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Inês Ribeiro Paciência

Association between sleep duration and blood pressure in adolescence

Porto - 2012

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Dissertação de candidatura ao grau de Mestre em Saúde Pública, apresentada à Faculdade de Medicina e ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto

Esta investigação foi realizada no Departamento de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública da Faculdade de Medicina da Universidade do Porto e no Instituto de Saúde Pública da Universidade do Porto, sob a orientação da Professora Doutora Elisabete Ramos, Professora Auxiliar na Faculdade de Medicina da Universidade do Porto.

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Esta dissertação teve por base dois manuscritos, apresentados na secção de resultados. Para a elaboração dos mesmos fui responsável pela análise dos dados e pela redacção da versão inicial.

- *Association between sleep duration during weekdays and blood pressure in adolescents*

- *Sleep duration and blood pressure: a longitudinal analysis from early to late adolescence*

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ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
BDI	Beck Depression Inventory
BMI	Body mass index
BP	Blood pressure
CDC	Centres for Disease Control and Prevention
CI	Confidence intervals
CVD	Cardiovascular diseases
DALYs	Disability adjusted life years
DBP	Diastolic blood pressure
EPITeen	Epidemiological Health Investigation of Teenagers in Porto
FFQ	Food frequency questionnaire
HSE	Health Survey for England
HR	Hazard Ratio
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socioeconomic status
SPSS	Statistical Package for the Social Sciences
THIN	Health Improvement Network

RESUMO

Introdução: A hipertensão é um problema de saúde com elevada prevalência em adultos. Nos últimos anos tem se observado um aumento na prevalência de hipertensão também entre os adolescentes. Durante o mesmo período, a duração do sono nos adolescentes tem diminuído, principalmente devido ao aumento do tempo dispendido em actividades extracurriculares e sociais.

Com o objectivo de identificar factores de risco modificáveis no desenvolvimento de pressão arterial elevada em adolescentes, diversos estudos avaliam o papel da dieta e da actividade física. No entanto, nos últimos anos o papel de outros factores de risco, como a duração do sono, particularmente a sua restrição, ganhou relevância. Vários estudos encontraram a curta duração do sono como determinante de hipertensão na infância e na idade adulta. No entanto, na adolescência, a associação entre a duração do sono e a pressão arterial não é clara, embora alguns estudos tenham encontrado uma associação inversa, outros não.

Objectivos: Avaliar a associação entre a duração do sono ao longo da adolescência e a pressão arterial aos 13 e 17 anos, através de uma abordagem transversal e longitudinal.

Métodos: A investigação foi realizada no âmbito da Coorte EPITeen (*Epidemiological Health Investigation of Teenagers in Porto*). O EPITeen é uma coorte de base populacional de adolescentes nascidos em 1990, que foram recrutados de escolas públicas e privadas da cidade do Porto no ano lectivo 2003/2004 (proporção de participação de 77,5%). No primeiro *follow*-up de avaliação da coorte, que decorreu no ano lectivo 2007/2008, 79,4% dos participantes foram reavaliados.

Nas duas avaliações, a informação foi recolhida através de dois questionários auto-aplicados, recolhendo informação sobre história individual ou familiar de doenças e características sociais, demográficas e comportamentais. A duração do sono foi obtida através do questionário e estimada pelas horas de deitar e de levantar reportadas. Foi realizado também um exame físico, e a pressão arterial foi medida com um esfignomanometro de mercúrio pelo método auscultatório e a hipertensão foi definida de acordo com os critérios da American Academy of Pediatrics.

Para avaliar a associação entre a duração do sono e a pressão arterial aos 13 anos foi estimado o odds *ratio* (OR) e respectivos intervalos de confiança a 95% (IC 95%), calculados através de modelos de regressão logística. Os coeficientes de regressão (β) e IC 95% foram estimados para avaliar a associação entre a duração do sono aos

13 anos e os níveis de pressão aos 17 anos. Todas as análises foram estratificadas por género e ajustadas para potenciais confundidores.

Resultados: A média (DP) de duração do sono aos 13 anos foi de 9.0 (0.80) horas por dia e diminuiu em média -0.77 (1.25) horas aos 17 anos. A diminuição foi maior nos rapazes comparativamente às raparigas.
A prevalência de pressão arterial elevada (PAS ou PAD superior ao percentil 90 para o género, idade e altura) aos 13 anos foi de 32.5% e diminui para 21.8% aos 17 anos. Em ambas as avaliações a prevalência de pressão arterial elevada (PAS ou PAD superior ao percentil 90 para o género, idade e altura) foi maior nos rapazes, 35,3% vs 30,1% aos 13 anos e 26,0% vs 18.1% aos 17 anos.
Na análise transversal, aos 13 anos, após ajuste, observou-se um maior odds de pressão arterial elevada com a maior duração de sono. O odds (IC 95%) de pressão arterial elevada foi de 1,56 (1,07-2,27) nas raparigas que dormiam entre 8,5 e 9,5 horas por dia e de 1,83 (1,23-2,70) naquelas que dormiam 9,5 ou mais horas, comparando com as raparigas que dormiam 8,5 ou menos horas. Aos 17 anos, observou-se uma associação positiva entre a duração do sono e pressão arterial sistólica significativa apenas nas raparigas (β=0.70, IC 95% 0.02-1.37). Nos rapazes, não foi encontrada associação significativa entre a duração do sono e a pressão arterial. Na análise longitudinal, não foi encontrada associação significativa entre a duração do sono e a pressão arterial nas raparigas. No entanto, nos rapazes, foi encontrada uma associação inversa entre a duração do sono e pressão arterial sistólica (β=-1.95, IC 95% -3.16 – -0.74).

Conclusão: No geral, a duração do sono e a prevalência de pressão arterial elevada nos adolescentes diminuiu dos 13 para os 17 anos de idade, em ambos os géneros.
Na análise transversal, a duração do sono associou-se positivamente com a pressão arterial, apenas nas raparigas. Na análise longitudinal, não foi encontrada associação entre a duração do sono aos 13 anos e a pressão arterial aos 17 anos nas raparigas, mas uma associação inversa foi encontrada entre a duração do sono e a pressão arterial sistólica, nos rapazes. Os resultados indicam que a duração do papel pode ter um papel na etiologia da hipertensão na adolescência.

ABSTRACT

Introduction: Hypertension is a health problem with high prevalence in adults. Over the last years it has been observed an increase in hypertension prevalence also among adolescents. During the same period, sleep duration in adolescents has decreased, mainly due to increased time spent in extracurricular and social activities.
In order to identify modifiable risk factors for BP in adolescents, several studies have focused their research on the role of diet and physical activity. However, in the last years the role of other factors such as sleep duration, particularly its restrictions, has gained attention. Several studies have found short sleep duration as a risk factor for hypertension in childhood and adulthood. However, in adolescence, the association between sleep duration and BP still unclear, while some studies found an inverse association and others found no association.

Aims: Evaluate the association between sleep duration throughout adolescence and blood pressure at 13 and 17 years of age, using both cross-sectional and longitudinal approach.

Methods: Eligible participants were urban adolescents, members of the Epidemiological Health Investigation of Teenagers in Porto (EPITeen). The EpiTeen is a population-based cohort of adolescents born in 1990, which were recruited from private or public schools in Porto in the 2003/2004 school year (78% participation at the individual level). In the first follow-up evaluation of the cohort, held in 2007/2008, 79.4% of the participants could be re-evaluated.
At both evaluations, data were collected using self-administered questionnaires, comprising information on individual and family history of disease, and social, demographic and behavioural characteristics. Sleep duration was obtained by questionnaire and was estimated by usual bedtimes and wake-up times. A physical examination was also performed, and blood pressure (BP) was measured with a mercury sphygmomanometer using the auscultatory method, and hypertension was defined according to the American Academy of Pediatrics criteria.
To evaluate the cross-sectional association between sleep duration and BP at 13-year-old, odds ratio (OR) and respective 95% confidence intervals (95% CI), were computed, using logistic regression models. Regression coefficients (β) and 95% CI were used to estimate the association between sleep at 13 years old and BP levels at 17 years old. All analyzes were stratified by gender and adjusted for potential confounders.

Results: The mean (SD) of sleep duration at 13 years of age was 9.0 (0.80) hours per day and decrease on average -0.77 (1.25) at 17 years of age. The decrease was higher in males than in females.

The prevalence of high blood pressure (SBP or DBP above the 90th percentile for sex, age and height) at baseline was 32.5% and decreased to 21.8% at follow-up. In both evaluations the high blood pressure (SBP or DBP above the 90th percentile for sex, age and height) prevalence was higher among males than in females, 35.3% vs. 30.1% at 13-year-old and 26.0% vs. 18.1% at 17-year-old.

In cross-sectional approach, at 13 years old, after adjustment, it was observed an increased odds of high blood pressure with long sleep duration. The odds (95% CI) of high blood pressure was 1.56 (1.07-2.27) among females sleeping more than 8.5h and lower than 9.5h per day and 1.83 (1.23-2.70) among those sleeping 9.5h or more, compared with those sleeping 8.5h or less. At 17 years old, it was observed a positive association between sleep duration and systolic blood pressure (SBP) significant only in females (β=0.70, 95% CI 0.02-1.37). Among males, no significant association was found between sleep duration and BP. In longitudinal approach, no significant association was found between sleep duration and BP levels in females. However, in males, an inverse association was found between sleep duration and SBP (β=-1.95, 95% CI -3.16 – -0.74).

Conclusion: In general, sleep duration and prevalence of high blood pressure in adolescents decreased from 13 to 17 years of age in both genders.

In cross-sectional approach, sleep duration was positively associated with BP, only among females. In longitudinal approach, no significant association was found between sleep duration at 13-years-old and BP levels at 17-years-old in females, but an inverse association was found between sleep duration and SBP, in males. These results suggest that sleep duration could play a role in the etiology of hypertension in adolescents.

ADOLESCENCE

Adolescence is the transitional period from childhood to adulthood and includes individuals aged between 10 and 19 years (1). This developmental period is characterized by many physiological, physical and biological changes, including major alterations in endocrine activity (2). A biological hallmark is the maturation of several endocrine systems, such as hypothalamus-pituitary-gonad axis resulting in increased release of sex steroids (3) from the gonads, adolescent growth spurt, skeletal changes (e.g. increase in hip width, in females) and increase in muscle and fat tissue (2).

Adolescence starts with puberty, during this period occurs a rapid biological changes in body size, shape and composition. On average females enter and complete each stage of puberty earlier (begins between 8 and 14 years) than males (begins between 9 and 15 years), although there is considerable individual variation in the development and maturation time line (2).

Adolescence is also characterized by changes regarding personal identity, including recognition of moral and ethical values and feelings of self-esteem (4), increase in group interactions and thus social behaviors (5) and affirmation in autonomous control over decisions, actions and emotions (6).

Behaviors and lifestyles developed during adolescence can influence behaviors and health in adulthood. So, although adolescence is in general a healthy period, adolescence is a period in life that presents specific health concerns and needs.

BLOOD PRESSURE

HIGH BLOOD PRESSURE IN ADULTS

Hypertension is a public health problem, once it is a chronic disease with high prevalence in developed countries, approximately 20% of middle-age population has high blood pressure, and it is associated with the occurrence of several diseases, namely cardiovascular diseases (CVD) (7-10), such as stroke, heart failure and peripheral vascular disease (11), premature mortality (9, 11-13) and also with a decrease in total life expectancy and life expectancy free of CVD, in both genders (14). Its high prevalence and strong association with the occurrence of several diseases, allow that worldwide 7 million deaths are attributed each year to high blood pressure (15).

Overall, 26.4% (95% CI 26.0-26.8) of the world's adult population in 2000 had hypertension (16).

Based on data from NHANES hypertension prevalence decreased between 1960 and 1991 (7). But this favorable trend does not happen in 1999, according to the Behavioral Risk Factor Surveillance System, self-reported hypertension was 24.9% in 1999 compared with 22.9% in 1991 (17). In the USA the prevalence of hypertension in adults, between 1999 and 2000, was 29% and the number has been increasing over the past decade, even with the advance in knowledge, treatment and disease control. According to data collected between 2005 and 2008 by Centres for Disease Control and Prevention (CDC) and NHANES, the overall prevalence of hypertension among persons aged ≥18 years was 29.9% (18) and it was higher among older, 33%–34% of men and women 45–54 years of age had hypertension, compared with 67% of men and 80% of women 75 years of age and over (19).

The prevalence of hypertension for the European was 44.2% compared with 27.6% in North America. The highest prevalence was in Germany (55%), followed by Finland (49%), Spain (47%), England (42%), Sweden (38%) and lower in Italy (38%) (20).

Others studies in European countries also reported a higher prevalence of hypertension in both genders. The highest prevalence was found among adult Greece population, it was reported 40.2% for men and 38.9% for women hypertension prevalence (21). Higher hypertension prevalence was also reported by other studies,

as in northeastern Spain (22) and in eastern Poland (23) whose prevalence was 39.1% and 39.42%, respectively; higher values of hypertension prevalence were reported among Polish females (41.70%) compared to males (35.77%). In French working women and men, the prevalence of hypertension was lower compared to other European countries - 9% and 16%, respectively (24).

Some studies across Europe have described differences in trend of hypertension prevalence. In Swiss adults the prevalence of hypertension has increased in the last years, the prevalence increased between 1997 (22.1%), 2002 (3.7%) and 2007 (24.2%). This increase could be due to an increase in true prevalence of hypertension, to a more widespread screening, decrease in the thresholds to define hypertension from ≥160/95 mmHg in 1993 to ≥140/90 mmHg afterwards and due to an increase in overweight and obesity prevalence (25).

As it was reported in Switzerland in Copenhagen, in adults aged 20 years and above, systolic and diastolic blood pressure increased between the first (1976-1978), 134.1±20.0 and 81.1±11.5 mmHg, and the second evaluation (1981-1983), 137.5±20.50 and 82.5±11.71 mmHg. However, from the second examinations a tendency of systolic blood pressure (SBP) and diastolic blood pressure (DBP) to decrease was observed – in survey 3 (1992-1994) the values for SBP were 135.2±20.96 and for DBP were 82.4±11.57 mmHg and in survey 4 (2001-2004) the values for SBP and DBP were 134.1±21.82 and 78.0±11.61 mmHg, respectively (26). In United Kingdom a decrease in the prevalence of hypertension was also reported, Thomas et al. describe the prevalence based on The Health Improvement Network (THIN) and on The Health Survey for England (HSE) and found that the overall prevalence of hypertension was lower in the 2003 HSE (32.9%) than in 1998 HSE (37.3%), in THIN population the prevalence of hypertension was 25.3% in 1998, 27.8% in 2003 and 26.9% in 2006 (27). Unlike previous studies that showed a trend in hypertension prevalence, in north-eastern Spain in adults aged 35-74 years, the authors reported a decrease in blood pressure, however the systolic and diastolic blood pressure were similar in the three assessments: in 1995 the SBP was 120 mmHg and DBP was 76mmHg in females and 131mmHg and 8mmHg in males, in 2000 the values of SBP and DBP was 125mmHg and 77mmHg and 134mmHg and 82mmHg in females and males, respectively, in 2005 the values of SBP was 122 mmHg in females and 128mmHg in males and DBP was 77mmHg and 80mmHg in females and in males (22).

There is evidence that antihypertensive treatment significantly decreases cardiovascular morbidity and mortality, however the proportion of hypertensive patients whose blood pressure is adequately controlled is relatively low (28). The increase in awareness of hypertension and associated risks is accompanied by an increase in the proportion of individuals with hypertension who receive treatment and in disease control (29). In USA (2005-2006), data from NHANES reported that 78% of hypertensive patients were aware of their condition, 68% were under treatment and that the prevalence of hypertension treatment increased with age and 64% of hypertensive patients who were treated had successfully controlled blood pressure (30).

The diverse European countries present different rates of awareness, treatment and control of hypertension. Greece was the country with the highest hypertension prevalence, and also the highest values of awareness (89.8%) and treatment (89.1%). However, compared to USA some European countries revealed a low rate of blood pressure control, such as Greece (15.2%) (21), Hungary (15%) (28), France (12.5%) (24) and Austria (10%) (28).

In Portugal, several studies estimate the prevalence and distribution of hypertension in adult population. The prevalence of hypertension observed in the different studies was high, ranges from 39%–57%, but similar to what was found in other European countries. Between 2001 and 2003, in adult population of Porto, blood pressure were evaluated twice, and the estimated hypertension prevalence was 56.3% (9% CI 52.7-60.0) and a higher value was measured in the first visit (63.4% vs. 60.2%) (31). In 2003, a cross-sectional study of a representative sample of the Portuguese population, aged 18 to 90 years, found that 42.1% of Portuguese had hypertension, and it was higher in men (49.5%) than in women (38.9%), although this difference is less marked in older age-groups (32).

A recent cross-sectional study of adults resident in mainland Portugal and the islands of Madeira and Azores treated at primary health care centers carried out between 2006 and 2007 found a prevalence of hypertension similar to the 2003 study, the prevalence was 42.62%. More recently, Machado et al. (2008) evaluated the prevalence in 900 residents in Porto, aged above 40 years (33). The prevalence of hypertension was 39.67% (95% CI 36.46-42.87), lower than what was found by Figueiredo et al. (2001-2003) in Porto (56.3%) (31), but similar to what was found by Macedo et al. in the northern region of Portugal (37.8%) (32).

Despite the high prevalence in Portugal, a cross-sectional that took place in 1999-2003 evaluated 2310 adults from Porto and found a low prevalence of awareness

(58.9% among females and 41.3% among males), treatment (71.7% among females and 60.2% among males) and control (23.0% and 22.8% among females and males respectively) of hypertension, (34). In 2003, using a representative national sample, an even worse profile was found,, only 46.1% of hypertensive patients were aware of their condition, 39.0% were treated and 11.2% had their blood pressure controlled (<140/90mmHg). Similar results were observed between 2006 and 2007 regarding to treatment, 47.62%, 36.16% and 16.22% hypertensive patients were under treatment receiving one, two, three or more drug classes, respectively (35).

Despite the 7.6 million premature deaths and 92 million disability-adjusted life years (DALYs) attributed to high blood pressure, observed in 2001 worldwide, with a highest distribution in eastern Europe and east Asia and the Pacific and among older (36); the total burden of hypertension increased by 30% from 1999 to 2000 compared with 1988 to 1994 in USA, the higher hypertension burden may reflect an increasing in hypertensive population who live longer as a result of healthy lifestyles and greater knowledge, treatment and control of hypertension related to effectiveness and quality improvement of health services and medical care (37).

Considering the increasing of prevalence and the greatest number of years with hypertension, it is important reinforce that even treated and controlled, those patients remain in risk for several diseases and also may have their quality of life affected. People who have any chronic disease show poorer physical and mental functioning compared with those who have no chronic diseases; each bad health condition contributes to decrease in quality of life (38). Adverse effects of treatment associated with hypertension, the number of years lived and hypertension-related diseases and simply being diagnosed with hypertension can decrease the quality of life of hypertensive population. Several studies show that people who had high blood pressure or who were on medication for high blood pressure score significantly lower than people without blood pressure (38, 39). Gusmão et al. demonstrated that hypertensive patients with no complications had a higher life quality compared with those with complications (40).

The increase in prevalence and treatment of hypertension represents also an increasing concern about the economic burden of hypertension. The American Heart Association recently reported the direct and indirect costs of high blood pressure as a primary diagnosis as $73.4 billion. At a community hospital in Buenos Aires, the cost associated to hypertension management program in middle-class patients 65 years or older was approximately $6,000. These estimates can reinforce the relevance of the

knowledge about the potential for prevention and provide an important input into health planning and other cost-utility decisions (36).

BLOOD PRESSURE TRACKING FROM ADOLESCENCE TO ADULTHOOD

Over the past decades, a large of longitudinal studies has been conducted to assess blood pressure tracking over time among early ages and adults (41, 42). Several studies have also revealed long-term persistent elevated blood pressure from adolescence into adulthood, and how the persistent elevation in blood pressure ultimately has developed into adult hypertension (43-45).

Data from 50 cohort studies shows a strong evidence for blood pressure tracking from childhood into adulthood. The reported blood pressure tracking correlation coefficients varied from -0.12 to 0.80 for SBP and from -0.16 to 0.70 for DBP. The results show that blood pressure tracking appears to increase with baseline age, compared to cohorts whose baseline ages were <5 years, those aged ≥15 years had a stronger tracking correlation (0.18 vs. 0.43 for SBP and 0.09 vs. 0.32 for DBP) (42).

In the Bogalusa Study, children who had high blood pressure were more likely to develop hypertension (3.6-fold for SBP and 2.6-fold for DBP) at the follow-up examination. Older age group (aged 10 to 14 years) were found to have stronger blood pressure tracking than those aged 5 to 9 years (45). Liang & Mi also reported that pubertal hypertension (OR=10.00, 95% CI 3.03-33.07) predicted a higher risk of adult hypertension than pre-pubertal hypertension (OR=2.71, 95% CI 0.83-8.85) and that 50% of adolescents with pre-hypertension or hypertension in puberty developed hypertension during adulthood, compared to 34.3% pre-pubertal hypertensive children (43).

The different studies reinforce the concept that blood pressure tracks from early life, namely from adolescence to adulthood and that elevated blood pressure in adolescence is likely to help predict adult hypertension. So it is important to diagnose and control blood pressure in children and adolescents and identify the determinants associated with hypertension to prevent the disease and its consequences in adults.

HIGH BLOOD PRESSURE IN ADOLESCENCE

Adolescence is a fast growth and maturation period during which blood pressure increases. Besides this physiologically expected change, high blood pressure is a increasingly common health problem, also in adolescents and is likely to become increasingly prevalent in younger ages, concomitant with the increase of obesity (11).

Between 1988 and 1999, the prevalence of pre-hypertension and hypertension increased by 2.3% and 1% respectively in children (46). Between the NHANES III and NHANES 1999-2000 levels of systolic and diastolic blood pressure increased on average by 1.4 mmHg and 3.3 mmHg, respectively, in children and adolescents from 8 to 17 years of age in USA (47). In a recent study Hansen et al. (48) reported that among 14 187 children and adolescents 3.6% were hypertensive and 3.4% were pre-hypertensive. Similar results regarding to hypertension prevalence were found in a sample of 6 790 adolescents (11-17 years) in Houston schools conducted from 2003 to 2005, the prevalence of hypertension was 3.2% and of pre-hypertension was 15.7% (49).

Across European countries the prevalence of hypertension at adolescence was higher than in USA, among 26 008 European children (aged 12±2.9 years) 35.4% had high DBP more often (50). The highest prevalence was found among Norwegian girls, of 16.6% of systolic hypertension and 0.4% of diastolic hypertension (51). Higher prevalence was also found in Italian adolescents, 11.8 % of them have systolic hypertension, while 6.9 % have diastolic hypertension (52). In 7 to 14-year-old Belgrade children high SBP was present in 4.7% of boys and in 5.3% of girls, high DBP was found in 5.6% of boys and in 4.8% of girls (53). Lower values were found among Belgian adolescents (15.8-19.6 years), 3% of girls and 5% of boys had systolic hypertension and diastolic hypertension was found in 5% of girls and in 1% of boys (54).

In Portugal, in a sample of adolescents aged 13 years, high prevalence of abnormal blood pressure was observed (22.0% of hypertension and 13.3% of pre-hypertension) (55). Lower values of hypertension prevalence were found in a sample of 1218 children and adolescents (12.98±3.12 years) - 9.8% and 18.2% had pre-hypertension from a study conducted in Central region of mainland Portugal (56). Another study, in a population of university students in Lisbon, aged between 18 and 25 years, found high prevalence of hypertension (24.9%) and high normal blood pressure (27.4%) (57).

In adolescence, hypertension is associated with an increased risk of cardiovascular disease, although not claim direct risk factor for cardiovascular events in childhood (10, 58-61). Currently, 20% of the adolescent population, in Houston, is at risk of developing cardiovascular diseases, which makes hypertension an essential concern in public health, so it is important to intervene and establish preventive measures (49).

RISK FACTORS FOR HIGH BLOOD PRESSURE

There are several factors that are recognize as risk factors regarding hypertension (62, 63) and many of them have been identified in development of high blood pressure among adolescents (64). These risk factors can be divided into two groups: non-modifiable risk factors, such as age, gender, ethnicity and genetic factors; and modifiable risk factors, as overweight, sedentary lifestyle, and diet.

One of the most important non-modifiable risk factor is age. Blood pressure tends to increase with age, this increase is due primarily to normal aging of the arteries, leading to loss of elasticity of their walls - arteriosclerosis and decreasing caliber of arteries (7, 65). Almost 62% (2/3) of the population with hypertension is 55 years-old and older (7, 63). According to National Center for Health Statistics the prevalence of hypertension increased from 7% among those aged 18-39 years to 67% among those aged 60 years and older.

During adolescence a tendency to a blood pressure rise was also observed (64), especially in the puberty. Some studies reported that the rate of change in blood pressure may be accelerate during this period, according to Shankar et al., the increases in blood pressure levels were higher among adolescents in puberty than either before or after this period (66). The data from the National Childhood Blood Pressure indicated that the rate of progression of pre-hypertension to hypertension in adolescence was approximately 7% per year (67).

Family history of hypertension also plays an important role in the pathogenesis of hypertension, and the prevalence of hypertension is higher among those with family history of hypertension. The relation between family history of hypertension and blood pressure has been demonstrated in several studies and this relation is the result of the sharing of genes and a common environment of the members of the same family (68). Fermino et al. verified that a significant part of blood pressure has a strong genetic components, 43 and 49% of the total variation in SBP and DBP was explained by genetic factors (69). Several studies observed that individuals with parental history of hypertension showed a significant elevation in blood pressure (64, 70), a positive association was found between hypertension and parental history of hypertension in adolescents (OR=8.6, 95% CI 3.51-20.59) (70) and in adults (OR=5.20, 95% CI 0.99-51.22) (71).

For a public health approach, modifiable risk factors, are particularly interesting because the intervention on those characteristics may allow the reduction in blood

pressure and in the incidence of hypertension (72). Most of studies have focused their research on the role of body mass index (BMI) (73), physical activity (54, 74) and food intake (75-77). Among the perinatal risk factors, birth weigh (78) and breastfeeding (79-81) are among the most frequently studied.

The relationship between BMI and blood pressure is well established. BMI has been associated with changes in blood pressure in a systematic review. A reduction of 7mmHg for DBP and 13mmHg for SBP pressure was observed after a weight loss of 11Kg. However, when it was observed a weight gain of 4Kg, diastolic and systolic blood pressure increased 2.2 and 6.1mmHg, respectively (73).

Physical inactivity contributes to increases in the incidence of hypertension. Among adolescents different results have been found regarding to association between physical activity and blood pressure. Nielsen et al. reported the importance of physical activity on blood pressure reduction and in interaction between BMI and fitness in relation to BP reduction, after adjustment, low physical fitness were associated with higher OR of hypertension in both genders (1.3 (95% CI 1.1-1.7) in boys and 1.5 (95% CI 1.3-1.8) in girls) (74). In a meta-analysis of 44 randomized interventions trials the changes of blood pressure in response to training (sports activities and physical exercise), after adjustment for the control observations, ranged from +9 to -20mmHg for systolic blood pressure and from +11 to -11mmHg for diastolic blood pressure. In addition, when normotensive and hypertensive subjects followed the same training program, the blood pressure decrease was greatest in the hypertensive subjects (54).

The potential effect of diet on blood pressure, beyond the effect resulting from overweight and obesity, has been also demonstrated. In Western populations high salt intake and low potassium intake was the major contributors to hypertension, low fish-fatty-acids intakes was also an important contributor in Netherlands (PAR=15%), UK (PAR=11%) and USA (PAR=16%), compared to Finland and Italy (75). The National Heart, Lung, and Blood Institute conducted two studies and their results suggested that blood pressure was reduced with a diet low in total and saturated fat and cholesterol, emphasizing the importance of fruits, vegetables, and fat-free products (82). These studies show the importance of healthy diet particularly of lowering sodium intake in adults. Similar results have been found among adolescents (76, 77, 83), reinforcing the role of diet in blood pressure at early ages and trough life.

Early life events, such as birth weight, play an important role in the development of hypertension.

A meta-analysis from 20 Nordic cohorts (197 954 participants) assessed the possible modification of the effect of birth weigh on SBP by age categories (7 categories - from 15 to 74 years of age) and found an inverse association between

birth weight and SBP. The association was stronger in older age groups and among females when birth weight was less than or equal to 4Kg. In younger males the birth weight and SBP association was estimated to be -0.75mmHg/kg and for each 10-year in age the association was estimated to be -0.26 mmHg/Kg; in females the birth weight and SBP association was estimated to be -1.74mmHg/kg and for each 10-year in age the association was estimated to be -0.53 mmHg/Kg (78). Low birth weight was also found as an independent predictor variable for adverse longitudinal trends in systolic blood pressure from childhood to adolescence (78).

Breastfeeding has been also analyzed as a potential risk factor for the development of hypertension in later life (79-81, 84). A review and meta-analysis involving 15 studies with 17 503 participants found lower values of blood pressure among breastfed subjects compared with bottle-fed infants with a larger effect on SBP (-1.4 mmHg, 95% CI -2.2;-0.6) than on DBP (-0.5 mmHg, 95% CI -0.9;-0.04) (79). Breastfeeding could influence blood pressure via a variety of mechanisms, including sodium intake restriction, increasing intake of long-chain polyunsaturated fatty acids, protecting against insulin resistance and through their protector effect on overweight (79).

However, in the last years the role of other factors such as sleep duration has gained attention (85-88).

SLEEP

SLEEP AND BLOOD PRESSURE IN ADULTHOOD

There is some consensus that, among adults, sleep duration plays an important role in blood pressure levels, being most studies based on data from patients with apnea but the idea that short sleep duration is associated with increasing values of blood pressure is becoming stronger, although not all studies point in that direction (89, 90). However, sleeping more than 9 hours per night has also been associated with an increased risk for morbidity and mortality (9).

Most studies revealed the existence of an inverse association between sleep duration and blood pressure levels or hypertension, nevertheless one of the major difficulties to compare results between studies became to the utilization of different cutoffs since no consensual cutoffs exits for sleep duration necessities.

In general, cross-sectional studies in middle-aged subjects (33-77 years) revealed significant associations between short sleep duration and high blood pressure or high prevalence of hypertension, two of these studies observed an inverse association only in women. Fewer studies have observed a higher blood pressure among long sleepers, one of them was reported a U-shaped association with sleep duration and blood pressure. The OR (95% CI) was 1.66 (1.35-2.04) for those reporting <6 hours sleep per night and 1.30 (1.04-1.62) for those reporting ≥9 hours per night compared to those sleeping 7-8 hours per night, even after adjustment for age, sex, race, apnea-hypopnea index and BMI. Some studies found no association between sleep duration and blood pressure among elderly adults, which suggest that associations between sleep duration and blood pressure may be modified by age (91, 92). Also longitudinal studies, has been shown short sleep duration to be associated with hypertension and significantly higher blood pressure in most studies. However, other studies found no association with sleep duration and hypertension (91, 92).

Studies based on experimental sleep deprivation have found that it leads to increased blood pressure (93, 94). However it is important to consider that, in these cases, the measurement of sleep duration was not performed in the usual participants' environment - one of the studies was performed in laboratory and the other in hospital, and consider the period of exposure assessment, usually short, that may be insufficient to evaluate exposure effect.

MECHANISMS

Different pathophysiologic mechanisms may explain the association between sleep duration and blood pressure, including endocrine and metabolic disorders (95-97), the sympathetic nervous system and hypothalamic-pituitary-adrenal axis activation (98, 99) and activity of the rennin-angiotensin-aldosterone system (94).

Circadian rhythms and sleep-wake cycle have influence on daily hormonal and metabolic changes, sleep restriction is associated with an elevation of sympathovagal balance, and most of endocrine organs respond to changes in sympathovagal balance, which can result in increase or decrease of hormones release and in metabolism change (100, 101).

Other mechanism that may be involved is the activation of sympathetic nervous system, which causes an increased synthesis of catecholamines and consequently an increase in blood pressure (102). Tochikubo, et al., found that increases in blood pressure were accompanied by increases in urinary excretion of noradrenaline, indicative of increased sympathetic nervous system activity (99). Sleep deprivation can also acts as a stressful stimulus (103) that is perceived by hypothalamic-pituitary-adrenal axis (major neuroendocrine mediator of stress response) and which induces the release of adrenocorticotropic hormone (ACTH), and ACTH subsequently initiates the liberation of glucocorticoids, such as cortisol (104). Higher cortisol levels have been associated to increased blood pressure and changes in metabolism functions (105).

The activation of rennin-angiotensin-aldosterone system is another potential way to explain the association between sleep duration and blood pressure (94, 106). The activation of this system causes an increased in rennin release, which catalyzes conversion of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II that is a potent vasoconstrictor and causes an increase in peripheral resistance, increasing blood pressure levels, angiotensin II also stimulate the release of aldosterone by the adrenal cortex. The increased release of aldosterone may have an effect on blood pressure levels by regulating sodium, potassium and body fluid balance, high concentrations of aldosterone induces an increase in sodium reabsorption, potassium excretion and water retention in the kidney, raising blood pressure (107).

Short sleep duration has also been associated with systemic inflammation, oxidative stress, and endothelial dysfunction (108, 109), all of these conditions favor the development of hypertension.

SLEEP IN ADOLESCENCE

Sleep duration is associated with several hormones that are involved in physiological changes that occur during puberty (110) which have an important role in the normal functioning of physiological mechanisms. Beyond age and puberty, gender is also associated with sleep duration. Several studies reported significant gender differences in adolescent sleep patterns, with females reporting longer sleep duration (111), there is evidence that puberty, and the fact that females start puberty earlier, may explain the longer sleep patterns of females (112).

Sleep duration, as an indicator of sleep needs, declines considerably from the newborn period to adulthood. Newborns typically sleep about 12-18 hours a day and decline to 7-9 hours in adults (113). Sleep during adolescence may be particularly important, since this phase is characterized by a fast biologic growth and development only overcome by the growth in the first year of life (114, 115).

Some studies have advanced reference values to sleep needs in children and adolescents (116, 117), but there is no recommended value for sleep duration (118).

The guidelines for sleep based on the recommendations of Witmans and Owens, included a period at least 10 hours of sleep per night for children between 8 and 11.9 years of age and 9 hours per night for adolescents between 12 and 17 years (119). The National Sleep Foundation defines hours for adolescents to be insufficient if <8 hours per night, borderline if 8 hours per night, and optimal if >9 hours per night (7).

However the magnitude of the decline varies from each study, it is consensual that from childhood to adolescence and throughout adolescence the total amount of sleep decreases (113, 118). A survey data show that the average total sleep time during the week decreased from 7 hours and 42 minutes at 13 years of age to 7 hours and 42 minutes at 19 years of age (111). A study reported that total sleep duration decreased from an average (SD) of 14.6 (1.4) hours at 1 year of age to an average of 10.1. (0.6) hours at 10 years of age (120). Iglowstein et al. also reported a decrease in total sleep duration from an average (SD) of 14.2 (1.9) hours at 6 months of age to an average of 8.1 (0.8) hours at 16 years of age. In addition, the variance showed the same declining trend, being the interquartile range of 2.5 hours at 6 months and 1.0 hours at 16 years of age (116). Similar results were found across European countries, sleep duration decreased by about 6 minutes, during childhood, with each year of age in all countries (121).

Many studies reported a decreasing in sleep duration among adolescents, with a strong trend for later bedtimes and earlier wake-up times on school days (111, 122-

125). Data from children aged 2 to 9 years from 8 European countries demonstrated that sleep duration differs significantly between countries within Europe, with children from northern Europe (Sweden, Germany, Belgium) showing longer sleep duration than children in southern (Italy, Spain, Cyprus) or eastern (Estonia, Hungary) Europe. Mean (SD) of sleep duration ranged from 9.5 (0.8) hours in Estonia to 11.2 (0.7) hours in Belgium (121). A study among 10- to 15-years-old South Australians identified declines in sleep duration on school days of approximately 30 min, over the last 20 years, this decline is almost due to later bedtimes (126). Many of USA adolescents not sleep enough, especially during the week, only 20% of adolescents had 9h of sleep on school nights, 45% sleep <8h (127) and 26% reported sleeping 6.5 hours or fewer hours on weekly period (111).

It is interesting to notice that, in USA, over 50% of adolescents recognize that they sleep less than they should to "feel their best", and 90% of parents believe their adolescents are getting sufficient sleep during the school week (127). School starting times and curricular activities are reported as major factors in restricting sleep (111, 128) and a significant oversleep at the weekends compared to weekday mornings (sleeping >2h later on weekend) (122). This extended sleep on weekends as a compensatory response to low sleep duration at weekday result in an inconsistent sleep schedule that can induce difficulties in falling asleep on weekdays. On the other hand, it is not kwon if the longer sleep duration on weekends minimizes the effects of short sleep duration on weekdays (122).

REASONS FOR SLEEP DEPRIVATION

For various reasons, sleep deprivation is increasingly common accompanying the social and environmental transformations (129). The adolescence period is also a period characterized by insufficient sleep whether by choice of life (imposed by family, time with friends, academic demands), social change (increased hours of television viewing, internet use), extracurricular activities (sports, music, and social clubs), decreased parental monitoring of bedtime and earlier school starting times that can result in later bedtimes (115, 122, 124, 125) or whether for physical or psychological problems (130).

Participation in extracurricular activities (including sports, music, and social clubs), jobs and academic demands compete for time during the day, resulting in later bedtimes (122). A hallmarks of the adolescence period is the increased freedom regarding parental control, including control over bedtime (131); Carskadon et al. report

that sleep deprivation results from later bedtimes as consequence of increased hours of television viewing and social activities (132).

Insufficient sleep duration also results from the interaction between biological (122, 133) and extrinsic factors (122). Zhdanova suggest that normal nightly melatonin secretion can play an important role in sleep regulation (134). Melatonin, which is secreted from the pineal gland during the night, transmits signals concerning light-dark cycles for the organization of seasonal and circadian rhythms (135) and when people are exposed to darkness, usually, precipitates sleepiness. The delayed release of melatonin found in adolescents causes a later onset of sleepiness, as well as a later natural wake time (122), and it was observed that older adolescents had a later phase of melatonin-secretion than younger adolescents (136).

Sleep duration in the general population decreased over the past 30 years (98, 137). In the USA, the National Sleep Foundation reported an increase of 12% to 16% of individuals who sleep less than 6 hours on working days between 1998 and 2005, most of which reflects a voluntary restriction of sleep (98). Sleep duration, in Western populations, have to been declining during the last century (138) in adults as well as in adolescents (139).

EFFECTS OF SLEEP DURATION ON ADOLESCENTS' HEALTH

Beyond the possible effect on blood pressure, sleep contributes significantly to several important cognitive functions and emotional performances (126, 140). Sleep affects our physical and mental health, and is essential for the normal functioning of all the systems of our body (141, 142).

In recent years, many studies reported sleep associated problems, in children and adolescents the prevalence of sleep problems have been estimated in 25% (143) and both excessive and insufficient sleep duration have been associated with health problems. However, a great number of adolescents are at risk for negative consequences of insufficient sleep rather than by excessive sleepiness.

Excessive sleepiness is associated with reduced in short-term memory and learning ability, low productivity, loss of some forms of behavioral control (140), as well as lower self-esteem and depressive symptoms (126). Less sleep duration is also associated to health problems, including academic difficulties, mood disturbances, and increases in risk-taking (115, 144, 145), daytime sleepiness, drowsy driving, headaches (146, 147), and increased cardiovascular morbidity (148, 149). However the role of sleep duration as risk factor for CVD remains unclear in this age group.

SLEEP AND BLOOD PRESSURE IN ADOLESCENCE

In childhood as in adulthood the association between sleep duration and blood pressure or hypertension is almost consensual. Some studies reported an association between short sleep duration and increased blood pressure (150-152).

In a cross-sectional study developed in Japan among children aged 5 and 6 years old the average SBP was significantly higher in children who have a longer duration of sleep (660 min.) compared to those who sleep less (≤ 585 min.); the total number of hours of sleep is significantly correlated with SBP (r =0.265, p =0.0039) but not with DBP (r =0.105, p =0.26) (150). Other study developed in children aged 7 years old it was also found an increased odds for blood pressure among those who sleep fewer hours, however the value of odds ratio found was not significant after adjustment to body weight or BMI (153). Similar to the studies described above, Nixon et al. found an increase in SBP in short sleepers, but this relationship did not hold after adjustment [OR=30.62 (95% CI=0.64-6.61)] (153).

In adolescence, the association between sleep duration and hypertension is less studied and unclear, while some studies found an association between short sleep duration and an increase in blood pressure (154), other study found a positive association between sleep duration and blood pressure (155) and others found no association (156, 157). In a cross-sectional study of adolescents aged 13-16 years short sleep duration was associated with 2.5-fold increase in the odds of developing high blood pressure or hypertension (154).

Guo et al. found short sleep duration (<8h) was a protective factor for hypertension among girls age 15 to 18 years, and there was a positive association between sleep duration and DBP among boys age 5 to 10 years. (155). However, recent cross-sectional studies found no association between sleep duration and blood pressure (159, 160), one considering short sleep duration less than 7 hours (156), and other assuming short sleepers as those who sleep <6h (157).

Thus, as sleep deprivation is a common phenomenon worldwide in modern society, generally as a consequence of bedtime restriction, and considering the higher prevalence of hypertension and their associated cost. Since, blood pressure in adolescence is associated with blood pressure in adults (41, 44), it is important to clarify the effect of this modifiable behavior at young ages to know the potential to prevent hypertension and its consequences later in life.

This research aimed to study the association between sleep duration during weekdays and blood pressure in adolescence, through the accomplishment of the following specific objectives:

1) Evaluate the association between sleep duration and blood pressure in 13-years-old adolescents;

2) Evaluate the association between sleep duration and blood pressure at early and late adolescence, using a cross-sectional and a longitudinal approach;

3) Describe sleep duration in 13 and 17-years-old adolescents.

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CHAPTERS

CHAPTER 1

Association between sleep duration during weekdays and blood pressure in adolescents

ABSTRACT

Background: In adults, sleep has shown an important role in cardiovascular risk factor. However in young adolescents the relation is unclear. The purpose of this cross-sectional study was to evaluate the association between sleep duration and blood pressure, at 13 years of age.

Methods: We evaluated 1771 adolescents at 13 years old as part of a population-based cohort study (EPITeen). Sleep duration was estimated by the difference between self-reported usual bedtimes and wake-up times and adolescents were classified in three categories: ≤8.5h (reference class), >8.5h and <9.5h and ≥9.5h. Blood pressure (BP) was measured with a mercury sphygmomanometer using the auscultatory method, and hypertension was defined according to the American Academy of Pediatrics criteria (≤90th percentile, between 90th percentile and 95th percentile and ≥95th percentile). To evaluate the association between BP and sleep duration, odds ratio (OR) and respective 95% confidence intervals (95% CI), were computed, using logistic regression models adjusted for body mass index (BMI) (model 1) and adjusted for caffeine intake and depressive symptoms in females and for caffeine intake and sports activities in males (model 2).

Results: The mean (SD) of sleep duration was 9.0 (0.80) hours per day. The prevalence of high BP (SBP or DBP above the 90th percentile for sex, age and height) was 32.5% and it was higher among males than in females (35.3% vs. 30.1%, *p*=0.019). In model 2, after adjustment, in females, a positive association was found between sleep duration and high BP (>8.5h and <9.5h: OR=1.56, 95% CI 1.07-2.27; ≥9.5h: OR=1.83, 95% CI 1.23-2.70). Among males, no significant association was found between sleep duration and BP.

Conclusion: Sleep duration was positively associated with the odds of high BP occurrence in both genders, although it was only significant in female adolescents, after adjustment for potential confounders.

INTRODUCTION

Hypertension is a increasingly common health problem in adults (1) and is likely to become increasingly prevalent at younger ages (2). Between 1988 and 1999, the prevalence of pre-hypertension (BP ≥ 90th percentile for height, age and sex) and hypertension (BP ≥ 95th percentile for height, age and sex) increased in U.S. children by 2.3% and 1% respectively (3).

Several non-modifiable (such as age and gender) and modifiable (such as obesity, sedentary lifestyle, and amounts of salt in the diet) risk factors can play a role in development of high BP in adolescents (4). In health promotion, the approach of modifiable risk factors is the most promising in terms of prevention.

Thus, several studies have focused their research on the role of food intake (1) and physical activity (5, 6) on BP. However, in the last years the role of other modifiable factors such as sleep duration has gained attention (7-10).

Different pathophysiology mechanisms may explain the association between sleep duration and BP. One important mechanism is related with the activity of the sympathetic nervous system, since sleep duration is associated with a sympathovagal balance, and most of endocrine organs respond to changes in such balance which might result in an increase or decrease of hormones release and in metabolism changes (11). Short sleep duration causes an elevated cortisol levels and an increase in BP (12) and an over activity of the renin-angiotensin-aldosterone system, endothelial dysfunction and renal impairment (8, 13).

The possible effect of sleep duration in BP becomes particularly relevant, since in the last 30 years a decrease in sleep duration in the general population was observed (14, 15), and sleep deprivation is a common phenomenon worldwide in modern society generally as a consequence of bedtime restriction (16). During adolescence, less parental control defining bedtime hour, increased school requirements and extracurricular activities, promote a reduction in sleep duration and increase the relevance of this behavior as determinant of BP values (17).

Several studies have found short sleep duration as a risk factor for hypertension in childhood (13, 18). However, in adolescence, the association between sleep duration and blood pressure is still unclear, while some studies found an inverse association (19), others reported no association (20, 21). As BP in adolescence is associated with BP in adults (22, 23), it is important to clarify the effect of this modifiable behavior at

young ages to know the potential to prevent hypertension and its consequences later in life.

The aim of this study was to evaluate the association between sleep duration and blood pressure in 13-year-old adolescents.

PARTICIPANTS AND METHODS

A cross-sectional study was developed as part of the Epidemiological Health Investigation of Teenagers in Porto (EPITeen). Eligible participants were adolescents born in 1990 and enrolled at public and private schools in Porto during the 2003/2004 school year, as previously mentioned (24). The ethics committee of Hospital S. João approved the study and informed consent was obtained from legal guardians of adolescents.

The evaluation included self-administered questionnaires, comprising information on social, demographic and behavioural characteristics and individual and family history of disease.

Information about sleep duration was estimated by the difference between usual bedtimes ("What time do you usually go to bed?") and wake-up times ("What time do you usually wake-up?"), regarding the weekdays and during school period.

Sleep duration was categorized into 3 classes: ≤8.5; >8.5 and <9.5; and ≥9.5 hours per day. Categorization was done according to the approximation to the tertiles of sleep duration.

The depressive symptomatology in adolescents was assessed by self-reported symptoms through the "Beck Depression Inventory II" (BDI-II) (25). The BDI-II is a 21-item self-report scale intended to assess the existence and severity of current (past two weeks) depressive symptoms. Each of the 21 items corresponding to a symptom of depression is summed to give a single score for the BDI-II. The total score can range from 0 to 63, in which higher scores reflect more severe depression. The BDI-II was previously validated in Portuguese adolescents population and 13 was the cut-off indicated to define adolescents presenting depressive problems (26).

As measure of physical activity we considered the practice of sports activities when the participant was engaged in some physical leisure time activity performed on a

repeated basis, spending at least 30 minutes a week and not included in the school curriculum.

Smoking habits and alcohol consumption in adolescents was assessed by self-administrated questionnaire. Adolescents were classified regarding their use of alcohol and their use of tobacco as never users, if they had never drank alcoholic drinks and if they have never smoked, and as drinkers or smokers, if they reported to use them or if they reported only to have experimented those substances.

The parental education level was measured as the number of successfully completed years of formal schooling and we classified the adolescents according to the parent with the higher education level.

Information about a medical diagnosis of hypertension was asked separately to the mother and the father. A family history of hypertension was considered present when at least one parent reported having been diagnosed with this condition.

A physical examination was also performed at school, by a team of experienced nurses, nutritionists and physicians. Weight and height were obtained with the subject in light indoor clothes and no shoes. Weight was measured in kilograms (Kg), to the nearest tenth, using a digital scale and height was measure in centimetres (cm), to the nearest tenth, using a portable stadiometer. In this study were considered 2 categories of BMI classified according to age- and sex-specific percentiles defined by the US Centres for Disease Control and Prevention (CDC) (27): $< 85^{th}$ percentile and $\geq 85^{th}$ percentile.

Blood pressure was measured, by trained doctors or nurses, in the right arm, based on the auscultatory measurements with a standard mercury sphygmomanometer, according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (3). Two measurements were performed after 10 minutes of rest, and calculated the average of both, if the difference between the two measurements was greater than 5 mm Hg a third measurement was performed and determined the average of the two closest measurements. Hypertension was defined according to the quantitative criteria of the American Academy of Pediatrics (5): pre- hypertension if SBP and/or DBP are above the 90^{th} percentile for sex, age and height and hypertension if SBP or DBP is above the 95^{th} percentile, but both below the 95^{th} percentile. To evaluate the association between sleep duration and BP, the categories pre-hypertension and hypertension were grouped into one category – high BP (SBP and/or DBP are above the 90^{th} percentile for sex, age and height).

Food intake was recorded using a food frequency questionnaire (FFQ) regarding the previous 12 months, completed by the adolescent at home with the help of their

parents or legal guardians. The FFQ was designed according to Willett and colleagues and adapted for the Portuguese population (28). The FFQ was then adapted for adolescents, including foods more frequently eaten by this age group, and the adolescents' version comprised 91 food items or beverage categories and a frequency section with nine possible responses ranging from never to six or more times per day. It also included an open-ended section for foods not listed in the questionnaire, but eaten at least once per week. To estimate caffeine intake from the evaluated food intake, the software Food Processor Plus (version 7, ESHA Research, Salem, OR, USA) based on values from the US Department of Agriculture was used. Caffeine intake was categorized according to the quartiles of intake into: ≤11.74; >11.74 and ≤23.61; >23.61 and ≤45.95; and >45.95 mg.

Among the participating schools, 2787 adolescents that were born in 1990 were registered. It was not possible to contact 44 of them, 584 did not return the signed informed consent form, and 2160 took part in at least some components of the study (77.5% participation). Among the 2160 participating adolescents, 126 adolescents (66 females) who had not been assessed for anthropometric measurements or blood pressure and 263 (102 females) adolescents who did not report data on sleep were not considered in this analysis. Thus, this study was based on the information of 1771 adolescents (948 females).

Compared with the 1771 adolescents included in this analysis, adolescents not included are mostly male than female (56.8% vs. 43.2%, $p< 0.001$) and had parents with a significant lower level of education. For the remaining variables (smoke, drink, sports activities and BMI) no significant differences were found between those included and those not included.

Statistical analysis

Shapiro-Wilk test was used to determine whether the outcome variables were normally distributed. To comparisons, we used the Kruskal-Wallis test for continuous and the Qui-square (χ^2) test to categorical variables. To evaluate the association between sleep duration and categories of BP, odds ratio (OR) and respective 95% confidence intervals (95% CI), were computed using unconditional logistic regression models, crude and adjusted for BMI (model 1) and for caffeine intake and BDI in females and for caffeine intake and sports activities in males (model 2).

All of the analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 18.0, and the level of statistical significance was set at 0.05.

RESULTS

The mean (standard deviation) of sleep duration was 9.0 (0.80) hours, being shorter in females 9.0 (0.82) hours than in males 9.1 (0.78), *p*=0.038. A total of 517 adolescents (29.2%) reported sleeping less than 8.5 hours per day, while 556 (31.4%) reported sleeping more than 9.5 hours. Regarding gender, sleeping less than 8 hours per day was reported by 122 (12.9%) females and by 81 (9.8%) males. Sleeping less than 7 hours was reported by 14 (1.5%) females and by 3 (0.4%) males.

The prevalence of high BP (SBP or DBP above the 90th percentile for sex, age and height) was 32.5% and it was higher among males than in females (35.3% vs. 30.1%, *p*=0.019). Among adolescents with family history of hypertension the percentage of females (34.4%) and males (41.4%) with high BP (SBP or DBP above the 90th percentile for sex, age and height) was higher than among those with no family history of hypertension (29.0% females and 34.8% males with high BP). However, the results were not statistically significant for both genders (*p*=0.243 in females and *p*=0.266 in males). High BP (SBP or DBP above the 90th percentile for sex, age and height) was significantly associated with BMI and alcohol consumption.

Among female adolescents, those who sleep ≤8.5 hours per day were less hypertensive, had parents with a higher level of education, drank more frequently alcoholic beverages, and were more likely to be depressed. We did not find significant differences in sleep duration according to family history of hypertension, smoke, sports activities, caffeine intake, BMI categories and age at menarche (table 1). Among males, we found differences on sleep duration regarding parents' education, sports activities and caffeine intake (table 2).

Table 3 displays the OR and 95% CI of high BP (SBP and/or DBP above the 90th percentile for sex, age and height) across categories of sleep duration by gender and adjusted for BMI (model 1); and for caffeine intake and BDI in females and for caffeine intake and sports activities in males (model 2). Compared with those who sleep ≤8.5 hours, females who sleep more have higher odds of high BP. After adjusting for BMI, caffeine intake and BDI, the magnitude of association increase and a dose-response effect was found [(OR=1.56 (95% CI 1.07-2.27) among those who sleep between 8.5h-9.5h and OR=1.83 (95% CI 1.23-2.70) among those who sleep ≥9.5 hours)]. Among males, despite there was a positive association between sleep duration and high BP, it did not reach a significant effect.

DISCUSSION

In our study, we found that sleep duration was higher in males than in females, which is in accordance with other studies that reported a highest prevalence of insufficient sleep among female adolescents (17, 29).

Regarding the effect of sleep in blood pressure, we found higher odds of being hypertensive among those who sleep ≥9.5 hours per day, statistically significant in females. This result is not in accordance with some studies (13, 18) that found an increased SBP in short sleepers, but it is in accordance with a study (19) that found a high BP values among those on the highest quartile of sleep duration (11.0-12.8 hours).

Data from previous studies seem to suggest that the association between sleep duration and BP follows a J-shaped curve, with both short (13, 30) and long (19) sleep duration being associated with an increased prevalence of hypertension. Our results tend to be close of this hypothesis since our reference class (≤8.5 hours) comprises 24.1% of adolescents who sleep between ≥8.0 hours and ≤8.5 hours, which indicates a very low prevalence of short sleepers. If a J-shaped curve was observed, our results can be in accordance with others that have a different cutoff.

The mechanism associated with long sleep duration and hypertension are less studied and remains unclear. Some studies have shown that long sleep is associated with less physical activity and consequently a higher blood pressure (31), but this association was not found in our study. Other potential mechanism is the cortisol, however we cannot evaluate its role because data on cortisol levels were not available.

We found a significative association between longer sleep duration and increased risk of high blood pressure only among females, future research is needed to understand the mechanism that could explain this gender difference. In adults, the endocrine environment during menopause has been reported as one possible explanation (7). A similar effect may be expected in adolescence. Other possible mechanism may be related with maturation, usually females are biologically more developed than males at the same chronological age (32). Thus, it is acceptable to assume that females at this age need less sleep duration and that makes the effect of long sleep more visible. However, in our study, the adjustment for age at menarche did not change the magnitude of association.

Gottlieb *et al.* found that both short and long sleep durations were significantly associated with depressive symptoms (31). In our study, we also found higher values

of depressive symptoms (BDI) among females with lower and higher sleep duration. As depressive symptoms may be related with sleep disturbances (33) and also with blood pressure (34), we decide to include this variable on the final model. Similar results were also found regarding caffeine intake (35). However, we cannot exclude the possibility that their effect may be as an intermediate step. Nevertheless, after adjustment, the association became stronger, so we believe the role as confounding is more relevant.

A possible limitation of this study is the methodology to estimate sleep duration. However, a study of high school adolescents found, for weeknights, a moderate correlation between actigraphy and self-reported total sleep time (r = 0.53) and high correlations between actigraphy and self-reported bedtimes (r = 0.70) and wake-up times (r = 0.77) (36). Thus, even the limitations on the accurate quantification of sleep time, we can accept that our measure is good enough to discriminate our participants according to their sleep duration.

Another limitation of our study is the BP measurement, because BP may vary throughout the day and between days (13) and the diagnosis of hypertension should be based on at least 3 separate occasions over a period of time (5). This may have resulted in overestimation of the prevalence of high BP, since in repeated assessments lower values would be expected (37, 38). Nevertheless, the BP measurement was taken at school, in the adolescents' normal environment, which would have helped reducing any "white-coat" effect (39).

Our study was conducted on a population-based cohort of adolescents and it is a representative sample of adolescents since school education is compulsory in Portugal until 15 years old. We also have a high proportion of participation and, in general, adolescents not included in the study were not significantly different from those that were included, except for gender and parents educational levels. Differences related to gender were minimized by stratification, nevertheless adolescents included had parents with a higher education which might have interfere in the results found. Several studies found that lower socioeconomic status (SES) can contribute to disparities in health, such as poor diet, lack of physical activity (40) and changes in sleep duration (41, 42). While Wells *et al.* found that sleep patterns are associated with socioeconomic status, with the wealthiest group showing the shortest sleep duration (18), other study shows an increased likelihood of short sleep duration for middle school and below (OR=1.13; 95% CI 1.03-1.20), compared to college or above (43). Our results are in accordance with those obtained by Wells, being the adolescents whose parents' education was higher the ones who reported less sleep duration. So, it is expected that our prevalence of short sleepers is overestimate. However, in our sample, the prevalence is so low that probably our associations are not biased.

The results on this study suggest that sleep duration could play a role in the etiology of hypertension, although it is necessary a better understanding of a potential J-shaped effect.

CONCLUSION

Our study provides evidence for an association between longer sleep duration and increased odds of high blood pressure in 13-year-old females but no significant association was found for males.

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Table 1: Females' characteristics at 13 years of age, according to categories of sleep duration.

VARIABLES	CATEGORIES OF SLEEP DURATION			*p* VALUE
	≤8.5 HOURS	>8.5 AND <9.5 HOURS	≥9.5 HOURS	
	n (%)	n (%)	n (%)	
FEMALES	299 (31.5)	364 (38.4)	285 (30.1)	
Blood Pressure				0.010
Normal	228 (76.3)	245 (67.5)	188 (66.4)	
Pre-hypertension	29 (9.7)	62 (17.1)	37 (13.1)	
Hypertension	42 (14.0)	56 (15.4)	58 (20.5)	
Parents' education				0.002
0-6 years	73 (26.2)	81 (23.6)	83 (32.8)	
7-9 years	44 (15.8)	78 (22.7)	65 (25.7)	
10-12 years	81 (29.0)	85 (24.8)	57 (22.5)	
≥ 13 years	81 (29.0)	99 (28.9)	48 (19.0)	
Family history of hypertension				0.939
No	187 (70.9)	218 (69.2)	165 (70.5)	
Yes	69 (26.1)	85 (27.0)	63 (26.9)	
Do not know	8 (3.0)	12 (3.8)	6 (2.6)	
Smoke				0.070
Never	205 (69.3)	272 (75.1)	212 (77.4)	
Ever	91 (30.7)	90 (24.9)	62 (22.6)	
Drink				0.002
Never	110 (37.3)	161 (44.8)	144 (52.0)	
Ever	185 (62.7)	198 (55.2)	133 (48.0)	
Sports activities				0.227
No	160 (54.6)	216 (60.7)	164 (60.5)	
Yes	133 (45.4)	140 (39.3)	107 (39.5)	
Quartiles of caffeine intake (mg)				0.066
≤11.74	51 (19.4)	84 (27.2)	72 (30.1)	
11.75-23.61	64 (24.3)	82 (26.5)	59 (24.7)	
23.62-45.95	70 (26.6)	75 (24.3)	49 (20.5)	
>45.95	78 (29.7)	68 (22.0)	59 (24.7)	
BDI*	7.0 (3.0; 12.0)	5.2 (2.0; 10.0)	6.0 (2.6; 10.5)	0.013
BMI (Kg/m^2)				0.080
< 85th percentile	224 (74.9)	288 (79.6)	204 (72.1)	
≥85th percentile	75 (25.1)	74 (20.4)	79 (27.9)	
Age at menarche				0.145
>12 years or not yet	108 (36.4)	112 (31.1)	100 (35.5)	
12 years	107 (36.0)	129 (35.7)	83 (29.4)	
>7 years and ≤11 years	82 (27.6)	120 (33.2)	99 (35.1)	

*Results are presented as median (25th percentile-75th percentile).

Table 2: Males' characteristics at 13 years of age, according to categories of sleep duration.

VARIABLES	CATEGORIES OF SLEEP DURATION			*p* VALUE
	≤8.5 HOURS	>8.5 AND <9.5 HOURS	≥9.5 HOURS	
	n (%)	n (%)	n (%)	
MALES	218 (26.5)	334 (40.6)	271 (32.9)	
Blood Pressure				0.108
Normal	143 (65.6)	205 (61.4)	184 (68.1)	
Pre-hypertension	27 (12.4)	66 (19.8)	40 (14.8)	
Hypertension	48 (22.0)	63 (18.8)	46 (17.1)	
Parents' education				0.003
0-6 years	48 (23.0)	54 (16.7)	60 (24.0)	
7-9 years	34 (16.2)	56 (17.3)	66 (26.4)	
10-12 years	60 (28.7)	101 (31.2)	67 (26.8)	
≥ 13 years	67 (32.1)	113 (34.8)	57 (22.8)	
Family history of hypertension				0.247
No	137 (72.9)	200 (69.0)	144 (67.0)	
Yes	45 (23.9)	84 (29.0)	69 (32.1)	
Do not know	6 (3.2)	6 (2.0)	2 (0.9)	
Smoke				0.275
Never	160 (77.3)	269 (82.5)	208 (82.2)	
Ever	47 (22.7)	57 (17.5)	45 (17.8)	
Drink				0.475
Never	91 (43.3)	158 (48.6)	122 (47.5)	
Ever	119 (56.7)	167 (51.4)	135 (52.5)	
Sports activities				0.014
No	108 (50.9)	125 (28.2)	113 (44.0)	
Yes	104 (49.1)	202 (61.8)	144 (56.0)	
Quartiles of caffeine intake (mg)				0.009
≤11.74	35 (17.9)	83 (27.4)	58 (26.0)	
11.75-23.61	43 (22.1)	78 (25.7)	57 (25.6)	
23.62-45.95	50 (25.6)	84 (27.7)	55 (24.6)	
>45.95	67 (34.4)	58 (19.2)	53 (23.8)	
Total BDI*	3.0 (1.0; 6.0)	3.0 (1.0; 6.0)	3.0 (1.0; 6.2)	0.973
BMI (Kg/m^2)				0.070
< 85th percentile	150 (69.1)	242 (72.5)	211 (78.1)	
≥85th percentile	67 (30.9)	92 (27.5)	59 (21.9)	

*Results are presented as median (25th percentile-75th percentile).

Table 3: Association between sleep duration and high BP in 13-year-old adolescents by gender.

VARIABLES	CRUDE OR (95% CI)	ADJUSTED OR (95% CI)	
		MODEL1	MODEL 2
FEMALES			
Sleep Duration			
≤8.5 hours	1	1	1
>8.5 and <9.5 hours	1.55 (1.10-2.18)	1.68 (1.18-2.40)	1.56 (1.07-2.27)
≥9.5 hours	1.62 (1.13-2.33)	1.61 (1.10-2.34)	1.83 (1.23-2.70)
Parents' education			
0-6 years	1	1	1
7-9 years	0.92 (0.61-1.39)	0.94 (0.62-1.44)	0.80 (0.50-1.26)
10-12 years	0.69 (0.46-1.03)	0.71 (0.47-1.08)	0.62 (0.40-0.97)
≥ 13 years	0.81 (0.55-1.20)	0.86 (0.57-1.28)	0.75 (0.49-1.16)
BMI (Kg/m^2)			
< 85^{th} percentile	1	-	1
≥85^{th} percentile	2.90 (2.13-3.96)	-	3.08 (2.20-4.33)
Quartiles of caffeine intake (mg)			
≤11.74	1	1	1
11.75-23.61	1.01 (0.66-1.54)	1.08 (0.69-1.67)	1.01 (0.65-1.54)
23.62-45.95	1.15 (0.75-1.77)	1.20 (0.77-1.86)	1.16 (0.76-1.79)
>45.95	1.06 (0.69-1.62)	1.13 (0.73-1.76)	1.07 (0.70-1.64)
BDI	0.99 (0.97-1.01)	0.99 (0.97-1.01)	0.99 (0.98-1.02)
Sports activities			
No	1	1	1
Yes	1.06 (0.79-1.40)	0.99 (0.74-1.34)	1.04 (0.76-1.42)
MALES			
Sleep Duration			
≤8.5 hours	1	1	1
8.5-9.5 hours	1.20 (0.84-1.71)	1.27 (0.88-1.86)	1.20 (0.82-1.77)
≥9.5 hours	0.89 (0.61-1.30)	1.01 (0.67-1.49)	0.91 (0.60-1.38)
Parents' education			
0-6 years	1	1	1
7-9 years	1.08 (0.69-1.70)	0.96 (0.60-1.55)	0.95 (0.57-1.57)
10-12 years	1.01 (0.66-1.52)	0.85 (0.55-1.32)	0.97 (0.61-1.54)
≥ 13 years	0.76 (0.50-1.16)	0.69 (0.45-1.07)	0.65 (0.41-1.04)
BMI(Kg/m^2)			
< 85^{th} percentile	1	-	1
≥85^{th} percentile	3.77 (2.73-5.21)	-	3.91 (2.75-5.57)
Quartiles of caffeine intake (mg)			
≤11.74	1	1	1
11.75-23.61	0.66 (0.42-1.02)	0.66 (0.41-1.04)	0.67 (0.43-1.04)
23.62-45.95	0.84 (0.55-1.28)	0.94 (0.60-1.47)	0.82 (0.53-1.25)
>45.95	0.89 (0.58-1.37)	0.99 (0.63-1.55)	0.88 (0.57-1.35)
BDI	0.98 (0.96-1.01)	0.98 (0.96-1.01)	0.98 (0.95-1.01)
Sports activities			
No	1	1	1
Yes	0.86 (0.64-1.15)	0.87 (0.64-1.18)	0.90 (0.59-1.23)

Model 1: OR adjusted for BMI in both genders.
Model 2: OR adjusted for caffeine intake (mg) and BDI in females and adjusted for caffeine intake (mg) and sports activities in males.

CHAPTER 2

Sleep duration and blood pressure: A longitudinal analysis from early to late adolescence

ABSTRACT

Background: Sleep duration has been associated to high blood pressure (BP) in children and adults. However, in adolescence, the association between sleep duration and BP still unclear, and no longitudinal studies have addressed this relationship. The purpose of this study was to evaluate the association between sleep duration at early and late adolescence and BP at 17 years old, using a cross-sectional and a longitudinal approach.

Methods: We evaluated, as part of a Portuguese urban population-based cohort (EPITeen), 1403 adolescents at both 13 and 17 years of age. Sleep duration was estimated by the difference between self-reported usual bedtimes and wake-up times at weekdays. BP was measured with a mercury sphygmomanometer using the auscultatory method, and hypertension was defined according to the American Academy of Pediatrics criteria (≤90th percentile, between 90th percentile and 95th percentile and ≥95th percentile). To evaluate the association between sleep duration and BP, β and respective 95% confidence intervals (95% CI) were computed, using linear regression models adjusted for body mass index (BMI) at 17 years old and practice of sports. Data was analyzed by gender.

Results: The mean (SD) of sleep duration at 13 years old was 9.0 (0.76) hours per day and decreases on average 46 minutes up to 17 years old. Regarding systolic blood pressure (SBP), the median (25th-75th) was 110.0 (103.5-119.0) in females and 114.0 (106.0-122.0) in males; for diastolic blood pressure (DBP) the values were 66.0 (60.0-71.0) and 69.0 (62.0-75.0), respectively. Both, SBP and DBP were significantly higher in males. In cross-sectional analysis, at 17y, after adjustment, a positive association was found between sleep duration and BP, significant only among females regarding SBP [0.67 (0.01; 1.33)]. Using the longitudinal approach, a positive but not significant association was found between sleep duration at 13 years old and SBP, in girls [0.67 (0.01; 1.33)]. In contrast, in males, we found an inverse association: -0.04 (-1.03; 0.95) regarding DBP and -1.76 (-2.96; -0.56) for SBP.

Conclusion: In cross-sectional study at 17 years sleep duration was positively associated with BP among females. In longitudinal approach, no association was found between sleep duration at 13 years old and BP at 17y, in girls, but showed an inverse association among males.

INTRODUCTION

Hypertension is an increasingly prevalent health problem in adults (1, 2) and adolescents alike, partially due to an increased prevalence of overweight (3). According to the National Health and Nutrition Examination Survey (NHANES), in adolescents the mean systolic blood pressure (SBP) was 1.4 mmHg higher and diastolic blood pressure (DBP) was 3.3 mmHg higher in 1990-2000 compared with 1988-1994 (4). As blood pressure (BP) in adolescence is associated with BP in adults (5, 6), it is important to identify modifiable risk factors that could be targets for preventive measures at young ages and to know if there is a window of opportunity for a potential intervention to prevent hypertension and its consequences later in life.

Sleep patterns among adolescents have been changing in last decades, accompanying the social constraints, and the increase interactions with peers, in school requirements and in extracurricular activities (7). During adolescence, sleep duration decreases from an average of 9.0 (0.7) hours per day at 13 years of age to 8.1 (0.7) hours at 16 years (8).

Sleep deprivation has been described as a possible cause of a set of different health consequences, such as decrease in cognitive performance, mood disturbances, depressive symptoms and metabolic changes (e.g. reduced leptin levels) (9, 10). More recently insufficient sleep has been implicated as a risk factor for development of hypertension amongst children and adults (11, 12).

Various mechanisms have been suggested as causal link between sleep duration and hypertension. The effect of sleep duration on the activation of the hypothalamic-pituitary-adrenal axis and on the rennin-angiotensin system may be plausible explanations (13, 14). However, in adolescence the association between sleep duration and BP remains unclear. Wells et al. (15), found that short sleep duration was associated with higher BP, while other studies reported a positive (16) or no association (17) between sleep duration and BP.

From the standpoint of public health, modifiable risk factors, such as behaviors and lifestyles, are the most promising to prevent hypertension and their consequences. Thus, understanding the role of sleep duration in the development of high BP during adolescence could be important to devise more effective interventions.

The aim of this study was to evaluate the association between sleep duration during adolescence and blood pressure at 17 years of age, using a cross-sectional and a longitudinal approach.

PARTICIPANTS AND METHODS

The study was developed as part of the Epidemiological Health Investigation of Teenagers in Porto (EPITeen). The ethics committee of Hospital S. João approved the study and informed consent was obtained from legal guardians of adolescents. Eligible participants were adolescents born in 1990 and enrolled at public and private schools in Porto, the first evaluation was conducted during the 2003/2004 school year, as previously mentioned (18). The second evaluation took place in the 2007/2008 school year and adolescents were evaluated following the same procedures and standardized questionnaires as it happened at baseline evaluation.

At baseline, 2160 adolescents agreed to participate and provided information at least for part of the planned assessment, resulting in a participation of 77.5%. Among the 2160 baseline participants, 1716 (79.4%) participated in the second evaluation of the cohort.

Both evaluations followed the same procedures and used standardized questionnaires. The evaluation included two self-administered questionnaires (one completed at home, another at school), comprising information on individual and family history of disease, and social, demographic and behavioral characteristics. A physical examination was also performed at school, by a team of experienced nurses, nutritionists and physicians and a 12-h overnight fasting blood sample was drawn from consenting participants.

Information about sleep duration was estimated by the difference between usual bedtimes (“What time do you typically go to bed?”) and wake-up times (“What time do you typically wake-up?”), regarding the weekdays and during school period.

The depressive symptomatology in adolescents was assessed by self-reported symptoms through the “Beck Depression Inventory II” (BDI-II) (19). The BDI-II is a 21-item self-report scale intended to assess the existence and severity of current (past two weeks) depressive symptoms. Each of the 21 items corresponding to a symptom of depression is summed to give a single score for the BDI-II. The total score can range from 0 to 63, which higher scores reflecting more severe depression. The BDI-II was previously validated in Portuguese adolescents population and 13 was the cut-off indicated to define adolescents presenting depressive problems (20).

As measure of physical activity we used the practice of sports activities considered when the participant was engaged in some physical leisure time activity performed on a

repeated basis, spending at least 30 minutes a week and not included in the school curriculum.

Adolescents were classified regarding their use of alcohol and tobacco as never users, if they had never drank alcoholic drinks and if they have never smoked and as drinkers or smokers, if they reported to use them or if they reported only to have experimented those substances.

The parental education level was measured as the number of successfully completed years of formal schooling and we classified the adolescents according to the parent with the higher education level. Information about a medical diagnosis of hypertension was asked separately to the mother and the father. A family history of hypertension was considered present when at least one parent reported having been diagnosed with this condition.

Weight and height were obtained with the subject in light indoor clothes and no shoes. Weight was measured in kilograms (Kg), to the nearest tenth, using a digital scale and height was measure in centimetres (cm), to the nearest tenth, using a portable stadiometer. In this study were considered 2 categories of BMI classified according to the percentiles for gender and age defined by the US Centres for Disease Control and Prevention (CDC) (21): $< 85^{th}$ percentile and $\geq 85^{th}$ percentile.

Blood pressure was measured, by trained doctors or nurses, in the right arm, based on the auscultatory measurements with a standard mercury sphygmomanometer, according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (3). Two measurements were performed after 10 minutes of rest, and calculated the average of both, if the difference between the two was greater than 5 mm Hg a third measurement was performed and determined the average of the two closest measurements. Hypertension was defined according to the quantitative criteria of the American Academy of Pediatrics (22): pre- hypertension if SBP and/or DBP are above the 90^{th} percentile for sex, age and height and hypertension, if SBP or DBP is above the 95^{th} percentile for sex, age and height, but both below the 95^{th} percentile. The categories pre-hypertension and hypertension were grouped into one category – high BP (SBP and/or DBP are above the 90^{th} percentile for sex, age and height).

Food intake was recorded using a food frequency questionnaire (FFQ) regarding the previous 12 months, completed by the adolescent at home with the help of their parents or legal guardians. The FFQ was designed according to Willett and colleagues and adapted for the Portuguese population (23). The FFQ was then adapted for adolescents, including foods more frequently eaten by this age group, and the adolescents' version comprised 92 food items or beverage categories and a frequency

section with nine possible responses ranging from never to six or more times per day. It also included an open-ended section for foods not listed in the questionnaire, but eaten at least once per week. To estimate caffeine intake from the evaluated food intake, the software Food Processor Plus (version 5.0, 1992, ESHA Research, Salem, OR) based on values from the US Department of Agriculture was used. Caffeine intake was categorized according to the quartiles of intake into: ≤11.74; >11.74 and ≤23.61; >23.61 and ≤45.95; and >45.95 mg.

Participants

Of the 1716 participants evaluated at the baseline (2003/2004) and at the second wave (2007/2008), we excluded 226 adolescents (91 females and 135 males) who had not been assessed for anthropometric measurements or blood pressure and 88 (45 female and 43 male) adolescents who did not report data to estimate sleep duration. Thus, this study was based on the information of 1403 participants (757 females and 646 males).

Compared with the 1403 adolescents included in this analysis, adolescents not included are mostly male than female (56.7% vs. 43.3%, p=0.001), had parents with a significant lower level of education, had higher sleep duration and higher DBP. For the remaining variables (SBP, drink, practice of sports and depressive symptomatology) no significant differences were found between those included and those not included (table 1).

Statistical analysis

Shapiro-Wilk test was used to determine whether the outcome variables were normally distributed. To comparisons, we used univariate analysis and Kruskal-Wallis test for continuous and by Qui-square (χ^2) tests to categorical variables. To evaluate the association between sleep duration and SBP and DBP, β and respective 95% confidence intervals (95% CI), were computed using linear regression models, crude and adjusted for BMI (model 1), practice of sports (model 2) and for practice of sports and BMI (model 3).

All of the analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 18.0, and the level of statistical significance was set at 0.05.

RESULTS

The mean (standard deviation) of sleep duration at 13 years old was 9.0 (0.76) hours and decrease to 8.25 (0.029) hours at follow-up (at 17 years old). The mean (SD) difference in sleep duration was -0.77 (1.25) hours per day, and the decrease was lower in females [-0.70 (1.27)] than in males [-0.86 (1.23)]. The decrease seems to be uniform across the sample, adolescents who had lower sleep duration at baseline, reported also fewer hours at follow-up and those who had higher sleep duration at baseline, despite decreasing their sleep duration, were the adolescents that had more hours of sleep duration at follow-up.

At 17-year-old, the mean (SD) of sleep duration was higher among females [8.29 (0.12) hours] than in males [8.20 (0.11) hours], but the difference did not reach statistical significance.

Regarding to BP levels at 17 years old, among females the median (25^{th}-75^{th} percentile) was 110.0 (103.5-119.0) for SBP and was 66.0 (60.0-71.0) for DBP; among males the BP levels were significantly higher than that observed in females, the median (25^{th}-75^{th} percentile) was 114.0 (106.0-122.0) for SBP and was 69.0 (62.0-75.0) for DBP. BP at 17 years old was positively associated with BMI at 13 and 17 years in both genders. Additionally, among females we found significant lower values of SBP at 17y with the increase of the age at menarche.

The prevalence of high BP (SBP or DBP above the 90^{th} percentile for sex, age and height) at 17y was 21.8%, higher among males (26.9%) than among females (18.1%), $p<0.001$. High BP was significantly associated with BMI in both evaluations among both genders.

Regarding to the relationship between sleep duration at 17 years-old and SBP and DBP at 17 years-old, higher levels of BP were observed among those who slept more hours in both genders (figures 1 and 2). The relationship between sleep duration at 13 years-old and SBP and DBP at 17 years-old was presented in figures 3 and 4. Among females, those who had higher sleep duration had higher levels of SBP [β=0.36 (95% CI: -0.65; 1.38)] and DBP [β=0.24 (95% CI: -0.52; 0.99)], but none of those association reach statistical significance. Among males, an inverse association was found, who had higher sleep duration had lower levels of SBP [β=-1.95 (95% CI: -3.16;-0.74)] and DBP [β=-0.13 (95% CI: -1.14; 0.87)].

After adjustment for BMI and practice of sports, the cross-sectional analysis, at 17y, showed a positive association between sleep duration and BP, but significant only

among females and only regarding SBP [β=0.67 (95% CI: 0.01; 1.33)]. Using the longitudinal approach, a positive but not significant association was found between sleep duration at 13 years old and BP, in females. In contrast, in males, we found an inverse association: -1.76 (-2.96; -0.56) regarding SBP and -0.04 (-1.03; 0.95) for DBP (Table 3).

DISCUSSION

In our study, we found that sleep duration decreased from 13 to 17 years of age, in both genders, which is in accordance with data previously described in literature (8). At 17-year-old, sleep duration is higher in females than in males, such as found in a review that summarizes the sleep patterns in young people aged 9.0-18.8 years over the last 30 years (24). However, other studies reported no differences in sleep duration between both genders (8, 25).

Regarding the effect of sleep duration at 17 years old on BP, we found that long sleep duration predicted higher levels of SBP, although statistically significant only in females. This result is not in accordance with studies reporting an increase in SBP in short sleepers (15, 26). However in our study the mean sleep at 17 years-old was 8 hours per day and few adolescents reported short sleep duration when compared to other studies (26-28), which may explained our result. Similarly, Sampei et al. (16) found high SBP values among schoolchildren who sleep more than 10 hours and found no association with DBP. Guo et al (29) found short slept duration (<8h) was a protective factor for high BP among girls age 15 to 18 years. The differences in this set of studies are supporting the possible J-shape curve, with higher BP values among those with short sleep but also among those with large sleep duration.

In longitudinal approach, we found no association between sleep duration at 13 years old and BP at 17 years old in females, but an inverse association was found in males. The result in males is in accordance with data on adults showing that those who sleep less hours were significantly more likely to be hypertensive over the follow-up period (30). However, to our knowledge, this is the first study that evaluates the association between sleep duration and BP through a longitudinal approach, among adolescents. It is interesting to notice that the association found between sleep duration at 13 years was stronger than the result regarding sleep at 17 years old. This could represent a higher effect of exposures at early adolescence. However, as it has

been described by Gangwisch, et al. regarding to the association between short sleep duration and BP (30), this could also represent a possible adaptive mechanisms associated with normal BP (31).

The explanation to have found an inverse association only in males may be related with differences on sleep needs by gender, with females need comparatively less sleep than males (24). Additionally, during adolescence females are biological more developed than males at same chronological age (32). So, if in males, sexual maturation occurs later, a delay in the decrease in sleep needs is also expected. Consequently, at the same chronological age, males probably need sleep longer. However, the adjustment for age at menarche, an indicator of sexual maturation in females, did not change the association.

In both cross-sectional and longitudinal approach, we found a stronger association regarding SBP levels than DBP. This result is in accordance with the higher variability of SBP values than DBP values (33) and with other studies that also found SBP more affected by sleep duration than DBP, both in children (16) and among adults (34).

A limitation of this study is the methodology to estimate sleep duration through self-reported questionnaire. However, a study of high school adolescents found that self-reported total sleep duration is moderately correlated with actigraphy ($r = 0.53$) and that self-reported bedtimes and wake-up time is highly correlated with actigraphy ($r = 0.70$ and $r = 0.77$, respectively) (35). Thus, even with the limitations on the accurate quantification of sleep time, we can accept that our measure is good enough to discriminate our participants according to their sleep duration. Another limitation of our study is related with the BP measurement, because BP may vary throughout the day and from day to day (26) and the use of one isolated measurement may have resulted in overestimation of the BP values (36, 37). Nevertheless, the BP measurement was taken at school, in the adolescents' normal environment, which would have helped reduce any "white-coat" effect (38). Additionally, even assuming an overestimation on BP values the effect should be independent on the sleep duration.

Although our study presents some limitations we have important strengths. The major strength of our study is the longitudinal approach since it allows assessing the effect of sleep duration at early adolescence on the BP in older adolescents.

Other strength is related with the population approach, as in Portugal school education is compulsory at 13 years old (age at the assembling of the cohort) and the proportion of participation was high at baseline and also at follow-up, we could expect a representativeness of our sample. Nevertheless, the exclusion of some participants with missing information may limit the extrapolation of our results. However, in general, no significant differences were found and differences related to gender were minimized

by stratification. Besides, those who were included in the study have shorter sleep duration, so it is expected that our prevalence of short sleepers is overestimated, but is not clear if that may affect the association between sleep duration and BP. The significant difference on DBP found between included and not included females is not clinically significant, since the levels observed were very close.

The results from this study suggest that sleep duration could play a role in the etiology of hypertension in older adolescents. Additionally, the association found with sleep duration at 13 years was stronger than the association found in the cross-sectional analysis at 17 years reinforcing that sleep duration can be a determinant of BP levels since young ages. But it is important to recognize that sleep quality can be important to understand the association between sleep duration and BP. Further studies are also needed to evaluate sleep needs in both genders and to understand their effect on BP levels.

CONCLUSION

In cross-sectional study at 17 years sleep duration was positively associated with BP among females. In longitudinal approach, no association was found between sleep duration at 13 years old and BP at 17y, in girls, but showed an inverse association, among males.

Our results support the relevance of sleep duration for healthy lifestyles, and as a possible target for preventive measures, however it is important to notice that, in our sample, the mean of sleep duration at 17 years of age was 8.25 hours.

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Table 1: Characteristics at 13 years of age among adolescents who participate only in first evaluation and among adolescents who participate in both evaluations.

Variables at 13 years old	Females n (%)			Males n (%)		
	Only participated at 13 years old 136 (15.2)	Participated in both evaluations 757 (84.8)	*p* value	Only participated at 13 years old 178 (21.6)	Participated in both evaluations 646 (78.4)	*p* value
Blood Pressure			0.918			0.223
Normal	63 (69.2)	536 (71.0)		95 (70.9)	421 (65.2)	
Pre-hypertension	13 (14.3)	97 (12.8)		14 (10.4)	105 (16.3)	
Hypertension	15 (16.5)	122 (16.2)		25 (18.7)	120 (18.6)	
Blood pressure*						
SBP	110.0 (101.0-121.0)	110.0 (103.5-119.0)	0.845	113 (106.00-123.00)	114.00 (106.00-122.00)	0.672
DBP	69.0 (63.0-78.0)	68.0 (62.0-72.0)	0.007	67.00 (60.00-70.00)	68.00 (61.00-72.00)	0.328
Sleep duration			0.001			0.02
≤8.5 hours	17 (26.6)	239 (31.6)		15 (22.7)	169 (26.2)	
8.5-9.5 hours	15 (23.4)	302 (39.9)		18 (27.3)	287 (44.4)	
≥9.5 hours	32 (50.0)	216 (28.5)		33 (50.0)	190 (29.4)	
Sleep duration**	9.25 (0.91)	8.99 (0.77)	0.014	9.27 (0.85)	9.06 (0.73)	0.07
Parents' education			0.041			<0.001
0-6 years	46 (36.2)	180 (24.9)		58 (35.8)	118 (18.6)	
7-9 years	26 (20.5)	145 (20.0)		27 (16.7)	124 (19.6)	
10-12 years	29 (22.8)	198 (27.3)		42 (25.9)	183 (28.9)	
≥ 13 years	26 (20.5)	201 (27.8)		35 (21.6)	209 (33.0)	
Family history of hypertension			0.255			0.230
No	70 (78.7)	470 (70.9)		78 (70.3)	382 (69.0)	
Yes	18 (20.2)	173 (26.1)		28 (25.2)	161 (29.1)	
Do not know	1 (1.1)	20 (3.0)		5 (4.5)	11 (2.0)	
Smoke			0.001			0.160
Never	57 (59.4)	562 (75.4)		103 (77.4)	514 (82.6)	
Ever	39 (40.6)	183 (24.6)		30 (22.6)	108 (17.4)	
Drink			0.777			0.871
Never	43 (44.3)	319 (42.8)		65 (48.1)	298 (47.4)	
Ever	54 (55.7)	426 (57.2)		70 (51.9)	331 (52.6)	
Practice of sports			0.452			0.937
No	57 (61.3)	421 (57.2)		59 (43.7)	273 (43.3)	
Yes	36 (38.7)	315 (42.8)		76 (56.3)	357 (56.7)	
Quartiles of caffeine intake (mg)			0.637			0.909
≤11.74	15 (28.8)	170 (25.8)		16 (27.6)	143 (25.0)	
11.75-23.61	15 (28.8)	171 (25.9)		12 (20.7)	142 (24.8)	
23.62-45.95	8 (15.4)	153 (23.2)		16 (27.6)	150 (26.2)	
>45.95	14 (26.9)	165 (25.0)		14 (24.1)	137 (24.0)	
BDI*	5.25 (3.00-13.00)	6.01 (2.00-10.00)	0.506	3.00 (1.01-7.00)	3.00 (1.01-6.01)	0.504
BMI (Kg/m^2)			0.906			0.871
< 85th percentile	78 (78.0)	592 (78.5)		101 (72.7)	473 (73.3)	
≥85th percentile	22 (22.0)	162 (21.5)		38 (27.3)	172 (26.7)	
Age at menarche			0.910			
>12 years or not yet	34 (34.3)	245 (32.7)				
12 years	32 (32.3)	258 (34.4)				
>7 years and ≤11 years	33 (33.3)	247 (32.9)				

* Results are presented as median (25th percentile-75th percentile). ** Results are presented as mean (SD).

BDI: Beck Depression Inventory; BMI: Body Mass Index

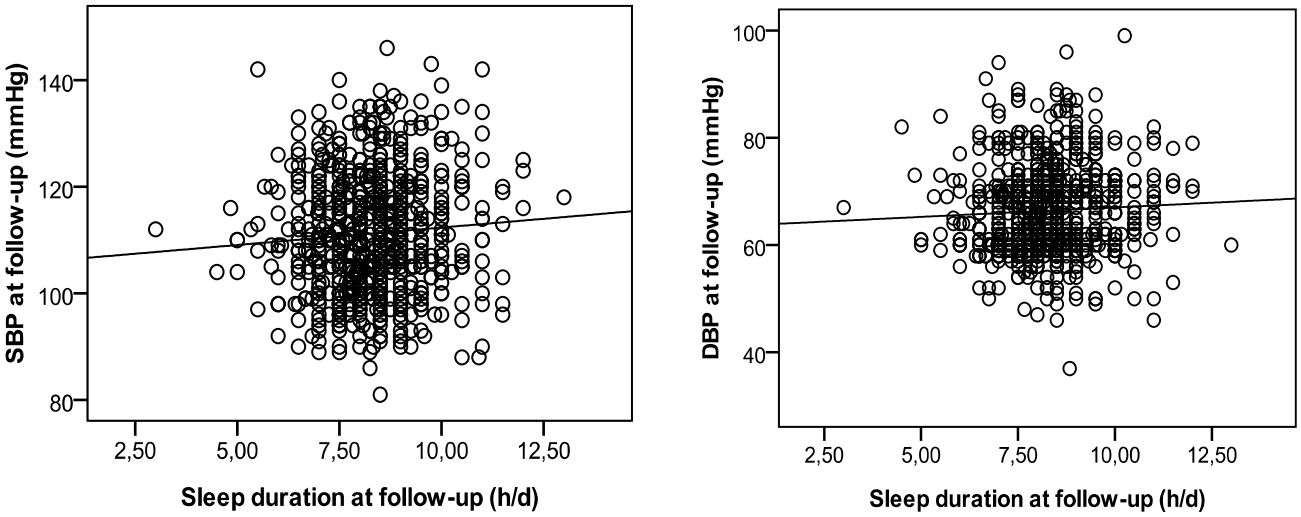

Figure 1: Scatter of sleep duration at 17years-old (follow-up), according to SBP and DBP at 17 years-old (follow-up), among females.

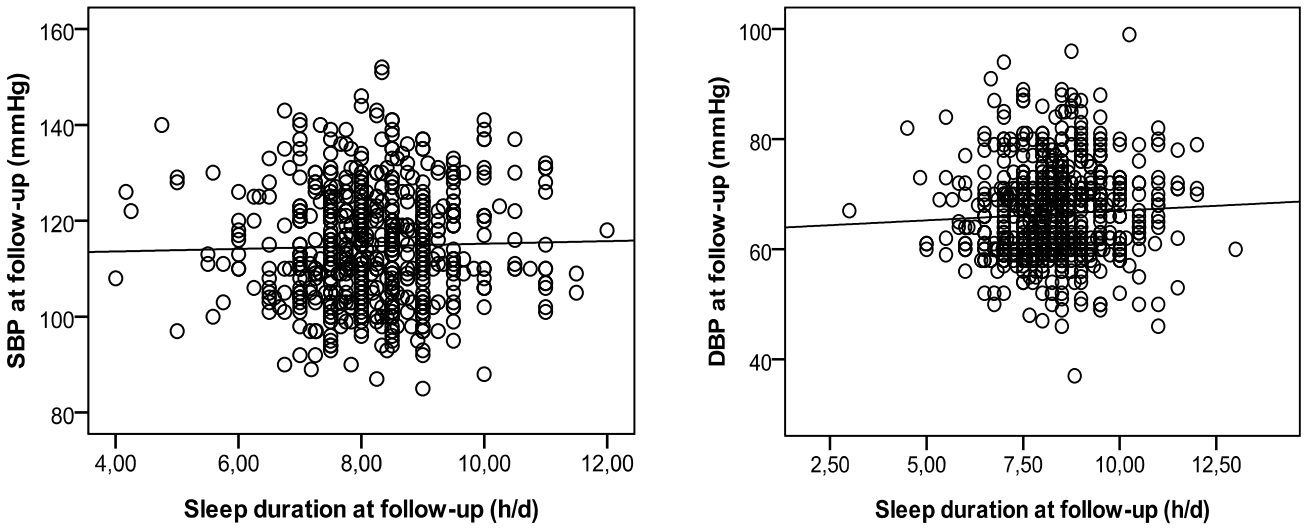

Figure 2: Scatter of sleep duration at 17 years-old (follow-up), according to SBP and DBP at 17 years-old (follow-up), among males.

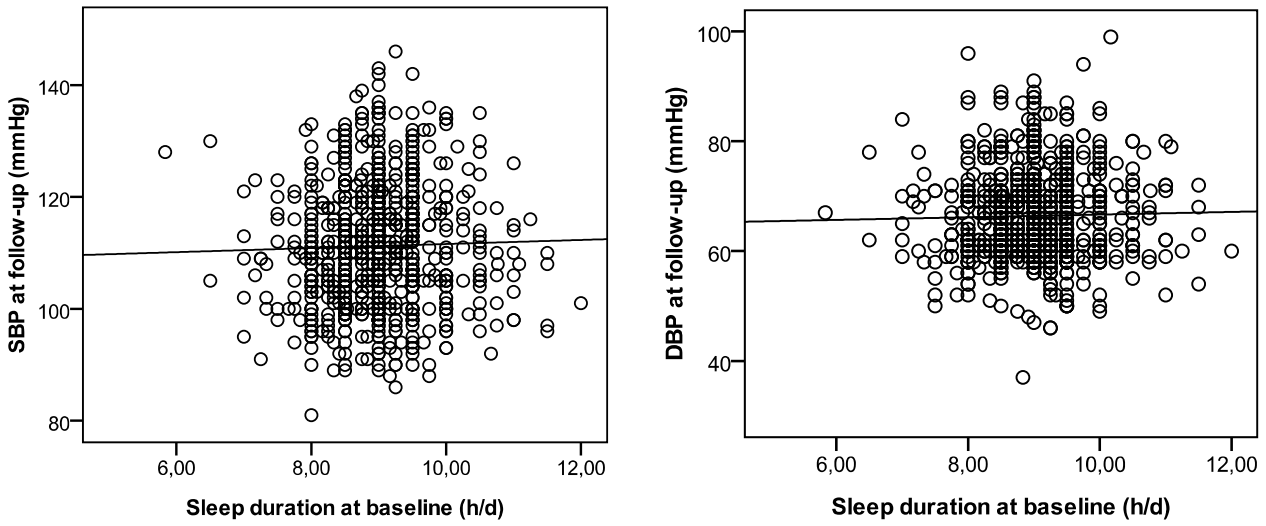

Figure 3: Scatter of sleep duration at 13years-old (baseline), according to SBP and DBP at 17 years-old (follow- up), among females.

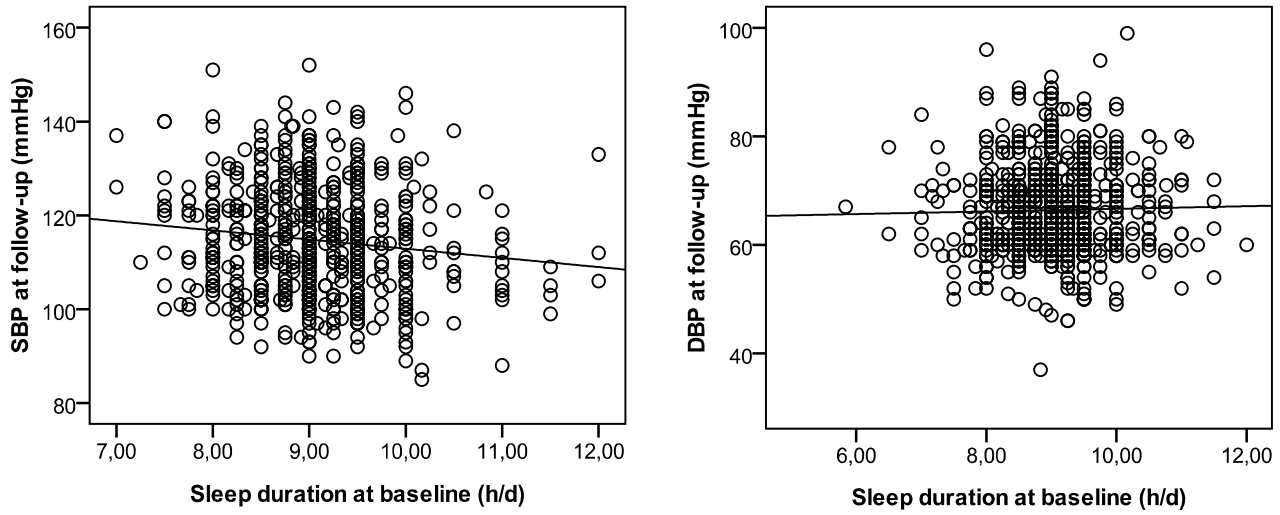

Figure 4: Scatter of sleep duration at 13 years-old (baseline), according to SBP and DBP at 17 years-old (follow- up), among males.

Table 2: Cross-sectional and longitudinal associations between sleep duration and blood pressure at 17years old.

	Crude β (95% CI)		Adjusted β (95% CI)*					
			Model 1		Model 2		Model 3	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Sleep duration at 17y								
Females	0.66 (-0.004; 1.31)	0.35 (-0.14; 0.84)	0.64 (-0.012; 1.29)	0.32 (-0.17; 0.81)	0.70 (0.02; 1.37)	0.38 (-0.12; 0.88)	0.67 (0.01; 1.33)	0.34 (-0.16; 0.84)
Males	0.27 (-0.56; 1.09)	0.11 (-0.57; 0.78)	0.31 (-0.50; 1.12)	0.15 (-0.52; 0.81)	0.09 (-0.74; 0.92)	-0.06 (-0.75; 0.63)	0.17 (-0.65; 5.82)	0.01 (-0.66; 0.68)
Sleep duration at 13y								
Females	0.36 (-0.65; 1.38)	0.24 (-0.52; 0.99)	0.20 (-0.80; 1.20)	0.16 (-0.60; 0.90)	0.36 (-0.70; 1.41)	0.15 (-0,64; 0.93)	0.21 (-0.83; 1.25)	0.08 (-0.70; 0.86)
Males	-1.95 (-3.16; -0.74)	-0.13 (-1.14; 0.87)	-1.69 (-2.88; -0.51)	0.03 (-0.96; 0.81)	-2.03 (-3.24; -0.81)	-0.21 (-1.22; 0.80)	-1.76 (-2.96; -0.56)	-0.04 (-1.03; 0.95)

* Model 1: β adjusted for BMI at 17 years old.
Model 2: β adjusted for practice of sports at 17 years old.
Model 3: β adjusted for practice of sports and BMI at 17 years old.

CONCLUSIONS

This research based on a population-based sample of Portuguese adolescents showed a decrease in sleep duration throughout adolescence. Sleep duration decreased from an average of 9.02 hours at 13 years of age to an average of 8.25 hours per day at 17 years of age. Also shown a relatively high prevalence of high blood pressure (SBP or DBP above the 90th percentile for sex, age and height) in both evaluations 32.5% at 13-year-old and 21.8% at 17-year-old.

After adjustment for potential confounders, at 13-year-old, in females, a positive association was found between sleep duration and high blood pressure (SBP and/or DBP are above the 90th percentile for sex, age and height). The odds (95% confidence interval) of high blood pressure was 1.56 (1.07-2.27) among adolescents sleeping more than 8.5h and lower than 9.5h per day and 1.83 (1.23-2.70) among those sleeping 9.5h or more, compared with those sleeping 8.5h or less. In cross-sectional analyzes at 17-year-old sleep duration was also positively associated with BP among females, but the associations reach statistical significance only for SBP [β = 0.67 (95% confidence intervals: 0.01; 1.33)].

The longitudinal analysis, showed, in males, an inverse association between sleep duration at 13 years and SBP at 17 years -0.04 (-1.03; 0.95) regarding DBP and -1.76 (-2.96; -0.56) for SBP.

These studies suggest that sleep duration could play a role in the etiology of hypertension. The association found with sleep duration at 13 years and blood pressure was stronger than the association found in the cross-sectional analysis at 17 years reinforcing that sleep duration can be a determinant of blood pressure levels since young ages.

However, it is important to notice that the mean of sleep duration, in our sample is relatively high compared with data described in the literature: close to 9 hours per day at 13-year-old and 8 hours per day at 17-years-old, and the number of adolescents with sleep duration lower than 8 hours is small in both moments. Additionally, as we only measured sleep duration we could not exclude the hypothesis that our results were attributable to the low sleep efficiency than to the short sleep duration.

In summary, our study provides evidence for a link between sleep duration and high BP, and the understanding the role of sleep duration in BP at younger ages is

essential for early intervention in order to prevent hypertension and those consequences. However, further research is needed to understand the biological mechanism that is involved in the effect of sleep duration on BP levels among adolescents, especially to understand gender differences.