more observable in adulthood. They concluded that after studying lung function in 8 year-old children participating in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study from the Netherlands and finding that it was not significantly associated with waist circumference or the BMI. A study from Puerto Rico used three obesity and adiposity measures, BMI, body fat percentage, and waist circumference to study in relation to asthma outputs. They found that BMI, but not body fat or waist circumference, was associated with the risk of asthma in children. They also found that the most significant association with high body fat and waist circumference was with exercise-induced asthma attacks in the past year, similarly to what we observed in our study (Forno et al., 2014). It has been suggested, however, in a comment by (Arteaga-Solis & Kattan, 2014) that this effect might be biased by the lower fitness of obese children, causing signs of fatigue and lack of breath. Although it might account for part of the association, the studies of adipokines, hormones produced by adipose tissue, show that there might indeed be a physiological link leading to exercise-induced bronchoconstriction (narrowing of the airways). A study in Korea showed that in 6-10 year old children levels of adipokines, namely leptin and adipokines, were significantly associated with the odds of experiencing exercise-induced asthma attacks (Baek et al., 2011). More evidence was contributed by a study of adolescents in Brazil, including groups with and without a history of exercise-induced asthma attacks, both groups having been diagnosed with obesity. At the baseline and after the intervention the researchers measured their body composition, serum leptin and adiponectin concentrations as well as lung function. They found that after a one year weight-loss intervention there was significant improvement of lung function together with a change in adipokine levels. Weight loss also resulted in lower frequency of exercise-induced asthma attacks in the studied adolescents (Da Silva et al., 2012). This suggests that the strong association between this asthma symptom and obesity in children is not likely to be explained only by misclassification.

We have found that obesity was associated not only with asthma but also with rhinitis symptoms, with an even stronger link observed for boys. As mentioned in the introduction, the link between rhinitis and obesity in paediatric populations has been studied very little, and the results are not consistent. As in our study, some authors have also found an association between an obesity and rhinitis. Carvoni (2011) described a significant association found between obesity and allergic rhinitis in a group of 5-16 year-old children and adolescents. Ciprandi et al.

(2011) studied adolescents with the mean age 12.8 years, and found that increased BMI values have an adverse effect on bronchial reversibility in patients with allergic rhinitis and asthma. Musaad et al. (2009) found the contrary, and the obesity in their study, among children 5-18 years old, was associated with lower allergic rhinitis risk in asthmatic individuals. Many authors, however, have not found any association between rhinitis and obesity in children. Ekström et al. (2014) used a longitudinal study to assess the effect of maternal BMI during pregnancy and its effect on asthma, rhinitis and eczema in offspring throughout life up until the children were 16 years old. They found that maternal obesity, through its influence on the obesity of their children, was significantly associated with asthma, but not with rhinitis or eczema. In another study in the US, of school-aged children, the researchers found that obesity increased the risk of acute otitis media but not of allergic rhinitis or chronic rhinosinusitis (Sidell et al., 2013). In Poland, in a large study including children, adolescents and adults from rural and urban areas of the country, it was shown that among 6-7 year-old children, only asthma but not rhinitis was associated with obesity, and in adult men, obesity and overweight protected against rhinitis (Sybilski et al., 2014). A study from Japan, focusing on 6-15 year-old children, found a U-shaped association between BMI and asthma, but not rhinitis or eczema (Tanaka et al., 2011).

Common risk factors suggested a plausible link between obesity and asthma and rhinitis in children; therefore, after establishing the existing associations between the obesity indicators and the symptoms of asthma and rhinitis, we proceeded to examine the role that environmental, behavioural, socioeconomic and early life factors play in these links.

It has been proposed that a built environment can play an important role in the link between obesity and asthma in childhood. Brisbon et al. (2005) in their article noted that a built environment can have an indirect effect on childhood asthma and obesity by limiting the opportunities for physical activity. The promotion of sedentary behaviours can not only lead directly to these two common paediatric diseases, as we have already explained in previous chapters, but can also trigger genetic influences and cause mechanical and immune modifications that might affect asthma. They also suggest that we should act against the common sources of these conditions present in a built environment to combat the epidemics.

In a recent study where children were examined and then followed for a period of two years, it was shown that abdominal obesity is a strong predictor for asthma, and increased screen time and decrease of physical activity in studied children caused an increase of abdominal fat and consequently led to asthma (Chen et al., 2014).

Both asthma and obesity have their origins early in life. Litonjua and Gold (2008) in their review underline the role of early life factors in obesity-related asthma in children. They

describe how the quality of maternal diet during gestation (especially Vitamin D, C, E and Polyunsaturated Fatty Acids deficiency), microfloral colonization of the gastrointestinal tract, and early adipokines distortion can lead to asthma, obesity and obesity-related asthma in children. (Litonjua & Gold, 2008).

We created adjusted models for the associations between asthma or rhinitis and obesity indicators that showed a significant association in the univariate tests. It was done for the significant results for the total sample and for each gender. We observed how adjusting in sequence for socio-demographic factors, diet and sedentary behaviours, tobacco exposure and early life factors modulated the previously encountered risks of developing asthma or rhinitis symptoms related to obesity.

If the odds ratio given by univariate analysis decreased after including a group of covariates, it means that these covariates can partially explain the increased risk of asthma related to obesity. However, we did not observe that in our models. In fact, only in one case did the ratio decrease and it was found statistically not significant, namely for the association between body fat in boys and lifetime wheezing history. It might suggest that this association can partially be explained by risk factors, especially by early life exposures, which most notably decreased the odds. Other clusters of factors also were shown to explain a small number of the associations observed. Adjusting for socio-demographic factors and heavy truck traffic in the residential area slightly decreased the odds of having had wheezing in the past year related to being overweight for the total sample. Socio-demographic factors and tobacco exposure in early life and currently were shown to partly explain the association between high body fat and lifetime rhinitis for the total population, and tobacco explained part of the same association found in boys. Heavy truck traffic seemed to partly explain the association between exercise-induced asthma and high fat in girls. None of these factors, however, had a strong enough impact to cancel the significance of the associations.

In all the remaining cases, for all associations and models, introduction of new covariates increased the odds ratios' values, and the risk in the final models was higher than the crude one and remained significant. It indicates that the association between increased weight and asthma symptoms in children is independent of common risk factors and is not coincidental.

Our results are in agreement with the evidence found in the literature. A study from the US, examining children at the age of 3, found an increased risk of asthma related to obesity, but the studied covariates, which were maternal depression, domestic violence, housing quality, and tobacco exposure, did not explain the association in the final model, but rather increased the risk size, as was also observed in our study (Suglia et al., 2011). Similarly, in a study also performed in the US among a cohort of children and adolescents, the association encountered

between BMI and asthma severity was not explained by the confounders, which in this case were gender, age, race, income, insurance, and tobacco (Michelson et al., 2009).

Oddy et al. (2004) in their study in Australia followed families from pregnancy until the age of 6, when the evaluation took place. They found that BMI had a U-shaped association with asthma risk, with higher risk for children with very high but also very low levels of BMI. Again, the risk remained after adjusting for gender, exclusive breastfeeding, gestational age, parental smoking, child care in the first 3 months of the child's life, maternal asthma, and presence of atopy.

9.7. Conclusion

We showed in this study that childhood obesity and especially high body fat levels increase the risk of asthma and rhinitis symptoms. Obesity seems to have a stronger adverse effect on asthma symptoms for girls than for boys. Girls also showed to have higher risk of developing asthma symptoms due to elevated body fat levels, while in case of the effect of high body fat on rhinitis the impact was stronger for boys than in girls. Symptom which showed the strongest association with childhood obesity was exercise-induced asthma attacks, particularly among girls.

These associations were shown not to be explained by the presence of common risk factors for obesity and asthma or rhinitis, and rather seemed to be independent on the covariates. We cannot, however, exclude the possibility that there are other risk factors, not included in our analyses, which could explain these associations. It should be noted that although the risk factors do not explain the association between asthma and obesity in childhood, that does not mean they play no role in it. As obesity increases the risk and severity of asthma, risk factors and unhealthy behaviours will still have an adverse effect on children's nutritional status and respiratory health.

10. Asthmatic overweight children – Are they born different?

10.1. Introduction

There is still one important issue to address regarding the role of risk factors in the link between asthma and obesity in children. As mentioned, obesity has been found to be a very strong determinant of the asthma phenotypes (Sutherland et al., 2012). That means that obese asthmatic children are not only significantly different from healthy children, but also from normal-weight asthmatics. As summarized in the article by Rasmussen and Hancox (2014), there are two main phenotypes of obese asthmatics described by far. One is the primary asthmatic (including children), often atopic and with severity increased by the higher weight levels. Second is the late-onset, non-atopic group, predominantly composed of adult women and characterised by neutrophil inflammation. The first one is most likely the phenotype we are dealing with in this study.

The high level of heterogeneity among clinical and epidemiological manifestations of asthma and rhinitis has led to differentiation into distinct asthma phenotypes which are defined as different observable characteristics of the same disease, as well as endotypes which are based on different pathophysiological origins of the same disease (Agache et al., 2012; Lötvall et al., 2011). In other words, a phenotype is a consistent grouping of these characteristics. When talking about asthma phenotypes, characteristics that are usually taken into account are: immunological profile, presence of symptoms, gender, age, severity of the disease, presence of atopy, and age of onset. These characteristics appear as the result of complex interactions between genes and environment (Wenzel, 2012) It has been shown that the clinical and immunological profile of children with this particular type of asthma is specific and differs from other phenotypes (Rasmussen & Hancox, 2014). It has even been asserted that in contrast to the usual asthmatic immunological profile with Th2 polarization, obese asthmatic children are skewed towards a Th1 response (Rastogi et al., 2012).

Little is known about the effects of risk factors on the different asthma phenotypes. In a large study from Canada, the Canadian Healthy Infant Longitudinal Study, the researchers focused their attention on childhood asthma phenotypes. It was suggested in an article by Subbarao et al. (2009) that the differentiation of highly heterogeneous asthma phenotypes is crucial for understanding specific risk factors and their timing, as the different phenotypes might be affected differently by *in utero*, early life and childhood exposures. It also argued that genetic susceptibility might be specific for some phenotypes, which might trigger the disease development differently through gene-environment interactions. The study put very little focus on the obese asthmatics phenotype, however, perhaps due to the relatively recent definition of this phenotype in children. In another study, it was shown that obese children might respond differently to environmental triggers and that traffic exposure to a pollutant PAH (Polycyclic

aromatic hydrocarbon) is more likely to cause asthma in obese than normal-weight children (Jung et al., 2014).

As it has been shown that the predisposition for asthma, rhinitis and obesity can already be detectable at birth, the effect of prenatal and early life factors might be an interesting target topic for a comparison of phenotypes. In a Danish cohort of children followed from pregnancy through childhood, they found that increased bronchial responsiveness in neonates was associated with asthma later in childhood (Bisgaard et al., 2012). In the same cohort, it was shown that a high neonatal measure of weight, length, BMI, and head circumference are also significantly related to asthma at the age of 7 years (Sevelsted & Bisgaard, 2012). This is part of a large amount of evidence linking birth weight with increased risk of asthma later in life (Bolte et al., 2004; Flaherman & Rutherford, 2006; Liu et al., 2014; Sin et al., 2004; Taveras et al., 2006; Xu et al., 2002). It has been shown that both low (Liu et al., 2014) and high birth weight (Flaherman & Rutherford, 2006; Sin et al., 2004) can contribute to the development of asthma and rhinitis, suggesting an U-shaped association between these factors.

Similarly, increased birth weight has also been associated with childhood obesity (Cnattingius et al., 2012; Sparano et al., 2013; Yu et al., 2011). A high birth weight was shown to be related to the risk of obesity in childhood (Padez et al., 2005; Sparano et al., 2013). Positive and significant correlations between birth weight and adiposity measures at 6-8 years have also been shown in our study (chapter 7). Altogether, this points to birth weight as a possible factor which might differentiate overweight-related asthma, wheezing, and rhinitis from other phenotypes of these diseases.

Taking the differences observed between normal weight and obese asthmatic children, and matching it with the fact that the differences between asthmatic and healthy as well as obese and normal-weight children can already be detected after birth, we hypothesized that overweight children with asthma and children with asthma and normal weight might also differ from each other at birth, supporting the hypothesis of overweight-related asthma in childhood being a distinct phenotype and the idea that these children are “born different”.

10.2. Objectives

The objective of this chapter was to verify whether overweight (including obese) and overfat (including high fat) children with at least one asthma, wheezing, or rhinitis episode in their lives are characterised by different birth weight than asthmatics with normal weight and thus to examine whether the distinct obesity-related childhood asthma phenotype is already manifested at birth.

10.3. Methodology

We have selected the respiratory variables describing the presence of asthma, wheezing, and rhinitis at least once in the child's life and two obesity indicators: nutritional status and body fat percentage. We have used the 4 groups of asthma/wheezing/rhinitis ever in combination with overweight (including obesity) as described in previous chapter.

As body fat was shown to better characterise the risk of asthma and rhinitis in our sample, we also created four groups for asthma, wheezing, and rhinitis ever in combination with overfat including high fat (OF), as we did with overweight. Consequently, the following groups were created:

A+OF+ group of asthmatic overfat children

A+OF- asthmatic children with normal fat levels

A-OF+ overfat, non-asthmatic children

A-OF- non-asthmatic children with normal fat levels

First, we performed an ANOVA test to compare the BMI z-score, %BF and age means between the created groups.

Further, we verified whether the mean birth weight differed between the groups. For this part of the analysis, birth weight was used as a continuous variable, expressed in kilograms with precision to the level of 3 decimal numbers. For each of the three respiratory variables, mean birth weight was compared among the four groups. The ANOVA mean comparison test was used followed by LSD (Fisher's Least Significant Difference) post-hoc test.

To adjust for possible confounders, we applied the univariate Analysis of Covariance (ANCOVA) test for the birth mean comparison between the groups. Confounders used for adjustment were gestational age, gender, maternal smoking during pregnancy, and socioeconomic status. The LSD post-hoc test was again used to perform pairwise comparisons. Graphs were created to illustrate the differences in estimated marginal means for birth weights among the groups.

All tests and graphs were done using the IBM SPSS statistics 21. Significance was considered with p value below 0.05.

10.4. Results

Descriptive statistics were performed to compare the mean BMI z-score, %BF and age of the children between the created groups of asthma-, wheezing- and rhinitis-related overweight and overfat. Results are presented in the Table 10.1.

Table 10.1 Comparison of mean BMI z-score, %BF and age values between the studied groups.

Overweight													
		Asthma				Wheeze				Rhinitis			
		A-O-	A+O-	A+O+	A-O+	W-O-	W+O-	W+O+	W-O+	R-O-	R+O-	R+O+	R-O+
BMI z-score	n	544	60	41	321	401	200	141	223	478	126	95	272
	Mean (SD)	0.21 (0.80)	0.08 (0.73)	1.64 (0.91)	1.49 (0.93)	0.19 (0.78)	0.22 (0.82)	1.47 (0.94)	1.54 (0.92)	0.21 (0.79)	0.15 (0.78)	1.57 (0.98)	1.49 (0.91)
	p value	<0.001				<0.001				<0.001			
%BF	n	544	60	41	321	401	200	141	223	478	126	95	272
	Mean (SD)	18.45 (3.10)	17.98 (3.33)	26.73 (5.02)	27.20 (5.68)	18.33 (3.04)	18.50 (3.31)	27.05 (5.10)	27.23 (5.88)	18.41 (3.09)	18.38 (3.16)	27.76 (6.93)	26.96 (5.01)
	p value	<0.001				<0.001				<0.001			
Age	n	542	60	40	321	399	200	140	223	476	126	94	272
	Mean (SD)	7.29 (0.61)	7.29 (0.55)	7.04 (0.54)	7.26 (0.61)	7.32 (0.61)	7.24 (0.60)	7.19 (0.59)	7.24 (0.61)	7.29 (0.61)	7.29 (0.61)	7.25 (0.57)	7.22 (0.62)
	p value	0.09				0.13				0.46			
Overfat													
		A-OF-	A+OF-	A+OF+	A-OF+	W-OF-	W+OF-	W+OF+	W-OF+	R-OF-	R+OF-	R+OF+	R-OF+
BMI z-score	n	565	61	40	304	413	213	132	211	491	142	84	258
	Mean (SD)	0.10 (0.57)	-0.01 (0.66)	1.83 (0.62)	1.84 (0.70)	0.10 (0.56)	0.10 (0.65)	1.82 (0.66)	1.85 (0.71)	0.10 (0.58)	0.12 (0.67)	1.91 (0.74)	1.82 (0.67)
	p value	<0.001				<0.001				<0.001			
%BF	n	560	61	40	300	409	212	130	209	487	141	84	254
	Mean (SD)	19.07 (3.57)	18.79 (4.40)	25.71 (5.56)	26.72 (6.38)	18.93 (3.45)	19.31 (4.13)	26.63 (5.55)	26.62 (6.71)	19.01 (3.57)	19.48 (4.14)	27.73 (7.48)	26.29 (5.82)
	p value	<0.001				<0.001				<0.001			
Age	n	565	60	40	304	413	212	132	211	491	141	84	258
	Mean (SD)	7.26 (0.62)	7.27 (0.53)	7.06 (0.57)	7.28 (0.61)	7.29 (0.62)	7.23 (0.58)	7.18 (0.63)	7.27 (0.59)	7.27 (0.62)	7.26 (0.59)	7.29 (0.60)	7.22 (0.61)
	p value	0.20				0.35				0.75			

Results presented as Mean (Standard Deviation)

P values presented were obtained using the ANOVA test and the value 0.05 was considered significant and underlined

Abbreviations: BMI- Body Mass Index; BF- Body fat; A- Asthma; W- Wheeze; R- Rhinitis; O- Overweight; OF- Overfat; "+" - presence of the symptom; "-"- absence of the symptom

10.4.1. Birth weight means comparisons

10.4.1.1. Overweight related asthma/wheeze/rhinitis

10.5.3.4.1. Crude

There were strongly significant differences in mean birth weight values among the four groups. In the Post-hoc analyses we observed that the biggest, strongly significant difference exists between A+O+ children (mean birth weight=3.424kg; SD=0.563) and A+O- children (mean birth weight =3.108kg; SD=0.695) with overweight children with asthma being 0.316kg heavier at birth than normal weight asthmatics (p=0.003). The difference was also strongly significant, though smaller, between A+O+ children and A-O- children (mean birth weight =3.188kg; SD=0.502 group with difference of mean equal to 0.236kg (p=0.007). Furthermore, there was a strongly significant difference of 0.203kg (p=0.006) between A+O- children (mean birth weight=3.108kg; SD= 0.695) and A-O+ children (mean birth weight=3.311kg; SD= 0.523). Finally, a strongly significant difference (p=0.001) was observed between A-O- children (mean birth weight=3188kg; SD= 0.502) and A-O+ children with a difference of 0.122kg.

In the case of wheezing ever, the biggest difference in mean birth weight values (0.222g (p=0.0002)), which was significant, was again found between W+O+ children (mean=3.361kg; SD= 0.616) and W+O- children (mean=3.139kg; SD= 0.575). The strongly significant difference of 0.159kg (p=0.004) was also found between the pairs W+O+ children and W-O- children (mean=3.202kg; SD=0.502kg); there was a difference of 101g (p=0.028) between W-O- children and W-O+ children (mean=3.303kg; SD= 0.468); and a difference of 0.164kg (p=0.002) between pair W+O- children and W-O+ children.

The pattern observed in the case of asthma and rhinitis was not reproduced for rhinitis. Two groups of asthmatics, overweight and normal weight, did not correspond to the opposite ends of the birth weight mean spectrum. However, the highest mean birth weight among the four groups was again found for overweight children with rhinitis, with the mean of 3.357kg (SD= 0.508). The lowest mean was found for the R-O- group with the value of 3.154kg (SD=0.526), which is 0.203kg lower than the R+O+ mean birth weight, and the result was significant. A significant difference was also found between R-O- and R-O+, with the latter group having a higher mean birth weight than the former by 0.159kg.

The results are illustrated in the Figure 10.1.

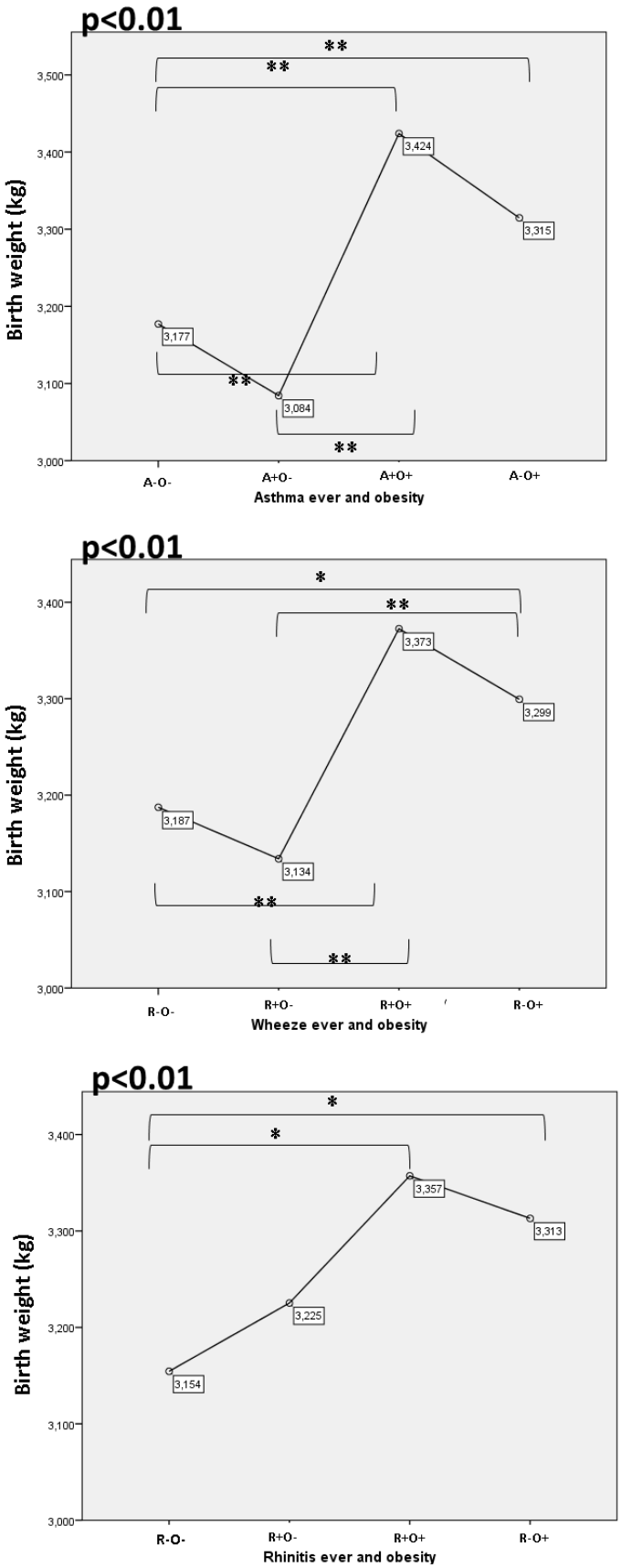


Figure 10.1Comparison of the mean birth weight between the four groups of children created based on asthma and nutritional status.

p- values presented were obtained using the ANOVA test. *-significant post-hoc p-value, **- strongly significant post-hoc p-value

10.5.3.4.2. Adjusted

Overweight-related asthma

After adjustment for gestational age, gender, maternal smoking during pregnancy and SES, the differences between overweight asthmatics and the remaining three groups became ever more pronounced. The estimated marginal mean of birth weight remained the highest for the group of asthmatic overweight children (A+O+) with the value of 3.442kg. This value was significantly different from the estimated marginal mean of all three remaining groups, with the highest difference observed between A+O+ and A-O- (difference of 0.258kg; p= 0.001); followed by A+O- (difference of 0.220kg; p=0.02). The difference from the group of overweight children without asthma was also statistically significant, suggesting that the high birth weight mean is not only a bias related to increased BMI (difference of 0.160kg; p=0.04). The differences between the three groups of A+O-, A-O+ and A-O- were much lower than between A+O+ and these groups, and the only significant difference observed between them was between A-O- and A-O+ (difference 0f 0.097; p=0.003). See Figure 10.2.

Overweight-related wheezing

Similarly to overweight-related asthma, the overweight-related wheezing group (W+O+) was found to have the highest estimated marginal mean birth weight, with the mean equalling 3.357kg. This was significantly higher than the estimated marginal mean of W-O- (difference of 0.166kg; p=0.0003) and the estimated marginal mean of W+O-. It elucidates again the significant difference existing already at birth between overweight and normal-weight wheezing children. The difference between W+O+ and W-O+ was only borderline significant (difference of 0.100kg; p=0.055). Other associations did not reach the level of significance. See Figure 10.2.

Overweight-related rhinitis

In results obtained using adjusted Analysis of Covariance (ANCOVA) tests, as in the crude ANOVA, rhinitis did not show the same trends as asthma and rhinitis in relation to birth weight. The highest estimated marginal mean birth weight was again observed for children in overweight-related rhinitis (R+O+), but the difference was only significant between this group and healthy children with normal weight (R-O-) (with the difference of 0.136kg; p=0.001). The difference was very similar to that for overweight children without rhinitis (R-O+), with the latter having only 0.02kg lower estimated marginal mean birth weight, and this result was not statistically significant. A statistically significant difference was also found between R-O- and R-O+ (difference of 0.136kg; p=0.01). Although only borderline statistically significant, we can also see a difference between the groups R+O- and R-O- (difference of 0.08kg; p=0.06), which

might suggest that independently of nutritional status, children who develop rhinitis by the age of 6-8 might also register increased birth weight values. Other associations did not reach the level of significance. See Figure 10.2

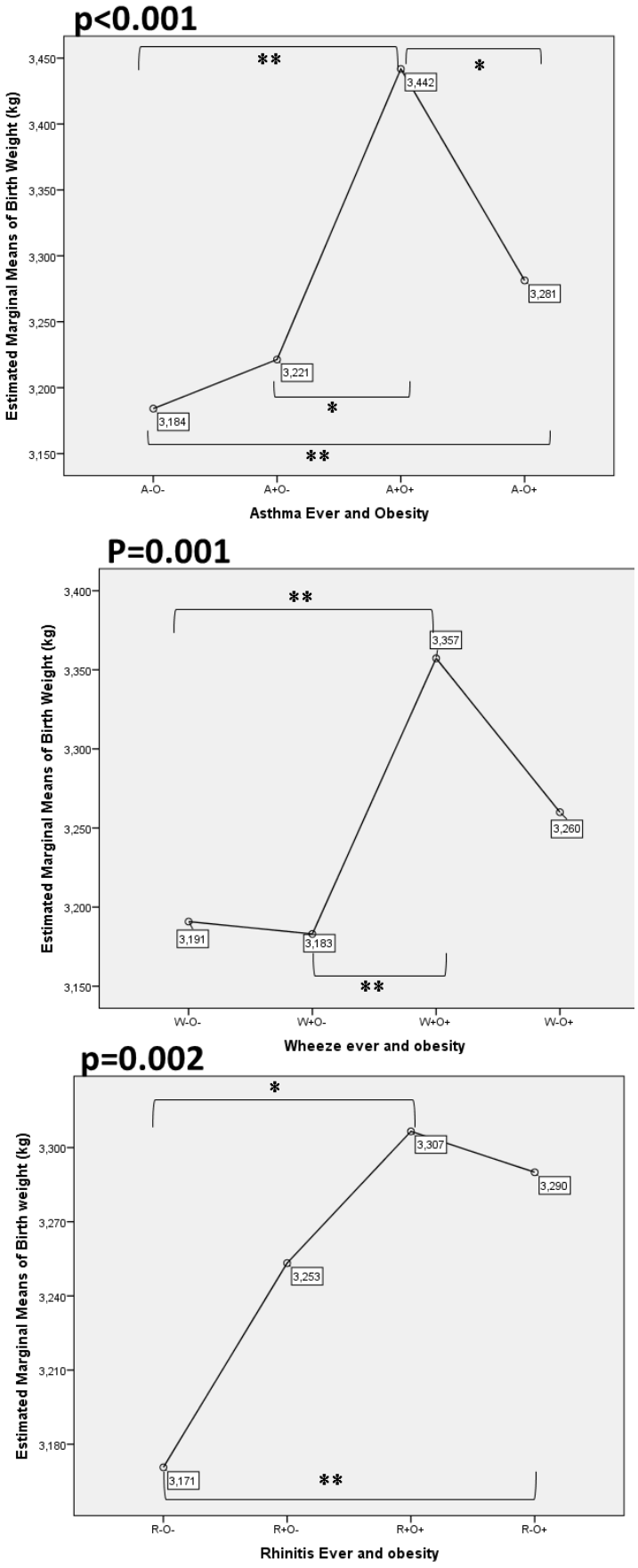


Figure 10.2Adjusted comparison of the mean birth weight between the four groups of children created based on asthma and nutritional status.

Results obtained using ANCOVA test adjusted for gender, gestational age, SES and maternal smoking during the pregnancy. p- values presented were obtained using the ANOVA test. *-significant post-hoc p-value, **- strongly significant post-hoc p-value

10.4.1.2. Overfat related asthma/wheeze/rhinitis

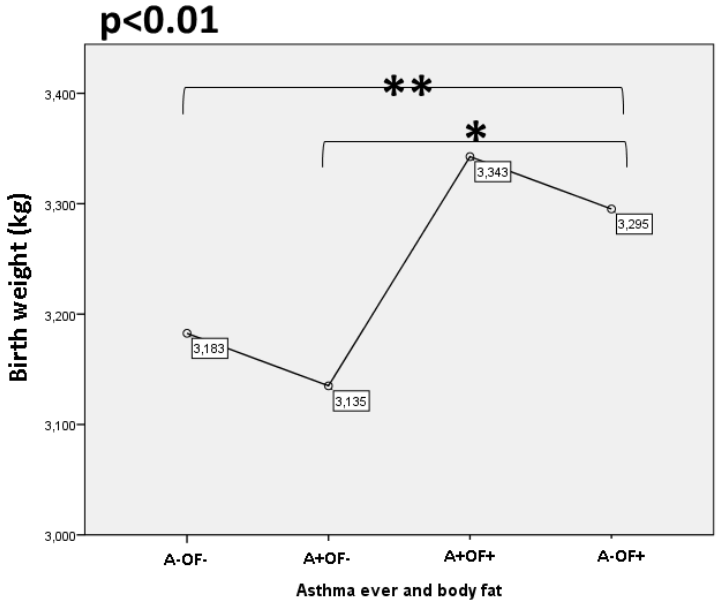
10.5.3.4.3. Crude

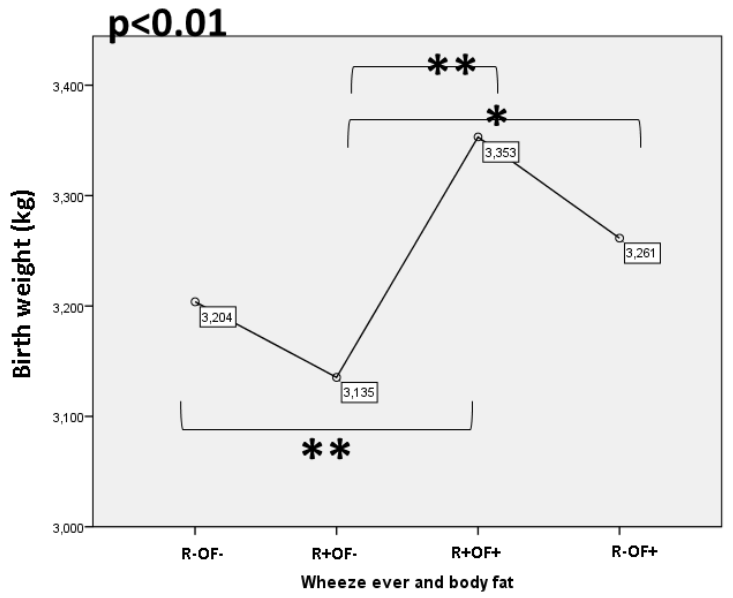
Means of birth weight patterns for the groups created with body fat levels were similar to those with obesity and overweight defined by BMI measure. In the ANOVA test there was a strongly significant difference between the groups in the birth weight values ($p<0.01$).

For asthma and wheezing, children in groups A+OF+ and W+OF+ had the highest mean values among the four groups (3.343kg; SD=0.668 and 3.353kg; SD=0.594 respectively). In contrast A+OF- and W+OF- had the lowest birth weight means (3.135kg; SD=0.682 and 3.135kg; SD=0.588 respectively). Again children being either overfat and having asthma or wheezing had even higher mean birth weights than children who were only overfat (3.295kg; SD=0.527 for A-OF+ and 3.261; SD=0.507 for W-OF+). When the post-hoc analysis was applied, a significant difference was found between pairs A-OF+ and A+OF- ($p=0.03$) as well as pairs A-OF+ and A-OF- ($p=0.003$). For wheezing, significant differences were found between pairs W-OF+ and W+OF- ($p=0.02$) compared to W+OF+ and W+OF- ($p=0.0003$) as well as W+OF+ and W-OF- ($p=0.005$).

For rhinitis, children in the group R+OF+ also had the highest mean birth weight among the four groups (3.346kg; SD=0.487), higher even than children with overfat only in group R-OF+ (3.280kg; SD=0.561). The second lowest mean was observed for R+OF- (3.227kg; SD=0.585) and the lowest for R-OF- (3.166; SD=0.516). Post-hoc differences were significant between R-OF- and groups R-OF+ ($p=0.10$) and R+OF+ ($p=0.003$).

The Figure 10.3 illustrates the mean values described above.





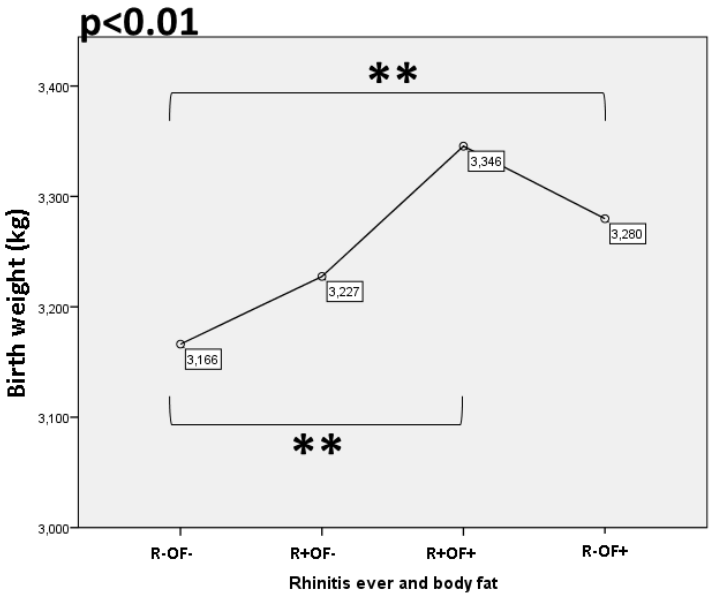


Figure 10.3Comparison of the mean birth weight between the four groups of children created based on asthma and body fat.

p- values presented were obtained using the ANCOVA test. *-significant post-hoc p-value, **- strongly significant post-hoc p-value

10.5.3.4.4. Adjusted

After adjusting the overfat-related asthma, wheezing and rhinitis results for covariates, a similar pattern was observed as in the case of overweight; however, the results were not as significant.

Overfat-related asthma

The highest estimated marginal mean value of birth weight was again observed for asthmatic overfat children (A+OF+) with the mean of 3.397kg, which was significantly higher than the mean of the A-OF- group, with the difference of 0.206kg (p=0.005). The difference was only borderline significant between A+OF+ and A-OF+ (difference of 0.140kg; p=0.07) and between A+OF+ and A*OF- (difference of 0.090kg; p=0.010). No other differences reached the level of significance. See Figure 10.4 for more details.

Overfat-related wheezing

The highest estimated marginal mean value, of 3.323kg, was observed for the wheezing overfat group (W+OF+), and the lowest, of 3.196kg, for wheezing children with normal weight (W+OF-); the difference between the two was statistically significant (difference of 0.127kg; p=0.01). A statistically significant difference was also observed between groups W+OF+ and W-OF- with the difference of 0.123kg (p=0.01). In addition, a borderline statistically significant difference was found between groups W+OF+ and W-OF+ (difference of 0.083kg; p=0.09). Other differences were not statistically significant. See Figure 10.4.

Overfat-related rhinitis

The highest estimated marginal mean value of the birth weight of 3.303kg was again found for the R+OF+ group and was significantly higher than that of R-OF-, with a difference of 0.122kg (p=0.02). R-OF- had also significantly lower estimated marginal mean value than R-OF+, with the difference of 0.081kg (p=0.02). No other result reached the level of significance. See Figure 10.4.

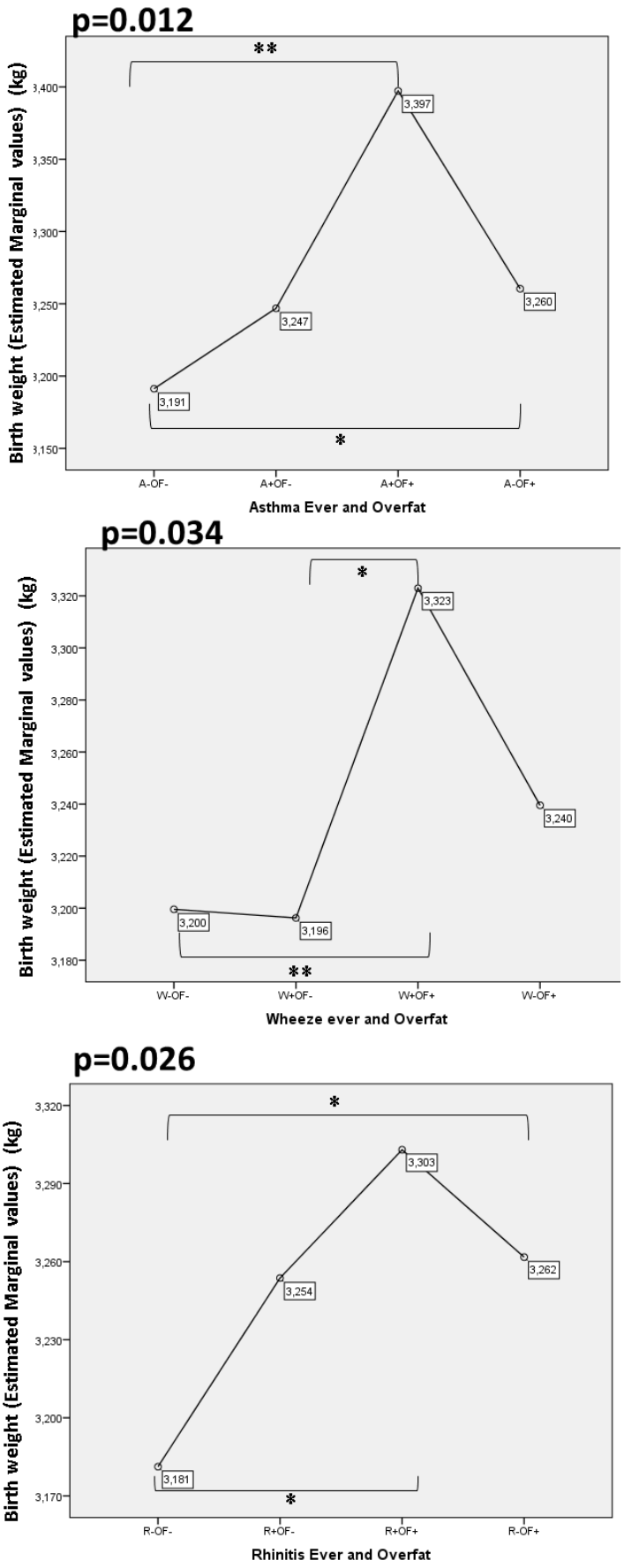


Figure 10.4. Adjusted comparison of the mean birth weight between the four groups of children created based on asthma and body fat.

Results obtained using ANCOVA test adjusted for gender, gestational age, SES and maternal smoking during the pregnancy. p- values presented were obtained using the ANOVA test. *-significant post-hoc p-value, **- strongly significant post-hoc p-value

10.5. Discussion

Birth weight mean was one strongly differentiating factor among the four groups of children with varying respiratory and nutritional status as well as body fat levels. Children with asthma, wheezing, or rhinitis who were also overweight or overfat were characterised by the highest birth weight means, which suggests that they might already have been born with a predisposition to these particular phenotypes of asthma, wheezing, and rhinitis. Interestingly, the groups of asthmatic and wheezing children with normal body weight and normal fat levels (but not the group of children with rhinitis) were characterised by the lowest birth weight values.

This might mean that high birth weight is a risk factor for developing obesity-related asthma, and in contrast, low birth weight may increase the risk of other asthma phenotypes. Simple mean comparisons, however, did not allow for any adjustments; we therefore used the ANCOVA analyses of covariance to adjust the analyses of birth weight for gender, gestational age and socioeconomic status of the family, factors which are strong determinants not only of birth weight but also obesity in children, and which could bias the results. Using this methodology, we confirmed our previous observations, and the differences between the overweight and overfat asthmatics and wheezing children became even more pronounced. In fact, the difference was found significant even when comparing the group of asthmatic overweight children with overweight children who did not have asthma. Furthermore, the difference in estimated marginal birth weight means between the two overweight groups, asthmatic overweight children and non-asthmatic overweight children, was over twice as big as the one between non-asthmatic children with normal weight and non-asthmatic overweight children. The same ratio was observed for wheezing and reproduced in the adiposity groups defined by body fat. These results consistently suggest that high birth weight might be a stronger risk factor for overweight-induced asthma in children than it is for overweight and asthma separately.

This cannot be explained by the current adiposity differences, since when we compare the BMI z-score and body fat percentage between these two groups we do not see any difference.

Moreover, these results suggest there are different effects of birth weight depending on different asthma phenotypes in children. We can see that the mean values of asthmatic and wheezing overweight children are clearly higher than any other group, suggesting that these individuals, who developed this phenotype of asthma by the age of 6-8, might already be different at birth; this indicates the role of the prenatal environment in the development of this

condition. Even after adjustment, the group of overweight and overfat asthmatics and wheezing children were characterised by significantly higher birth weight than their asthmatic and wheezing peers with normal body weight and fat levels. That suggests that the elevated mean of birth weight is not related simply to overweight status, or to the presence of asthma only, but rather is specific for this subpopulation of children.

To our knowledge, the difference in birth weight between the different asthma phenotypes in childhood has never been studied before. However, these differences might have been reflected in the U-shaped associations found between birth weight and risk of asthma later in life. Both low (Liu et al., 2014) and high birth weights (Flaherman & Rutherford, 2006; Sin et al., 2004) have been shown to predispose children to asthma. In our study we also found a higher risk related to both low and high birth weight, though high birth weight was seen to have a stronger effect. In chapter 9 we described in detail some studies that observed similar results. In the ISAAC study performed in 1995 in Germany with 5-7 year-old children, the researchers found a U-shaped association between birth weight and prevalence of asthma and current wheezing. They did not however take into account the child's current BMI, and we therefore do not know if the U-shaped risk in consequence was related to an obese-asthma phenotype (Bolte et al., 2004). Another study describing a U-shaped association between asthma risk at 14 and 31 years and Ponderal Index at birth included the BMI at 14 and 31 years of age in their analysis, using it as covariate in the adjustment of the model, and concluded that the Ponderal Index is associated with the risk of asthma independently of the BMI (Xu et al., 2002). In this study, however, obesity-related asthma was again not taken into consideration as a separate phenotype with a possibly different risk related to birth size. We did not observe a U-shaped association, either when analysing children with asthma, wheezing, and rhinitis as a whole, or when divided according to phenotypes. Looking at our results, we can, however, hypothesize that the commonly observed U-shaped effect of birth weight on asthma might be a result of the two phenotypes being at opposite ends of the birth weight spectrum. The risk observed for low birth weight might be associated with increased risk of asthma/wheezing with normal body weight and fat levels, while the risk observed for high birth weight might lead to development of the obese (overweight) phenotype of these conditions.

Our results suggest that high birth weight might be related to the overweight/obese asthmatic phenotype in children and be a risk factor for its development. An increased birth weight might be related to increased exposure to adipokines, hormones originating from adipose tissue. This exposure could start as early as through maternal increase in fat tissue, which would be reflected in the child's birth weight. Indeed, a meta-analysis of forty-four studies published between 1994 and 2009 found a positive correlation in all studies between cord-blood leptin and neonatal weight and leptin explained 21% of the variation in birth weight (Karakosta 2011). In

another study, maternal circulating levels of leptin were found to be an even better predictor of the child being large for his/her gestational age than glucose intolerance and lipid levels (Retnakaran 2012). The result of in utero exposure to disrupted levels of leptin and other adipokines might stimulate asthmatic inflammation. Indeed, it was shown in the study of a birth cohort of seven hundred and forty mothers with their newborns that cordblood concentration of adiponectin was associated significantly with incidence of wheezing and asthma, but no association was however showed for leptin (Rothenbacher 2007).

The child's own adipokines regulation could also be affected, beginning in early life, and as it is more likely for high birth weight children to continue having increased body weight (Li et al., 2014), adipokines levels could have a continuously pro-inflammatory profile. It was shown in a study of prospective cohort by the Centre for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) that children who are born with high weight are more likely to be in the group at risk, which is characterised by rapidly increasing levels of leptin from birth until the age of 9. Leptin was also associated with the body size of the child at all ages (Volberg 2013). That suggests that high birth weight would increase body weight throughout childhood, and through alterations in the metabolism of leptin might lead to asthmatic symptoms, resulting in the development of obesity- or overweight-related asthma in children. This concurs with our finding for the children assigned to this asthma and wheezing phenotype being characterised by the highest birth weight values among all groups.

10.6. Conclusion

Our results support the premise that overweight asthmatic children might be characterised by different birth weight values than their peers with normal body weight levels. Birth weight and other risk factors might be associated differently with obese asthmatic than other phenotypes of this disease. This in turn means that they may require a distinct approach in treatment, prevention and intervention programs. Studying the differences in the response to commonly described risk factors separately for children with different nutritional status might pave the way for important progress in management of the difficult disease which is obesity-induced asthma. Perhaps recognizing this group of children as a separate target and diagnosing distinct triggers for them could allow the disease to be controlled through simple lifestyle changes. It might be that the failure to distinguish between obese and normal-weight asthmatic children might lead to overlooking important risk factors that trigger asthma development and worsening of symptoms. Some factors that are protective for one phenotype might turn to be harmful for another. Studying these differences would not only lead to a better understanding of the severe and complex form of asthma that is the obesity-induced phenotype, but could also help in devising more effective interventions and preventions. It would surely be beneficial,

since this phenotype is characterised by worse disease control and lower rates of response to treatment, and would therefore produce higher economic costs to families and public health systems. Future studies are necessary, using larger samples which also measure social stratification in order to investigate whether the obese asthmatics phenotype can be predicted by different environmental, social, and lifestyle factors, and describe the epidemiology of obesity-induced asthma in children as a distinct subpopulation of asthmatics.

11. Final conclusion

11.1. Main findings

Our study has shown that some very common paediatric diseases of affluence, specifically asthma, rhinitis and obesity, have reached levels that merit concern in the district of Coimbra. We found that 10.6% of 6-8 year-old children living in Coimbra district have asthma, and 34.4% have experienced wheezing at least once in their lives, which might mean that there is a fraction of children with undiagnosed asthma or with a high risk of developing this disease in the future. Moreover, 23.1% of the children report having rhinitis, with nearly 20% currently actively experiencing the disease. As expected, there is a tendency toward higher prevalence among boys compared with girls.

A large number of children were classified as overweight or obese, with prevalence of 23.3% and 10.8% respectively. This means that over one third of all children from the studied population are above their recommended weight, and have a higher risk of developing comorbidities such as cardiovascular disease or type-2 diabetes, among many other problems (Biro & Wien, 2010). In addition, they are more likely to have lowered quality of life, more likely to become victims of bullying, and they have a tendency toward lower self-esteem (Griffiths et al., 2006; Robertson, Thorogood, Inglis, Grainger, & Stewart-Brown, 2012; Strauss, 2000; Williams et al., 2011).

As described, the fact that these conditions are considered diseases of affluence indicates the important role of socioeconomic, environmental, and lifestyle risk factors in their development. We therefore studied a group of potential factors which might explain the high levels of these diseases observed in our study.

We have shown that a high birth weight, living in more urban areas of the district studied, and being exposed to second-hand tobacco smoke, especially in early life, were the strongest predictors of childhood obesity, high body fat levels, and abdominal obesity. In the case of asthma, early life factors such as high birth weight, never having been breastfed, and being exposed to second-hand tobacco smoke early in life were the factors most strongly related to the disease's development. In addition, the children's participation in vigorous physical activity seemed to have an important protective role against this disease.

Factors such as never being breastfed, longer time spent watching TV, and having heavy trucks passing rarely or never near the residential area were shown to increase the risk of rhinitis.

Not only were the studied diseases at high levels in our population, but we also found a significant association between them, showing that childhood obesity and high body fat levels

are related to increased risk of asthma and rhinitis and the reason for these associations seems to exist independently from the presence of common risk factors. This does not, however, mean that the role of risk factors in the development of obesity-related asthma and rhinitis in children is not affected by those risk factors. As it was shown that obesity preceded the asthma and rhinitis diagnosis, and that it might actually not simply be associated with them but cause them, any risk factor increasing the odds of a child becoming obese increases the risk of the same child developing obesity-induced asthma or rhinitis.

Furthermore, we hypothesised that overweight-induced asthma, a commonly described distinct phenotype of asthma, might be triggered by different factors than the same disease in normal-weight children, and that rather than studying all asthmatic children as one group, we should stratify the analyses to be able to observe the risk related to specific phenotypes. Our sample was relatively small to allow for stratification, but we studied the role of birth weight in the development of two phenotypes of asthma and rhinitis, for overweight and normal-weight children. Birth weight seemed like a factor worth having a closer look at, as it has been shown to have the strongest effect on asthma, rhinitis, and obesity in our population.

11.2. Strengths and limitations

This is a cross-sectional study of the population of 6-8year old children living in the Coimbra district. The study's big strength is that it is based on a sample that is representative for the population of children within this age span living in the area. Our sample had a slight overrepresentation of children living in more urban areas of the district, which have been corrected for by applying the post-stratification weights for the urbanization level of the residential area. We managed to gather data from the group that best represents the socio-demographic profile of the local population, with children from all types of residential areas, both private and public school students, and varying socioeconomic status. This allowed us to apply the results obtained in this study to the whole population of 6-8 year old children living in the Coimbra district with greater confidence. Moreover, as estimated based on the data from the 2011 Census (INE, 2011a), the total number of children 6-8 years old living in Coimbra was approximately 8,200, of whom we were able to contact 1,777 to ask them to participate in our study, accounting for around 22% of the total population targeted. Further, our study included 1,043 children, which is nearly 13% of all the targeted population.

Other important strengths of the study include the anthropometric measurements used, which have a methodological advantage over self- or parent-reported measures (Brettschneider, Ellert, & Schaffrath Rosario, 2012; Huybrechts et al., 2011; Huybrechts, De Bacquer, Van Trimpont, De Backer, & De Henauw, 2006; Tokmakidis, Christodoulos, & Mantzouranis,

2007). These measurements were performed with high precision, by a well-trained group of researchers. In addition, instead of only measuring weight and height, which is a very common approach, due to the ease and low cost of these measurements, we included a complex of measurements such as waist and arm circumference, suprailiac, subscapular and tricepital skinfolds. These measures together allowed us to obtain more complete information on each child's adiposity: we could thus not only use nutritional status measured with BMI, but also investigate other aspects of adiposity such as body composition (percentage of fat in the total body mass) and distribution (fat accumulation in abdominal regions).

A big strength of the study is surely the application of the ISAAC methodology (Asher et al., 1995). These tools have been widely used in numerous centres worldwide. They provide solid, verified, unified, and proven tools for defining asthma, rhinitis, and their symptoms in paediatric population. In addition, the ISAAC environmental questionnaire, although created for studying asthma, rhinitis, and eczema risk factors, contains questions which can be applied to the study of childhood obesity, which is a great advantage in our study, whose aim was the verification of the role of common risk factors of these diseases in the association between asthma, rhinitis, and obesity in children. It also has the great advantage of allowing our study to be compared to those using the same methodology in different places around the world.

Meticulously prepared and performed data collection was followed by solid statistical analyses, using advanced methods such as factorial analyses, generalized linear models (GLMs) and multivariate testing, to obtain the most reliable results and minimize the effects of confounders and bias.

Our study has much that is new to offer scientific circles. To begin with, the prevalence of asthma and rhinitis and their symptoms among this age group in Coimbra (or central Portugal generally) has never been described in the literature before. Furthermore, it has never actually been measured in children in this region, only in adults (Sa-Sousa et al., 2012) or adolescents (Rosado-Pinto, 2011). Our study contributed to filling this information gap, a task which, in view of the serious public health problem posed by asthma and rhinitis, is of great importance.

Another new element, not previously discovered as far as we know, was the differences we found in birth weight between the asthma and rhinitis phenotypes with different nutritional status and body fat levels. It had been shown that children with overweight and/or overfat-related asthma generally have significantly larger birth weight values, even compared to overweight children without asthma or asthmatic children with normal body weight and fat levels. This shows how early the differences between the phenotypes can be spotted. This is an

important finding and could potentially set the template for a new approach in the study of childhood asthma phenotypes and their early origins.

Despite the strengths described above, the study also has its limitations. The most obvious limitation is the questionnaire-based data concerning asthma and rhinitis and environmental and socioeconomic factors. This method of acquiring information is always prone to bias related to self-reporting (Celis-Morales et al., 2012; Kim et al., 2012; Schoeller et al., 2013). People very often unconsciously misreport the truth, either through faulty memory or by subconsciously trying to give the "right answers" instead of presenting the actual reality. This is what is called the "social desirability bias" and is the main disadvantage of self-reported data (Grimm, 2010; Krumpal, 2011), especially concerning topics charged with social stigma, such as, in our case, obesity, tobacco, and dietary intake, among others (Klesges et al., 2004; Krumpal, 2011; Miller et al., 2014). It is especially troubling as the inaccuracies are often not independent of social factors, and some social groups are more likely than others to misreport the facts (Dowd & Zajacova, 2010). We have tried to correct for that fact by adjusting the tests for socioeconomic status, which is one of the most common factors influencing the reliability of self-reported data (Tate, Dezateux, Cole, & Davidson, 2005). Nevertheless, studies validating the questionnaire-based information, including the ISAAC tools, show that these are still legitimate tools in epidemiological studies (Crutzen & Göritz, 2010; Gorozave-Car, 2013; Nwaru et al., 2011).

This problem is even more complex when it comes to obtaining information retrospectively, asking people about events that occurred some years back. That relates to so-called "memory bias," which in our case might have affected the reliability of information on early life data, such as gestational age, birth length and weight, breastfeeding, pregnancy, smoking in the first year of life, etc. Although memory bias has been shown to affect the accuracy of this kind of data, the scale of the bias is not considered high. Although in developing countries, memory bias could influence the birth weight record on a larger scale (Channon, Padmadas, & McDonald, 2011), in the developed countries the accuracy seem to be high (Dietz et al., 2014; Natland, Andersen, Nilsen, Forsmo, & Jacobsen, 2012; Wodskou, Hundrup, Obel, & Jørgensen, 2010).

Memory bias should not change our main results, unless the misreporting of the data is more likely to occur in one of the studied groups, e.g. for mothers of children with asthma, rhinitis obesity, overfat, abdominal fat etc. As long as the error is nondifferential with respect to outcome and comparable between the groups, it should not influence the results significantly. Socioeconomic status is considered an important factor influencing the accuracy of

retrospectively obtained self-reported birth weight data (Tate et al., 2005) so it is recommended that analyses be adjusted for this factor, as we did in our study.

Although the sample size is sufficient for the given hypothesis, and is a representative sample containing a relatively large portion of the entire targeted population of 6-8 year-old children living in the Coimbra district, a larger sample could allow for further stratifications, and would perhaps enable a more detailed analysis of differences in the roles of risk factors in the modulation of obesity and high fat related asthma and rhinitis and asthma and rhinitis of children with normal body weight and fat levels.

11.3. Future indications

As mentioned above, a larger sample of children would be beneficial and give more opportunities to study an interesting group of obese asthmatic children. There would also be some advantage in doing a longitudinal study design, where not only the bias related to retrospective data would be minimized, but also the timing of events could be taken into consideration. Determining the age of onset of asthma and rhinitis as well as repeatedly measured childhood anthropometric data could allow for a more detailed analysis of the obesity-asthma/rhinitis interactions throughout the child's life. Obesity and asthma/rhinitis incidence, as opposed to simple prevalence, could be investigated. The effects of weight loss and gain could form could add important layers to our knowledge. Perhaps repeating measurements of adipokines levels from birth onward could shed light on the role of these hormones in asthma/rhinitis and obesity interactions, especially on the role of elevated birth weight in the development of obesity-related asthma in contrast to asthma in children with normal weight.

Our results suggest that the tendency towards the narrowing of the asthma definition down to subgroups such as phenotypes or endotypes is crucial in order to achieve more effective prevention, intervention and treatment and provide evidence-based information for patients, their families, and general practitioners. The evidence provided by the study, confirming a high level of heterogeneity in asthma, highlights the necessity of individualized, phenotype- or patient-specific treatment strategies (Bush, 2004; Chung, 2011; Ducharme, 2012; Thompson, Morin, & Davis, 2011; Yorgancioglu, 2012). This seems especially important in the light of the high cost of asthma and rhinitis treatment (Barnett & Nurmagambetov, 2011; Karaca-Mandic, Jena, Joyce, & Goldman, 2012; Meltzer & Bukstein, 2011).

Even if lifestyle and environmental factors do not explain the association between asthma, rhinitis, and obesity, they trigger these diseases. Lifestyle factors seem to have intergenerational effects. Factors such as maternal obesity, pregnancy weight gain, and maternal behavioural and lifestyle factors, can contribute significantly to development of these diseases

through the pre-natal environment (Florath et al., 2014; Kumar et al., 2010; Olson et al., 2009; Sebert, Sharkey, Budge, & Symonds, 2011; Sly, 2011). A permanent conversion to a healthy lifestyle should be advised rather than punctual interventions, which are often applied only when the problem has already become detectable. Meanwhile, the organism might already be on the trajectory to the development of a pathological condition and some processes might be difficult to reverse. In terms of disease prevention, it is true that "What you can do today; you should have started doing yesterday!"

12. References

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Appendix 1. Aprovação da Direção-Geral de Inovação e de Desenvolvimento Curricular:

Exmo(a)s. Sr(a)s.

O pedido de autorização do inquérito n.o 0043300002, com a designação Associação entre asma e obesidade em crianças com 6-7anos de Coimbra: o papel dos factores ambientais e familiares., registado em 08-04-2011, foi aprovado.

Avaliação do inquérito:

Exmo(a) Senhor(a) Dr(a) Cristina Maria Proença Padez

Venho por este meio informar que o pedido de realização de inquérito em meio escolar é autorizado uma vez que, submetido a análise, cumpre os requisitos de qualidade técnica e metodológica para tal devendo, no entanto, ter em atenção as observações aduzidas.

Com os melhores cumprimentos

Isabel Oliveira

Directora de Serviços de Inovação Educativa

DGIDC

Appendix 2. Authorization of child's participation in the study

DEPARTAMENTO DE CIENCIAS DA VIDA

FCTUC FACULDADE DE CIÊNCIAS E TECNOLOGIA
UNIVERSIDADE DE COIMBRA

Estudo da associação entre Obesidade e Asma em crianças com idades compreendidas entre os 6 e 7 anos do município de Coimbra- papel de factores ambientais e familiares.

Conheça os valores de peso e alturado seu filho(a)

A prevalência da asma e obesidade tem aumentado nas últimas décadas e constitui um problema para os doentes porque vai piorar significamento a sua qualidade de vida. As duas condições – asma e obesidade - parecem coexistir e a relação entre as duas tem sido estudada em vários centros de investigação, incluindo o nosso. Em 2009 obtivemos financiamento pela Fundação para a Ciência e Tecnologia (SFRH/BD/66877/2009) para iniciar um novo projecto que pretende avaliar o papel dos factores ambientais e familiares em associação entre Obesidade e Asma em crianças com idades compreendidas entre os 6 e 7 anos do município de Coimbra.

O projecto envolverá as escolas do ensino básico em Coimbra que concordaram em participar neste estudo. Vamos pesar o seu filho(a) numa balança apropriada, medir a sua altura, o perímetro da barriga e o braço e as pregas cutâneas. São medidas simples, efectuadas por pessoas devidamente treinadas, sem qualquer risco ou desconforto para a criança. No próprio dia, vai ficar a saber quanto pesa e mede o seu filho pois vamos enviar um cartão com os respectivos dados. Estas medidas serão conjugadas com alguns dados familiares, ambientais e da condição respiratória (inquérito anexo) que serão extremamente úteis para uma análise mais profunda do crescimento e saúde da criança.

Para que este segundo projecto possa ser efectuado é imprescindível a sua colaboração, pois só assim poderemos obter informações que vão ter utilidade ao nível do nosso país e que contribuirão para o conhecimento sobre as condições de saúde das crianças e os factores do risco para a asma, alergia e obesidade. Para que possamos avaliar o seu filho, precisamos que nos dê a sua autorização por escrito, no termo de consentimento, e que preencha os dados do inquérito que enviamos, devolvendo-o logo que possível. **O inquérito é anónimo, não teremos qualquer identificação do seu filho(a) pois a folha inicial em que nos deve dar autorização, a parte inferior deve recortar e guardar consigo e a parte superior será destacada do restante inquérito e ficará na Escola.**

Este projecto é coordenado pelo **Centro de Investigação em Antropologia e Saúde do Departamento de Ciências da Vida da Universidade de Coimbra, em colaboração com o Instituto de Patologia Geral, Faculdade de Medicina Universidade de Coimbra.**

Colocamo-nos à sua inteira disposição para esclarecer qualquer dúvida ou informação mais detalhada pelo telefone 910 874 073 da pessoa responsável por este projecto (Dra Magdalena Muc) , ou por e-mail para magdalenamuc@gmail.com **Obrigada pela sua colaboração.**

A Coordenadora do Projecto e Coordenadora do Centro Investigação em Antropologia e Saúde

(Professora Doutora, Cristina Padez)

Estudo da associação entre Obesidade e Asma em crianças com idades compreendidas entre os 6 e 7 anos do município de Coimbra- papel de factores ambientais e familiares.

Termo de consentimento

Eu_____
_____

Encarregado de educação do aluno(a) _____

Nº_____ Turma_____ Ano_____ da Escola_____

Dou o meu consentimento para que o meu filho(a) participe neste estudo.

Assinatura:_____Data_____/_____/ 2011

NOTA: Quando devolver o inquérito deve destacar e ficar com o duplicado (parte inferior desta folha). A parte superior na qual consta o nome do encarregado de educação e da criança, ficará na Escola. Assim, garantimos que o inquérito (e as medidas realizadas nas crianças) será anónimo.

……

Duplicado para o encarregado de educação

Estudo da associação entre Obesidade e Asma em crianças com idades compreendidas entre os 6 e 7 anos do município de Coimbra- papel de factores ambientais e familiares.

Termo de consentimento

Eu
_____

Encarregado de educação do aluno(a) _____

Nº_____ Turma_____ Ano_____ da Escola_____

Dou o meu consentimento para que o meu filho(a) participe neste estudo.

Assinatura:_____Data_____/_____/ 2011

Appendix 3. ISAAC-based Asthma, rhinitis and environmental questionnaire and the measurements template

Inquerito

Nesta folha estão questões sobre o nome, escola. E data de nascimento do seu filho. Por favor escreva as respostas a estas perguntas no respectivo espaço.

Para todas as outras questões só e necessário marcar com um visto (√) o quadrado certo. No caso de se enganar, faca uma cruz nesse quadrado e marque com um visto (√) a resposta correcta. Escolha apenas uma opção, a não ser que haja indicações contrárias

Exemplos de como marcar questionários: | 6 | Idade anos

1. Sim ☐ Não ☐

ESCOLA:

DATA DE HOJE: Dia | Mês | Ano

DATA DE NASCIMENTO DA CRIANCA: Dia | Mês | Ano

(Marque com um visto (√) todo o resto do questionário)

O SEU FILHO E: rapaz ☐ rapariga ☐

O seu filho(a) nasceu com quantas semanas da gravidez?

Peso do filho ao nascer: ……..*

Comprimento do filho ao nascer:……..*

Questionario principal sobre a asma

Questionario para 6-7 anos

O seu filho já alguma vez teve pieira ou assobios (silvos) no peito?

□ Sim

□ Não

SE RESPONDEU "NÃO" POR FAVOR PASSE A QUESTAO 6.

O seu filho teve pieira ou assobios (silvos) nos últimos 12 meses?

□ Sim

□ Não

SE RESPONDEU "NÃO" POR FAVOR PASSE A QUESTAO 6.

Quantos ataques de pieira teve o seu filho nos últimos 12 meses?

□ Nenhum

□ 1 a 3

□ 4 a 12

□ Mais de 12

Nos últimos 12 meses, quantas vezes, em media, o seu filho acordou devido a pieira?

□ Nunca

□ Menos de uma noite a semana

□ Uma ou mais noites por semana

Nos últimos 12 meses, a pieira foi suficientemente forte para limitar a conversa do seu filho a apenas uma ou duas palavras entre duas respirações?

□ Sim

□ Não

Já alguma vez o seu filho teve asma?

□ Sim

□ Não

Nos últimos 12 meses alguma vez sentiu pieira no peito do seu filho durante ou depois de fazer exercício?

□ Sim

□ Não

Nos últimos 12 meses, o seu filho teve tosse seca a noite além da tosse associada a constipação infeção respiratória?

□ Sim

□ Não

9. O seu filho foi diagnosticado com asma pelo o médico? *

□ Sim

□ Não

10. O seu filho esta sobre o tratamento contra asma? *

□ Sim

□ Não

11. Se sim, o que tipo de medicamento esta a tomar? *……

12. Alguém da família teve ou tem asma? *

□ Sim

□ Não

13. Se sim, esta pessoa e:*

□ Mãe da criança

□ Pai da criança

□ Irmão/Irmã da criança.

□ outro membro da família. Quem?.....

14. Alguém da família teve ou tem rinite?*

□ Sim

□ Não

13. Se sim, esta pessoa e:*

□ Mãe da criança

□ Pai da criança

□ Irmão/Irmã da criança.

□ Outro membro da família. Quem?.....

Questionário principal sobre a rinite para 6-7 anos

Já algum vez o seu filho teve crises de espirros, corrimento, nasal, ou nariz entupido, quando NÃO ESTA constipado ou com gripe?

□ Sim

□ Não

SE RESPONDEU "NÃO" POR FAVOR PASSE A QUESTAO 6.

Nos últimos 12 meses, o seu filho teve crises de espirros, corrimento nasal ou nariz entupido, quando NÃO ESTA constipado ou com gripe?

□ Sim

□ Não

SE RESPONDEU "NÃO" POR FAVOR PASSE A QUESTAO 6.

Nos últimos 12 meses, esse problema de nariz foi acompanhado por olhos lacrimejantes e com comichão?

□ Sim

□ Não

Em qual (quais) dos últimos 12 meses, ocorreu esse problema nariz? (Por favor marcar com (√) as respostas certas)

□ Janeiro	□ Abril	□ Julho	□ Outubro
□ Fevereiro	□ Maio	□ Agosto	□ Novembro
□ Marco	□ Junho	□ Setembro	□ Dezembro

Nos últimos 12 meses, este problema no nariz afectou as actividades diárias do seu filho?

□ Nada

□ Pouco

□ Mais ou menos

□ Muito

Já alguma vez o seu filho teve febre dos fenos?

□ Sim

□ Não

Situação familiar

Quantos irmãos e irmãs mais velhos o filho(a) tem? ☐

2. Quantos irmãos mais novos o filho tem? ☐

3. O filho(a) nasceu em Portugal?

□ Sim

□ Não

4.Se não nasceu em Portugal, quantos anos vive em Portugal? ☐

5. Qual e o nível de escolaridade da mãe (tutora) da criança?

□ Ens. Básico 4 anos

□ Ens. Secundário 6 anos

□ Ens. Secundário 9 anos

□ Ens Secundário 12 anos

□ Ens. Superior

6. Qual e o nível de escolaridade da pai (tutor) da criança?

□ Ens. Básico 4 anos

□ Ens. Básico 6 anos

□ Ens. Secundário (9 anos)

□ Ens Secundário (12 anos)

□ Ens. Superior

7. O qual e a proffisao da mãe (tutora) da criança?*

8. O que e a ocupação da pai (tutor) da criança?*

Aleitamento materno

O seu filho(a) foi amamentado(a)?

□ Sim

□ Não

Quanto tempo o seu filho(a) foi amamentado? *

□ 0-3 meses

□ 3-6 meses

□ 6- 9 meses

□ Mais que 9 meses

Quanto tempo o seu filho(a) foi EXCLUSIVAMENTE amamentado (sem introduzir outro tipo de alimentos)?*

□ 0-3 meses

□ 3-6 meses

□ 6- 9 meses

□ Mais que 9 meses

Alimentação

Nos últimos 12 meses comeu ou bebeu

Carne

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Peixe (incluindo o marisco)

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Fruta

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Vegetais (verdes e raízes comestíveis)

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Leguminosas (ervilhas, feijões, lentilhas)

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Cereais (incluindo pão)

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Massa

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Arroz

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Manteiga

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Margarina

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Frutos secos

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Batatas

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Leite

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Ovo

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Fast food/hamburgers

□ Três ou mais vezes por semana

□ Uma vez ou duas a semana

□ Nunca ou ocasionalmente

Actividade fisica

1. Quantas vezes por semana o seu filho(a) tem uma actividade física vigorosa que o leva a ficar ofegante?

□ Três ou mais vezes por semana

□ Uma vez ou duas por semana

□ Nunca ou ocasionalmente

2. Durante uma semana normal, quantas horas por dia (24horas) e que o seu filho(a) vê televisão?

□ 5 horas ou mais

□ mais de 3 horas mas menos de 5 horas

□ mais de 1 hora mas menos de 3 horas

□ menos de 1 hora

Fonte de energia

1. Em sua casa, qual e a fonte de energia utilizado para cozinhar

□ Electricidade

□ Gás

□ Carvão

□ Outro

2. Em sua casa, qual e a fonte de energia utilizado no aquecimento?

□ Electricidade

□ Gás, querosene, parafina

□ Madeira, carvão, óleo

□ Outro

Medicamentos

1. Nos primeiros 12 meses da vida do seu filho(a), deva-lhe habitualmente paracetamol?

□ Sim

□ Não

2. Nos últimos 12 meses quantas vezes em media, o teu filho(a) tomou paracetamol?

□ Pelo menos 1 vez por mês

□ Pelo menos 1 vez por ano

□ Nunca

3. Nos primeiros meses de vida o seu filho(a) tomou antibióticos?

□ Sim

□ Não

Ambiente

1. Passam muitos camiões na rua onde vive, nos dias de semana?

□ O dia inteiro

□ Frequentemente ao logo do dia

□ Raramente

□ Nunca

2. Tinha um gato em casa durante o primeiro ano de vida do seu filho(a)?

□ Sim

□ Não

3. Teve um gato em casa nos últimos 12 meses?

□ Sim

□ Não

4. Tinha um cão em casa durante o primeiro ano de vida do seu filho(a)?

□ Sim

□ Não

5. Teve um cão em casa nos últimos 12 meses?

□ Sim

□ Não

6. No primeiro ano de vida o seu filho(a) teve contacto frequente (pelo menos uma vez por semana) com animais de quinta?

□ Sim

□ Não

7. A mãe teve contacto frequente (pelo menos uma vez por semana) com animais de quinta enquanto esteve grávida?

□ Sim

□ Não

Tabaco

1. A mae (ou a pessoa do sexo feminine que toma conta da crianca) fuma?

□ Sim

□ Não

2. Se sim, quantos cigarros por dia?

□ ≥ 5

□ de 5 a 10

□ de 10 a 15 (include)

□ de 15 a 20 (include)

□ Mais de 20

3. A mãe fumava durante de gravidez?

□ Sim

□ Não

4. Se sim, durante quanto tempo a mãe estava a fumar durante de gravidez?

□ 0-3 meses da gravidez

□ 3-6 meses da gravidez

□ 6- meses da gravidez

5. A mãe (ou a pessoa do sexo feminino que tomava conta da criança) fumava durante o primeiro ano de vida da criança?

□ Sim

□ Não

6. Quantas pessoas do agregado familiar fumam? ☐

Habitos de consumo*

1. Onde vai habitualmente fazer as suas compras alimentares?*

□ Mercearias tradicionais/frutaria/talho/peixaria

□ Minimercados e/ou supermercados

□ Grandes superfícies (Ex. Continente, Jumbo)

□ Outros. Onde?.....

2. Quais são os motives da sua escolha?*

□ Porque tem grande diversidade de produtos- tem todos os produtos alimentares

□ Por causa da qualidade dos produtos

□ Por causa dos preços

□ Porque fica próximo da minha residência

□ Porque fica próximo do meu trabalho

□ Porque tenho facilidade em estacionar o carro

□ Por causa do atendimento

□ Outros. Quais?.....

3.Como se desloca ate ao supermercado? *

□ A pé

□ Em carro próprio

□ De autocarro

□ De táxi

Outro. Qual? ……..

4.Indique qual o **codigo postal** da sua residencia _____-____

MEASURES

Date of the measurement.....

Asthma and Obesity in Children

MEASURE	VALUE	UNIT
Height		m
Weight		kg
Arm circumference		cm
Waist circumference		cm
Skin-fold triceps		mm
Skin-fold suprailiac		mm
Skin-fold subscapular		mm

Appendix 4. Articles Published using the data from the study.

Exposure to Paracetamol and Antibiotics in Early Life and Elevated Risk of Asthma in Childhood

Muc, M., Padez, C., & Pinto, A. M. (2013). In *Neurobiology of Respiration* (pp. 393-400). Springer Netherlands.

Exposure to Paracetamol and Antibiotics in Early Life and Elevated Risk of Asthma in Childhood

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M. Muc, C. Padez, and A. Mota Pinto

Abstract

Prospective studies on increased risk of childhood asthma due to exposure to paracetamol and antibiotics in early life have yielded contradictory results. Therefore, the aim of the present study was to investigate the association between administration of paracetamol and antibiotics in the first 12 months of life and delayed asthma symptoms later in childhood. This is a cross-sectional study that included 1,063 children from the primary schools in Coimbra, Portugal. ISAAC-based environmental and core asthma and rhinitis questionnaires were used to obtain information about children's respiratory health and administration of paracetamol and antibiotics. We found that early paracetamol use significantly increased the risk of asthma ever (at least one episode in life) (OR = 2.9; 95 % CI:1.8–4.5), current asthma (OR = 2.4; 95 %CI:1.5–3.6), wheezing ever (OR = 2.5; 95 %CI:1.8–3.4), rhinitis ever (OR = 2.4; 95 %CI:1.7–3.3), and current rhinitis (OR = 2.8; 95 %CI:2.0–3.9). Antibiotic exposure showed a similar effect with the risk for current asthma (OR = 1.6; 95 %CI:1.0–2.5), asthma ever (OR = 2.0; 95 %CI:1.3–3.1), wheeze ever (OR = 2.3; 95 %CI:1.7–3.2), and rhinitis symptoms (OR = 1.8; 95 %CI:1.3–2.6, OR = 1.8; 95 %CI:1.3–2.6, OR = 1.9; 95 % CI:1.2–3.0 for rhinitis ever, current rhinitis, and tearing, respectively). We further found that increased frequency of paracetamol use during the last 12 months preceding the study facilitated the appearance of allergic symptoms, suggesting a dose-dependent associations. In conclusion, the study shows a significant association between exposure to paracetamol

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and antibiotics in the first 12 months of life and both prevalence and severity of asthma and rhinitis symptoms in children 5–9 years old.

Keywords
Antibiotics • Asthma • Children • Paracetamol • Rhinitis • Wheeze

1 Introduction

A rapidly increasing prevalence of atopic diseases world-wide has led to a research interest in the possible underlying reasons (Eder et al. 2006), although a consensus regarding the asthmatic and allergic states has not yet been reached. On the list of putative factors increasing the prevalence of asthma is the early use of paracetamol and antibiotics (Rusconi et al. 2011).

Paracetamol was indicated as a candidate asthma facilitating factor in 1998, suggesting that the switch in the use pattern from aspirin to paracetamol in early childhood could increase susceptibility to allergic diseases by enhancing the Th2 response (Varner et al. 1998). Indeed, paracetamol is currently the most commonly used analgesic and antipyretic prescribed to pediatric patients as an alternative to aspirin that may be associated with the Reye syndrome (Newson et al. 2000; Rahwan and Rahwan 1986).

A large amount of epidemiological data demonstrating the role of paracetamol and antibiotic use in infancy for the development of asthma comes from the International Study of Asthma and Allergies in Childhood (ISAAC) (Foliaki et al. 2009; Beasley et al. 2008) or, like this work, from studies using the ISAAC tools (Barragan-Meijueiro et al. 2006).

A frequently described phenomenon justifying the rising prevalence of allergic diseases, including asthma, is the 'hygiene hypothesis', underlining the importance of microflora, especially gastrointestinal, in the development of a healthy immune system (Strachan 1989). Prescription of antibiotics applied in early life can alter microflora, prevent the boosting of immune system activity, and lead to increased allergic sensitization (Schaub et al. 2006). The perinatal period is characterized by the development of a Th1/Th2 balance, which could be distorted if exposed to antibiotic action (Prescott et al. 1999). Nevertheless, the results of studies are contentious. The ISAAC study resulted in many publications supporting the role of antibiotics in the development of atopic diseases. Data obtained from 193,412 children representing 29 countries show a significantly increased risk of allergic disorders in children who get antibiotics in the first year of life (Foliaki et al. 2009). There is increased risk for current asthma, asthma ever (at least one episode in life), severe asthma, or current rhinoconjunctivitis. Similar results were revealed for the cohort of 1,401 children from the US. This longitudinal study, initiated during pregnancy, show significantly higher risks for asthma and allergy, even stronger if the diagnosis takes place before the age of 3 (Risnes et al. 2011). On the other hand, no association between antibiotic and atopic diseases has been reported in 5 introspective studies in England (Celedon et al. 2002).

The objective of our study was to examine the association between antibiotics and paracetamol intake in the first year of life and the development of asthmatic symptoms in childhood.

2 Methods

The questionnaire was approved by the DGIDC (Direção-Geral da Educação) and the study had the approval of a local Ethics Committee.

This cross-sectional study evaluated 1,063 children from the first and second grade of primary school in the district of Coimbra, Portugal and was performed from September 2011 to June 2012. To assess data on respiratory conditions, the core ISAAC based asthma and rhinitis

questionnaires were used. For the analyses of the environmental and family factors, an ISAAC-based environmental questionnaire was applied. The questionnaires, translated to Portuguese, were used with the authorization of the national coordinator of the ISAAC initiative in Portugal. Parents filled out a questionnaire regarding the paracetamol and antibiotic exposure of children: In the first 12 months of your child's life, did you usually give paracetamol for fever? In the past 12 months, how often, on average, have you given your child paracetamol? In the first 12 months of life, did your child have any antibiotics?

Asthma ever was determined as a positive response to a question of a child ever having an asthma attack, and current asthma as at least one wheezing episode in the last 12 months of life or at least one night of cough attack not related to infection. Severity of the disease was estimated based on the responses to three questions about the number of wheeze attacks in the last 12 months, number of wake-up episodes caused by wheeze and problems in speaking caused by wheezing. Rhinitis ever was defined as ever having a problem of sneezing, running or blocked nose not caused by infections and current rhinitis as the same symptoms occurring in the last 12 months. Prematurity was defined as gestational age under 37 weeks.

Demographic data were presented in the percentage terms. Chi^2 test was run to calculate the prevalence differences between children exposed or not to antibiotics and paracetamol. Binary and Multinominal Logistic Regression were run to estimate the risk of atopic disease symptoms, depending on drug exposure, adjusted for children's age and sex, family history of asthma and rhinitis, and prematurity. Statistical software SPSS v 19 was used for data analysis.

3 Results

A total number of 1,063 questionnaires were returned by the parents of children. The children with severe chronic diseases not related to asthma or allergies were excluded from the study giving the final number of 1,037 children studied. The mean age of the children was 7.2 years (range 6–9 years) and 51 % of the children were girls, 49 % boys. Boys had a general tendency to have a higher prevalence of respiratory symptoms, although only current asthma prevailed significantly ($p < 0.05$). An attack of wheeze at least once in children's lives was reported by 35.2 % of parents and an attack during the last 12 months by 11.8 %. An asthma episode at least once in the child's lifetime was experienced by 10.4 %. A night cough attack was experienced by 24.3 % and exercise-induced asthma by 6.4 % children. Symptoms of rhinitis, at least once, were experienced by 22.8 % children during the last 12 months. Tearing and itchy eyes occurred in 9.6 %. Administration of paracetamol in the first year of life was reported in 21.3 % and antibiotics in 23.1 % children. In the last 12 months, 72.7 % of children were given paracetamol at least once and 12.7 % at least once per month. The full demographic characteristics can be found in Table 53.1.

Administration of paracetamol in early life significantly increased the prevalence of asthma ever (OR = 2.9; 95 %CI:1.8–4.5), current asthma (OR = 2.4; 95 %CI:1.5–3.6), wheezing ever (OR = 2.5; 95 %CI:1.8–3.4), rhinitis ever (OR = 2.4; 95 %CI:1.7–3.3) and current rhinitis (OR = 2.8; 95 %CI:2.0–3.9), episodes of itchy and tearing eyes (OR = 2.9; 95 %CI:1.8–4.5), and night cough attacks (OR = 3.1; 95 % CI:2.2–4.4) (Table 53.2). Among children who were given paracetamol in the first year of life, 53.6 % reported wheezing symptoms at least once later in life, compared with 30.8 % who did not receive the drug ($p < 0.01$). Not only the prevalence but also severity of symptoms appeared strongly associated with paracetamol administration in the first 12 months of life, such as the number of wheeze attacks in the last year (OR = 2.3; 95 %CI:1.4–3.8 for 1–3 attacks, OR = 2.7; 95 %CI:1.3–5.7 for 4 or more attacks), the number of wake-up episodes caused by the attacks (OR = 2.7; 95 %CI:1.5–4.9 for less than one per week and OR = 2.9; 95 % CI:1.2–7.0 for one or more per week).

Table 53.1 Demographic and prevalence data of the studied population

Variable	Yes (n)	Yes (%)
Sex F/M	529/508	51/49
Prematurity	191	19
Family history of asthma	427	41.5
Family history of rhinitis	445	43.5
Wheeze ever	357	35.2
Wheeze in the past 12 months	120	11.8
4 or more attacks of wheeze in the past 12 months	33	3.3
Sleep disturbance from wheeze, 1 or more nights a week in the past 12 months	23	2.3
Speech limited by wheeze in the past 12 months	18	1.8
Asthma ever	106	10.4
Wheeze during or after exercise in the past 12 months	65	6.4
Night cough in the past 12 months	248	24.3
Nose symptoms ever	233	22.8
Nose symptoms in the past 12 months	198	19.4
Nose and eye symptoms in the past 12 months	98	9.6
Nose symptoms affecting activities a lot in the past 12 months	4	2.0
Hay fever ever	13	1.3
Paracetamol intake in the first 12 months	218	21.3
Paracetamol intake at least once per month in the past 12 months	130	12.7
Paracetamol intake at least once the past 12 months	744	72.7
Antibiotic intake in the first 12 months	237	23.1
Number of participants	n = 1,037	

Prevalence of the factors included in this study was presented as the number and percentage of individuals declaring the existence of a factor

Table 53.2 Odds ratios (OR) for symptoms depending on paracetamol exposure in the first 12 months of life, with the level of significance (p) and confidence intervals (CI), both unadjusted and adjusted for sex, age, prematurity, and positive history of asthma and rhinitis

	Paracetamol exposure in the first 12 months of life					
	Unadjusted			Adjusted		
	OR	p	95 %CI	OR	p	95 %CI
Asthma ever	3.168	<0.001	2.074–4.838	2.851	<0.001	1.825–4.454
Current asthma (wheeze in the past 12 months)	2.615	<0.001	1.740–3.931	2.362	<0.001	1.532–3.642
Exercise induced asthma in the past 12 months	2.692	<0.001	1.598–4.534	2.392	0.002	1.381–4.143
Wheeze ever	2.598	<0.001	1.909–3.537	2.478	<0.001	1.794–3.422
Rhinitis ever	2.738	<0.001	1.974–3.799	2.372	<0.001	1.682–3.344
Current rhinitis	3.247	<0.001	2.311–4.562	2.754	<0.001	1.962–3.937
Night cough attacks in the past 12 months	3.427	<0.001	2.482–4.733	3.104	<0.001	2.205–4.370
Four or more wheeze attacks in the past 12 months	2.757	<0.001	1.345–5.652	2.711	0.008	1.286–5.717
One or more wake up episodes with wheeze/week in the past 12 months	2.642	<0.001	1.126–6.201	3.094	0.021	1.294–7.399
Nose and eye symptoms in the past 12 months	3.313	<0.001	2.143–5.124	2.876	<0.001	1.824–4.534

A similar association was found for antibiotics. The use of antibiotics resulted in increased risk of current asthma (OR = 1.6; 95 %CI:1.0–2.5), asthma ever (OR = 2.0; 95 % CI:1.3–3.1), wheeze ever (OR = 2.3; 95 % CI:1.7–3.2), night cough attacks (OR = 1.9; 95 %CI:1.3–2.6), and all rhinitis symptoms (OR = 1.8; 95 %CI:1.3–2.6, OR = 1.8; 95 %

Table 53.3 Odds ratios (OR) for each symptom depending on the antibiotic exposure in the first 12 months of life, with the levels of significance (p) and confidence intervals (CI) both unadjusted and adjusted for sex, age, prematurity, and positive history of asthma and rhinitis

	Antibiotic exposure by 12 months					
	Unadjusted			Adjusted		
	OR	p	95 %CI	OR	p	95 %CI
Asthma ever	2.094	0.001	1.364–3.216	1.963	0.003	1.251–3.081
Current asthma (wheeze in the past 12 months)	1.676	0.015	1.104–2.543	1.596	0.038	1.026–2.483
Exercise induced asthma in the past 12 months	1.537	0.125	0.888–2.659	2.465	0.266	0.780–2.465
Wheeze ever	2.292	<0.001	1.699–3.092	2.326	<0.001	1.702–3.180
Rhinitis ever	1.882	<0.001	1.357–2.611	1.836	0.001	1.302–2.589
Current rhinitis	1.884	<0.001	1.336–2.657	1.808	0.001	1.258–2.599
Night cough attacks in the past 12 months	1.909	<0.001	1.385–2.632	1.852	<0.001	1.315–2.608
Four or more wheeze attacks in the past 12 months	1.554	0.255	0.727–3.320	1.482	0.275	0.679–3.233
One or more wake up episodes with wheeze/week in the past 12 months	1.539	0.349	0.625–3.791	1.119	0.662	0.427–2.932
Nose and eye symptoms in the past 12 months	1.869	0.006	1.193–2.927	1.856	0.018	1.162–2.966

CI:1.3–2.6, and OR = 1.9; 95 %CI:1.2–3.0 for rhinitis ever, current rhinitis, and tearing and itching eyes, respectively). Although antibiotic intake was associated with the prevalence of asthma, it did not seem to influence its severity. We found no association between antibiotic intake and the number of wake-up episodes or speech problems, nor with the disturbance of daily activities caused by symptoms. A list of selected odds ratios was presented in Table 53.3.

We further found that increased frequency of paracetamol use during the last 12 months preceding the study facilitated the appearance of allergic symptoms, suggesting a dose-dependent associations. Here, risk of current asthma was OR = 3.3; 95 %CI:1.5–7.6, exercise-induced asthma (OR = 3.9; 95 %CI:1.2–12.1), night cough attacks (OR = 5.4; 95 %CI:2.9–9.9), current rhinitis (OR = 5.3; 95 %CI:2.7–10.5), and tearing and itchy eyes (OR = 6.7; 95 % CI:2.5–18.3). Finally, we found a strong association between the intake of paracetamol early in life and that during the last 12 months preceding the study; 30.6 % of the children who were given paracetamol in the first year of life also received paracetamol at least once per month during the last 12 months compared with just 7.8 % of those not having paracetamol exposure early in life ($p < 0.01$).

4 Discussion

The major finding of our study was that children exposed in early life to paracetamol or antibiotics appeared to have highly increased risk of developing asthma and rhinitis by the age of 5–9 and they also had more severe symptoms than those unexposed. We found positive associations between the use of paracetamol and antibiotics and the appearance of asthma ever or current asthma and rhinitis ever or current rhinitis. We also found an association between the dose-dependent current use of paracetamol and both prevalence and severity of current respiratory symptoms. Our results demonstrate that parents who gave paracetamol to their children early in life continue its administration later in life, and do so at higher doses. These associations remained strong after adjustments for sex, age, family history of asthma and rhinitis, and prematurity.

The present results are consistent with other epidemiological data, demonstrating an important role of antibiotics and paracetamol in the development of allergic diseases. A multicenter study on a sample of 205,487 children aged 6–7 from 31 countries, originating from the phase three of the ISAAC program, found that the intake of paracetamol in the first year of life increases the risk of

asthma, rhinoconjunctivitis, and eczema (Beasley et al. 2008). That study also verified the role of antibiotic intake in the prevalence of atopic diseases. Exposure to antibiotics in the first 12 months of life had a strong impact on future respiratory health. The reported use of antibiotics was strongly associated with increased risk of current asthma symptoms, severe asthma, and asthma ever and less, but still significantly, with current symptoms of rhinitis (Foliaki et al. 2009). These results were corroborated in other studies as well (Gonzalez-Barcala et al. 2012; Kozyrskyj et al. 2007).

The mechanisms behind these associations are unclear. Yet some plausible explanations could be proposed. Evidence exists that frequent increases of body temperature above 38 °C reduce the risk of asthma later in life (Williams et al. 2004). Therefore, antipyretic effects of paracetamol and antibiotics could reduce the protective role of fever, increasing the risk of asthma and allergies. Another theory suggests that the substitution of the anti-inflammatory ibuprofen for paracetamol has been a real cause of a higher allergic susceptibility. That claim is based on the fact that ibuprofen could have a protective effect against atopic diseases (Varner et al. 1998). Finally, paracetamol can lead to asthmatic inflammation by lowering glutathione level, which impairs the antioxidant defences (Rahman and MacNee 2000) and triggers inflammation through disruption of Th1-Th2 cytokine responses (Dimova et al. 2005).

'Hygiene hypothesis' (Strachan 1989) combined with 'antioxidant hypothesis' (Soutar et al. 1997) propose that decreased exposure to microbes and diet changes in the last decades (lower intake of antioxidants) could be responsible for a rapid increase in asthma prevalence in industrialized countries. Others also believe that administration of antibiotics early in life has a destructive effect on microflora, preventing the immunological system from correct maturation (Verhulst et al. 2008).

Despite the evidence from epidemiological studies, prospective research on the subject is less consistent. A birth cohort study including 16,933 6–7-year-olds from Italy analyzed the association between antibiotic and paracetamol use and asthma symptoms, using the ISAAC questionnaire. The focus was on two different phenotypes of asthma: early (first 2 years of life) and late onset of wheezing (during the last 12 months). A positive association has been confirmed only with the former (Rusconi et al. 2011), which is explained by the fact that early wheeze caused by viral infection is often misdiagnosed as asthma or allergy, and treated with paracetamol and antibiotics. Another cohort study of 198 children at high atopic risk also questions the true association between paracetamol and antibiotic use and asthma symptoms (Kusel et al. 2008). The authors reported that children who are given antibiotics in the first year of life have over twice the odds for asthma diagnosis, but this association became insignificant after adjustments for antibiotic predictor score, sex, first year pets, childcare, and general practitioner visits.

The above-mentioned inconsistencies are most frequently explained by 'reverse causation'. According to this assumption, children with respiratory disorders, including asthma, are more likely to be prescribed antibiotics and paracetamol (Kummeling and Thijs 2008). Following this reasoning, intake of drugs is a consequence rather than cause of atopic diseases. Conflicting results may be due also to another confounder – 'indication'. In infancy it is difficult to distinguish the allergic from viral or bacterial infection symptoms, which all are treated by paracetamol and antibiotics, and those infections could be a real underlying trigger for further development of asthma and allergies (Kummeling and Thijs 2008). However, studies on *in utero* exposure to paracetamol demonstrate increased risk of wheezing in children whose mothers received the drug, and such results are devoid of the 'indication' confounder (Bakkeheim et al. 2011).

5 Conclusions

Although the cross-sectional studies are prone to bias due to the lack of chronological information about the dosage and onset of symptoms, a strong association between early administration of antibiotics and paracetamol should not be

ignored. Further investigation should be focused on different phenotypes and epigenetic character of these associations. Unnecessary exposure to paracetamol and antibiotics, especially in infancy, should be avoided.

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Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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Prevalence of asthma and rhinitis symptoms among children living in Coimbra, Portugal.

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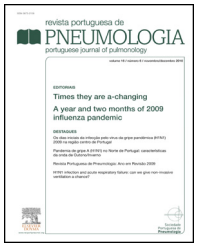

BRIEF COMMUNICATION

Prevalence of asthma and rhinitis symptoms among children living in Coimbra, Portugal

Prevalência dos sintomas de asma e rinite nas crianças a viver em Coimbra, Portugal

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Asthma is the most common chronic disease in pediatrics. Most data on the prevalence of childhood allergic diseases come from the International Study of Asthma and Allergies in Childhood (ISAAC) phase II held in 1995 and phase III from 2002. ISAAC created a methodology for studying two age groups 6–7 and 13–14 years old.[1] In 2002, according to the data gathered in the phase III of ISAAC, the prevalence of asthma among Portuguese children from 6 to 7 years old was 9.4%, 29.1% for rhinitis and 28.1% for wheezing.[2]

In the last decade, little information on the prevalence of childhood asthma and rhinitis in Portugal has been documented, and to the best of our knowledge, none in Coimbra. In 2002, 5 centers from 5 Portuguese cities joined the ISAAC project: Lisbon, Oporto, Coimbra, Portimão and Funchal. The Coimbra research center only studied 13–14 years old adolescents.[2]

The district of Coimbra, with a total area of 3974 km^2, is located in central Portugal and has 434,311 inhabitants. Coimbra is the biggest city in the central region, and the 6th largest in Portugal.[3]

The most recent published data on childhood asthma prevalence in Portugal come from the Lisbon 2008 study where the prevalence of asthma, allergic rhinitis and wheezing was 5.6%, 43.0% and 43.3%, respectively,[4] and from Matosinhos (data from 2009) where the prevalence of asthma among the children 0–7 years old was 9.56%.[5] A large national prevalence study based on The Portuguese National Asthma Survey reported the prevalence of 6.2% of current asthma for the Central region and 7.2% for the age group <18 years in the whole country.[6]

The objective of this study was to assess the prevalence of asthma and rhinitis in the population of 6–8 years old children from the district of Coimbra.

ISAAC based core asthma and rhinitis questionnaires, containing questions about the prevalence and frequency of asthma and rhinoconjunctivitis symptoms of a child in the past 12 months and in a lifetime, were handed into the legal guardians of children in the 1st and 2nd grades of primary school in Coimbra. The Estimated number of children from the 1st and 2nd grade in the Coimbra district was 8200 (National Census 2011). The sample size was calculated based on the confidence interval of 95%, prevalence of 10%[2] and for the narrow margin of error of 2% that a sample of 782 individuals would be enough.

The response rate was 65% ($N = 1063$) and there was no significant difference between the private vs public schools ($p = 0.88$) as well as so among the urban, suburban and rural zones ($p = 0.42$). After excluding children with chronic disease as opposed to atopic, a sample of 1037 children from 32 schools (28 public and 4 private) in the Coimbra district were included in the analysis, 50.8% were girls and 49.2% boys (95%CI 45.9–52.0), the mean age was 7.26 years old

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Table 1 Prevalence of asthma and rhinitis symptoms among 6–7 year old Portuguese children living in the district of Coimbra in 2012 estimated using the ISAAC tools in comparison to the data from Portuguese cities from 2002 obtained within the ISAAC phase III.

	Portugal 6–7 (2002)	Portugal 13–14 (2002)	Coimbra 6–7 (2012)	Coimbra 13–14 (2002)	Oporto 6–7 (2002)	Oporto 13–14 (2002)	Lisbon 6–7 (2002)	Lisbon 13–14 (2002)	Portimão 6–7 (2002)	Portimão 13–14 (2002)	Funchal 6–7 (2002)	Funchal 13–14 (2002)
	Prevalence % (n)											
Total *n*			**1037**	**1177**	**2464**	**3336**	**2477**	**3024**	**1069**	**1109**	**1819**	**3161**
Wheeze ever	28.1 (1512)	21.8 (2576)	34.4 (347)	20.6 (242)	10.0 (246)	22.1 (736)	30.2 (748)	25.9 (784)	28.4 (304)	18.2 (202)	25.3 (460)	19.4 (612)
Wheeze in the past 12 months	12.9 (692)	11.8 (1398)	11.9 (120)	10.7 (126)	2.3 (56)	13.1 (437)	14.2 (351)	14.6 (443)	13.2 (141)	9.7 (108)	11.0 (200)	9.0 (284)
4 or more attacks of wheeze in the past 12 months			3.1 (31)	2.6 (31)	2.7 (67)	2.6 (87)	3.4 (83)	3.5 (105)	2.5 (27)	2.2 (24)	2.1 (38)	1.9 (60)
Sleep disturbance from wheeze, 1 or more nights a week in the past 12 months			2.2 (22)	1.0 (12)	2.5 (61)	1.5 (51)	3.4 (84)	2.1 (62)	3.6 (38)	1.8 (20)	4.1 (74)	1.5 (46)
Speech limited by wheeze in the past 12 months			1.9 (19)	2.2 (26)	10.0 (247)	2.8 (95)	2.9 (72)	3.5 (107)	2.1 (22)	2.1 (23)	3.3 (60)	2.7 (84)
Asthma ever	9.4 (505)	14.7 (1737)	10.6 (107)	12.2 (144)	5.7 (140)	15.1 (504)	7.8 (194)	15.6 (472)	4.9 (52)	12.4 (138)	14.2 (259)	15.2 (479)
Wheeze during or after exercise in the past 12 months			6.4 (65)	19.5 (229)	30.8 (759)	21.0 (701)	7.1 (176)	24.8 (751)	5.5 (59)	18.2 (202)	7.0 (117)	21.2 (670)
Night cough in the past 12 months			24.2 (245)	30.5 (359)	26.1 (644)	32.9 (1097)	32.7 (809)	35.4 (1070)	29.4 (314)	31.4 (348)	32.9 (599)	34.1 (1079)
Nose symptoms ever	29.1 (1565)	37.1 (4383)	23.1 (234)	31.8 (374)	22.1 (544)	41.8 (1394)	31.2 (774)	39.7 (1202)	28.0 (299)	34.4 (382)	27.0 (492)	32.6 (1031)
Nose symptoms in the past 12 months	24 (1291)	26.5 (3131)	19.7 (199)	23.9 (281)	7.5 (186)	31.7 (1056)	26.3 (651)	29.0 (878)	23.1 (247)	21.7 (241)	21.6 (393)	21.4 (675)
Nose and eye symptoms in the past 12 months			9.3 (94)	6.5 (76)	0.7 (18)	10.3 (344)	10.1 (249)	10.6 (320)	8.2 (88)	7.2 (80)	9.4 (171)	8.9 (280)
Nose symptoms affecting activities a lot in the past 12 months			1.6 (3)	0.3 (3)	2.7 (67)	0.5 (18)	1.0 (25)	0.6 (17)	0.9 (10)	0.2 (2)	1.5 (28)	1.1 (36)
Hayfever ever	4.2 (227)	7.5 (134)	1 (10)	14.0 (165)	7.4 (182)	5.0 (168)	2.7 (67)	6.4 (194)	3.6 (38)	7.3 (81)	6.7 (122)	8.7 (275)
Symptoms of rhino conjunctivitis in the past 12 months			18.4 (186)	6.5 (76)	16.8 (413)	10.3 (342)	10.0 (247)	10.5 (317)	7.9 (84)	7.1 (79)	9.2 (167)	8.7 (276)

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(95%CI 7.22–7.30). As the attendance of children from urban zones was higher than expected (72% compared to 57% for the district[3]) we applied the post-stratification weights for the zone type. At least one episode of asthma in a lifetime was reported in 10.4% of the studied population (95%CI 8.6–12.3). At least one wheezing episode was experienced by 35.2% (95%CI 32.3–38.2) of the studied children and 11.8% (95%CI 9.8–13.8) had at least one attack within the past 12 months. Prevalence of lifetime rhinitis and current rhinitis was 22.8 (95%CI 20.2–25.4) and 19.4 (95%CI 17.0–21.9) respectively. In our study, the prevalence of lifetime asthma was 10.4% (95%CI 8.6–12.3) which is slightly higher than the national prevalence recorded in 2002 (9.4%) and higher than most cities in 2002 with the exception of Funchal (14.2%).

The national prevalence of wheezing in children aged 6–7 years old measured using the ISAAC tools in a lifetime in 2002 was 28.1%. Our study revealed a very high prevalence of wheezing episodes at least once in child's life, 35.2% (95%CI 32.3–38.2). This is not only higher than all of the values reported in 6–7 year old children in 2002, but also higher than all of the adolescent prevalence.[2] Although the prevalence could be biased by the understanding of the term ''wheeze'' (in Portuguese ''pieira''), which differs between the health specialists and parents,[7] it is unlikely as the methodology used in all the studies was the same. There is no reason to think that the common understanding of this term could change significantly over a decade. With the lack of data from Coimbra center on our age group from both 1995 and 2002, and the 10 years interval between the studies, we cannot be sure if the prevalence increased during this period, or if Coimbra indeed has a higher prevalence of lifetime wheezing than other Portuguese cities.

In Lisbon, where a group of 342 students between 5 and 12 years of age participated in a study, the lifetime asthma rate was lower than in the phase III of ISAAC study (5.6% compared to 7.8% in the phase III); however wheezing episodes occurring at least once in a lifetime were reported in 13.1% more children than in 2002.[4] These results suggest that the wheeze prevalence could indeed be increasing among Portuguese children.

The prevalence comparisons between our study and data gathered during the phase III of ISAAC in Portugal are presented in Table 1.

It has been estimated that, in Portugal, we can expect 20,250 new cases of asthma annually.[8] Asthma and allergic diseases continue to be a global health concern, and Portugal does not seem to be an exception.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study received sufficient information and gave their written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Conflicts of interest

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