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SCIENTIFIC INVESTIGATIONS

Adiposity and Physical Activity Do Not Mediate the Longitudinal Association Between Sleep Quality and Arterial Thickness Among Adolescents

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Study Objectives: Sleep is a behavior with the potential to affect cardiovascular health. Given the fact that adiposity and physical activity seem to be related to cardiovascular risk factors during growth, it is still unclear whether sleep quality could affect arterial thickness among adolescents. Thus, the objective of the current study was to analyze the effect of sleep quality on arterial thickness and identify the possible mediation role of physical activity and trunk fat in adolescents.

Methods: This was a longitudinal study (12-month follow-up) composed of 71 adolescents with ages ranging from 11 to 14 years at baseline (absence of any known chronic diseases, and no regular medicine use). All variables were assessed twice (baseline and 12-month follow-up): (1) sleep quality was reported using the Mini Sleep Questionnaire (MSQ); (2) physical activity was estimated using pedometers; (3) trunk fat was assessed using a densitometry scanner; and (4) carotid intima-media thickness (CIMT) and femoral intima-media thickness (FIMT) were assessed using ultrasonography.

Results: Adolescents who presented poor sleep quality demonstrated significantly increased FIMT (r = .299, 95% confidence interval .071 to .498) and for every point increase in the MSQ score from baseline to follow-up there was a 1.12% (95% confidence interval 0.26 to 1.98) increase in FIMT over time. Moreover, trunk fat and physical activity did not mediate the association between sleep quality and arterial thickness, but FIMT had a positive and independent relationship only with trunk fat.

Conclusions: Sleep quality was positively associated with FIMT among adolescents, whereas physical activity and adiposity did not mediate this process.

Keywords: exercise, intima-media thickness, sleep habits

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep is a behavior with the potential to affect cardiovascular health. Adiposity is associated with cardiovascular disease risk factors during growth.

Study Impact: Arterial thickness seems to be affected by sleep quality in adolescents. Trunk fat had a positive and independent effect and sleep quality a direct effect on femoral intima-media thickness among adolescents.

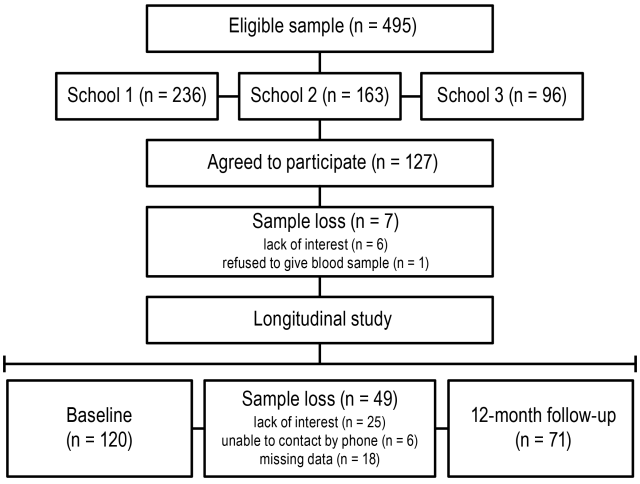
INTRODUCTION

Given epidemiological and technological transitions, chronic diseases have become the greatest cause of death worldwide.[1] In this sense, cardiovascular outcomes such as dyslipidemia, high blood pressure, and arterial thickening are more commonly observed in children and adolescents than some decades ago, constituting a concerning phenomenon that seems to be, mainly, affected by lifestyle factors such as insufficient physical activity, sedentary behavior, and high-fat dietary patterns, which lead to childhood obesity and lower physical fitness, among the greatest risk factors for cardiovascular diseases.[2–5]

Insufficient physical activity, sedentary behavior, and poor dietary patterns are unhealthy agents affecting pediatric cardiovascular health, and constituting the most commonly investigated variables in this age group.[2–5] However, other factors such as sleep quality could also affect cardiovascular health. Although sleep is a vital behavior for humankind,[6] its effect on cardiovascular parameters has been less investigated than other more traditional cardiovascular disease risk factors. Epidemiological data report that fewer than 20% of adolescents sleep ≥ 8 hours per night, whereas poor sleep quality harmfully affects mental status and leads to weight gain.[7]

Among adults, sleep deprivation has been linked to arterial thickening.[8] However, among pediatric groups, despite a growing body of evidence linking poor sleep quality with cardiovascular disease risk factors,[6,9] the effect of sleep on arterial thickness of adolescents is unclear. Moreover, arterial thickness is affected by adiposity[3] and habitual physical activity,[10] which are also associated with sleep quality.[11,12] It is unclear if these variables could be potential mediators of the association between sleep quality and arterial thickness. Therefore, the

Figure 1—Flow chart of the longitudinal study (Presidente Prudente, Sao Paulo, Brazil, 2013–2014).



objective of this longitudinal study was to analyze the effects of changes in sleep quality on carotid intima-media thickness (CIMT) and femoral intima-media thickness (FIMT) of adolescents, as well as to identify the possible mediation role of physical activity and adiposity on this phenomenon.

METHODS

Sampling

The longitudinal study entitled "Effect of habitual physical activity and adiposity on the cardiovascular system of adolescents: cohort of 12 months" was approved by the Ethics Committee of the Sao Paulo State University (UNESP [process: 322.650/2013]) from Presidente Prudente city, State of Sao Paulo, Brazil. All the procedures described in this manuscript were performed by trained researchers of the Laboratory of InVestigation in Exercise (LIVE), Department of Physical Education, UNESP.

During 2013–2014, our research staff carried out the sampling process. Initially, school units of the metropolitan area of the city were contacted in order to communicate the realization of this longitudinal study and request authorization from the Municipal Authorities to contact the students and legal guardians. After this initial authorization, the principal of each selected school unit was contacted by phone to clarify the aims and all procedures involved in the data collection. In total, seven school units were invited to participate in the study, of which three schools agreed to host the research. In each participant school unit, all adolescents between 11 and 14 years of age were invited to participate (n = 495). At baseline, the inclusion criteria adopted were as follows: (1) aged between 11 and 14 years; (2) regularly enrolled in the school unit; (3) absence of any previously diagnosed diseases; (4) no regular medicine use; and (5) written parental consent and adolescents' assent, both signed.

After the aforementioned procedures, 120 adolescents (boys and girls) composed the sample at baseline, whereas the 12-month follow-up measures involved 71 adolescents (38 males and 33 females) (**Figure 1**). All adolescents regularly registered in the three schools that agreed to host the research received a formal invitation to participate in this longitudinal study. Taking into account all potential adolescents in the three schools, 495 adolescents aged between 11 to 14 years old were initially eligible to participate; however, only 127 agreed to participate in the baseline measures. The main reasons for not agreeing to participate were related to lack of interest, too busy to participate, and, mainly, fears about blood collection. At 12-month follow-up, reasons to quit were related to lack of interest and inability to contact by phone. At baseline, adolescents who dropped out (n = 49) were similar to adolescents who remained in the longitudinal study (n = 71) in terms of trunk fat (TF) ($P = .268$), physical activity ($P = .568$), score for sleep quality ($P = .578$), CIMT ($P = .811$), and FIMT ($P = .615$). The sample size of 71 participants gave a statistical power of 80% to detect significant ($Z = 1.96$) coefficients of correlation (standardized score [r]) ≥ 0.33 in our statistical analysis.

Experimental Design

Initially, during face-to-face interviews, adolescents reported sex, chronological age, and sleep quality in accordance with a specific questionnaire. Subsequently, weight, height, and adiposity were assessed. Arterial thickness was measured by a trained doctor in a private hospital during the morning. Blood samples were collected for analysis of lipid variables. The adolescents registered the number of steps per day for 7 consecutive days using pedometers in order to estimate the level of physical activity. All methodological measurements were performed twice (at baseline and after 1 year of follow-up), whereas some variables were treated as absolute changes (Δ [sleep score and steps/day]) or relative changes (Δ% [arterial thickness and adipose tissue]).

Arterial Thickness (Dependent Variable)

Measures of CIMT and FIMT were performed on frozen pictures on the R wave that were recorded from the far wall of the arteries in end diastole[13] by one experienced medical doctor who was responsible for the clinical measurements at both moments of the research. The medial doctor was blinded regarding the names of the adolescents. An ultrasound machine (brand Philips, model Philips HD 11 XE, Barueri, Brazil), equipped with a high-resolution, multifrequency linear transducer adjusted to 12 MHz was used to examine both arteries on the right side of the body, in a private hospital. During the carotid artery procedures, the neck was lightly hyperextended and inclined to reach an angle of approximately 45 degrees. In parallel, during the femoral artery measure, the leg was extended on the stretcher, and the measure was taken near the inguinal line.[14] Reproducibility measures were provided by CIMT (intraclass correlation coefficient: 0.57; $P = .029$) and FIMT (intraclass correlation coefficient: 0.91; $P = .001$).[3,10]

Sleep Quality (Independent Variable)

Sleep quality was assessed through face-to-face interviews, using the Mini Sleep Questionnaire (MSQ), previously translated/validated for Brazilian Portuguese by Falavigna et al.[15]

The MSQ is composed of 10 questions related to sleep quality including insomnia symptoms, snoring, and difficulty sleeping. Every question contains a Likert scale with 7 possible responses, generating a score ranging from 10 to 70 points (in the MSQ, a higher score denotes poorer sleep quality). Following the cutoff points proposed by the authors who developed the questionnaire,[15] a score ≤ 24 points was considered as "good sleep" and ≥ 25 points as "poor sleep."

Physical Activity (Mediation Variable)

Pedometers (Digi-walker, model SW200, Yamax, Shropshire, United Kingdom), were used for 7 consecutive days (worn on the hip) to estimate the level of physical activity through step counts. Before the data collection, the battery status of each device was tested using a voltmeter. Through the pedometers, it was possible to identify movements on the vertical axis. All participants were instructed to remove the device during periods of sleep and water-based activities. At the end of each day, before sleep, the adolescents were instructed to register the number of steps performed on that day. Only adolescents who presented data on 7 consecutive days in both assessments were considered eligible for the study.

Adiposity (Mediation Variable)

TF was estimated using a densitometry scanner (General Electrics; model Lunar – DPX-NT, General Electric Healthcare, Little Chalfont, Buckinghamshire, United Kingdom) equipped with the software GE Medical System Lunar (version 4.7). All the manufacturer's recommendations were taken into consideration before each assessment. The whole body was analyzed with the adolescents remaining immobile for approximately 15 minutes in the supine position, with their arms and legs extended on the stretcher. Shoes and any metal objects were removed before the examination. One researcher was responsible for all measurements, which were performed in a room with a constantly controlled temperature.

Covariates

After 12 hours of overnight fasting, blood samples were collected in a private laboratory. Total cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, and triacylglycerol were analyzed using an enzymatic colorimetric kit processed in an Autohumalyzer (Dimension RxL Max, model Siemens Dade-Behring). A continuous score was developed using the four variables previously mentioned. Each lipid variable was standardized ([value – mean]/standard deviation; high-density lipoprotein-cholesterol Z-scores were multiplied by −1). The Z-scores of the individual lipid variables were then summed to create a cluster of lipid variables, which are identified in the current study as "dyslipidemia."[10]

During face-to-face interviews, sex and chronological age were established. Body weight was measured using an electronic scale (Filizzola PL 150, model Filizzola Ltda, Brazil), and height using a wall-mounted stadiometer (Sanny, model American Medical of the Brazil Ltda, Brazil). All anthropometric measurements were performed according to standardized techniques. Subsequently, the peak height velocity was estimated using mathematical equations proposed by Mirwald et al.[16] Maturity offset was expressed in time (years) (negative score [time to reach peak height velocity] and positive score [the adolescent had already reached peak height velocity]).

Statistical Analyses

Descriptive statistics were composed of mean and confidence interval of 95% (95% CI). Absolute change (Δ) and relative change (Δ%) were performed using the 1-year follow-up database. The *t* test for independent samples compared numerical variables according to sex, whereas the Pearson correlation was used to assess the relationship between these variables. Structural equation models were used to assess the relationship between sleep quality and arterial thickness (CIMT Δ% and FIMT Δ%), taking into account the possible mediation role of physical activity and TF.

To test mediation, all procedures were conducted based on recommendations by Baron and Kenny.[17] To test mediation, three equations are required: (1) the mediator (physical activity/TF) is regressed on the exposure (sleep quality); (2) the outcome (CIMT and FIMT) is regressed on the exposure; and (3) the outcome is regressed on the exposure, adjusted for the mediator. To attest mediation, the exposure is required to be significant in predicting the mediator in the first equation, the exposure is required to be a significant predictor of the outcome in the second equation, and the mediator is required to significantly predict the outcome as well as to remove, in part or totally, the effect of exposure in the outcome. Moreover, indirect effect was estimated through the bootstrap re-sampling method (1000 reps). Mediation models were adjusted by the covariates (sex, age [baseline], maturity offset [baseline], Z score dyslipidemia [baseline], CIMT [baseline], and FIMT [baseline]). The relative chi-square test was used as a fit index. Statistical significance was set at 5% ($P < .05$). Analyses were performed using the software BioEstat (version 5.0) and Stata (version 15.1).

RESULTS

The current longitudinal study was composed of 71 adolescents; at baseline, 52.1% (n = 37) were classified as having poor sleep, whereas the percentage was 50.7% (n = 36) at follow-up (McNemar test with $P = 1.000$). The MSQ score did not change from baseline to follow-up (baseline: 25.6 ± 7.6 and follow-up 24.7 ± 6.8 [$P = 0.240$]; mean difference = −0.88 points [95% CI = −2.38 to 0.60]). Boys and girls were similar ($P > .05$) in terms of age, body weight, and height, and also cardiovascular outcomes (**Table 1**). When compared to boys, girls presented a higher score of maturity offset and elevated CIMT (**Table 1**). Moreover, there was a significant relationship between worsening sleep quality and an increase in FIMT ($r = .299$, 95% CI .071 to .498), whereas TF had a positive relationship with FIMT ($r = .354$, 95% CI .132 to .543) (**Table 2**). For every point increase in the MSQ from baseline to follow-up there was a 1.12% (95% CI 0.26 to 1.98) increase in FIMT.

There was no significant relationship between sleep quality and CIMT, whereas physical activity demonstrated a positive relationship with CIMT ($r = .214$, 95% CI = .026 to .402)

Table 1—General characteristics of the adolescents stratified by sex (Brazil, n = 71).

Variables	Boys (n = 38)	Girls (n = 33)	*P*
Chronological age (years) $_{baseline}$	11.6 (11.4 to 11.9)	11.6 (11.4 to 11.9)	.925
Body weight (kg) $_{baseline}$	49.2 (45.2 to 53.1)	51.3 (46.5 to 56.1)	.492
Height (m) $_{baseline}$	1.54 (1.52 to 1.56)	1.55 (1.52 to 1.57)	.621
TF (%) $_{baseline}$	34.0 (30.1 to 37.8)	28.8 (24.5 to 33.1)	.079
Maturity offset (years) $_{baseline}$	0.053 (−0.181 to 0.284)	−1.64 (−1.94 to −1.35)	.000
Dyslipidemia (Z score) $_{baseline}$	0.115 (−0.698 to 0.930)	−0.10 (−0.83 to 0.62)	.687
CIMT (mm) $_{baseline}$	0.445 (0.434 to 0.456)	0.470 (0.453 to 487)	.019
CIMT Δ%	0.29 (−2.39 to 2.98)	0.321 (−2.69 to 3.33)	.989
FIMT (mm) $_{baseline}$	0.37 (0.34 to 0.40)	0.395 (0.374 to 0.417)	.205
FIMT Δ%	1.60 (−5.51 to 8.72)	−5.199 (−13.87 to 3.47)	.231
Physical activity Δ	6131.2 (−679.0 to 12941.2)	1566.2 (−8373.3 to 11505.7)	.445

Values are presented as mean (95% CI). Δ = absolute change between both moments of the study, Δ% = relative change between both moments of the study, CIMT = carotid intima-media thickness, FIMT = femoral intima-media thickness, TF = trunk fat.

Table 2—Relationship between sleep quality, arterial thickness, physical activity, and trunk fat in adolescents (Brazil, n = 71).

	Sleep Quality Δ	CIMT (mm) Δ%	FIMT (mm) Δ%
Dependent variables			
CIMT (mm) Δ%	.019 (−.215 to .251)	–	–
FIMT (mm) Δ%	.299 (.071 to .498)	–	–
Mediation			
Physical activity Δ (steps/day)	.011 (−.223 to .244)	.098 (−.138 to .324)	.121 (−.116 to .345)
TF (%)Δ	.134 (−.103 to .356)	.175 (−.061 to .392)	.354 (.132 to .543)

Values are presented as *r* (95% CI). Δ = absolute change between both moments of the study, Δ% = relative change between both moments of the study, CIMT = carotid intima-media thickness, FIMT = femoral intima-media thickness, TF = trunk fat.

(**Figure 2A**). In terms of FIMT, there was a positive relationship between sleep quality and FIMT (r = .253, 95% CI .084 to .421), whereas physical activity did not mediate this relationship (**Figure 2B**). In this model, worsening sleep quality was related to increased FIMT with a small magnitude (6.4%), in which each point increase in MSQ increased FIMT values 0.95% (95% CI 0.196 to 1.704).

Sleep quality and TF were not related to CIMT (**Figure 3A**). Sleep quality and FIMT were related to each other with a small magnitude (5.9%), given that for every point increase in the MSQ from baseline to follow-up there was a 0.89% increase in FIMT values (95% CI 0.12 to 1.66), whereas TF did not mediate this relationship. However, TF had a positive and independent relationship with FIMT (small magnitude 4.4%) (**Figure 3B**). All structural equation models were fit according to the relative chi-square test.

DISCUSSION

The current study identified that after 1 year of follow-up, worse sleep quality was related to increased FIMT, whereas physical activity and TF did not mediate this relationship. In addition, FIMT had a positive and independent relationship with TF, but not physical activity.

Sleep is a behavior with the potential to affect cardiovascular health, mainly because it exerts a chronic effect over the human system. It is important to highlight that sleep comprises not only time sleeping (the most investigated sleep outcome), but many other components of its quality (eg, difficulty in falling asleep, midsleep awakenings, early awakening in the morning, snoring, feeling tired upon awakening, excessive daytime sleepiness, and restless sleep). In fact, short sleep duration has been related to metabolic outcomes and CIMT in young adults.[8,18] Therefore, the absence of measures of sleep duration should be recognized as a limitation in our study.

We found a positive relationship between poor sleep quality and FIMT, which also demonstrated a positive relationship with TF, but not physical activity. The pathways to support these findings are not entirely clear, although it is possible to presume that patterns of sleep may have an influence on the autonomic nervous system and this fact, at least in part, could be related to alterations in FIMT. Poor sleep quality decreases parasympathetic modulation and, consequently, may increase sympathetic modulation in children,[19] leading to vasoconstriction.[20] Moreover, higher sympathetic modulation may promote alterations related to the inflammatory process,[21] and is also associated with obesity among young people,[22,23] and in this way, these aspects may have influenced the elevated FIMT in our study.

In parallel, given the fact that poor sleep quality seems to affect autonomic modulation in terms of elevated sympathetic modulation, it is important to take into consideration the possible role of adventitial autonomic dysfunction[20] on arterial

Figure 2—Structural equation modelling, physical activity.

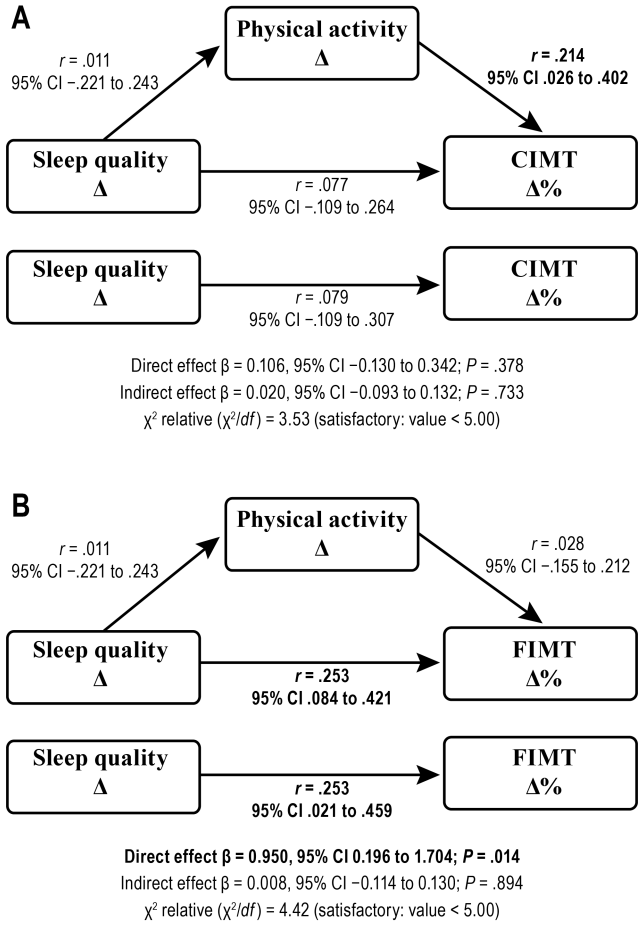
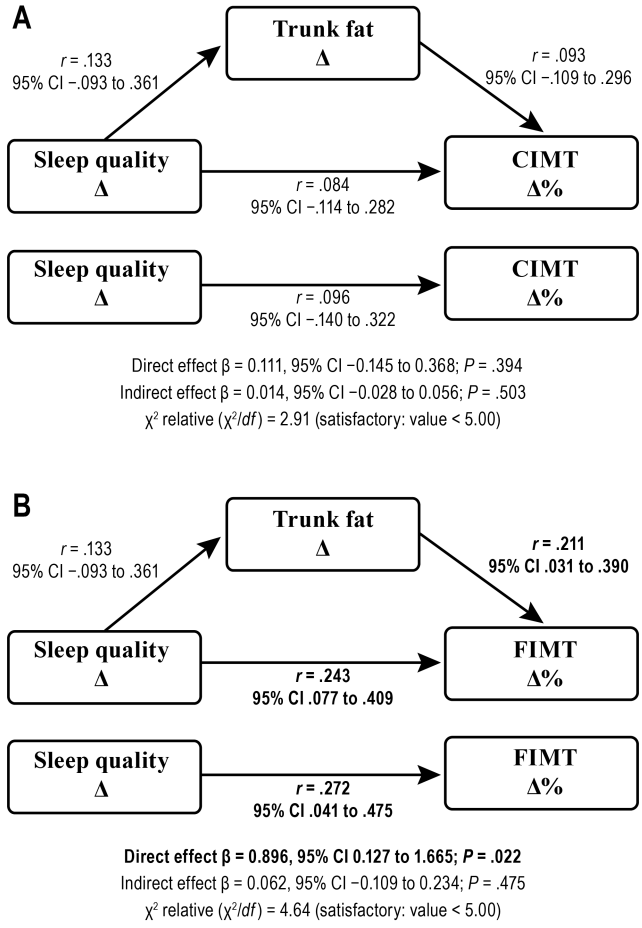


Figure 3—Structural equation modelling, trunk fat.



Adjusted by sex, age (baseline), maturity offset (baseline), Z score of dyslipidemia (baseline), CIMT (baseline) **(A)** and FIMT (baseline) **(B)**. Data are presented in values of Pearson coefficient of correlation (*r*) and 95% confidence intervals (95% CI). Total, direct, and indirect effect are presented in values of β (95% CI) estimated through the bootstrap resampling method and statistical significance ($P < .05$). Δ = absolute change between assessments of the study, Δ% = relative change between assessments of the study, CIMT = carotid intima-media thickness, FIMT = femoral intima-media thickness.

Adjusted by sex, age (baseline), maturity offset (baseline), Z score of dyslipidemia (baseline), CIMT (baseline) **(A)** and FIMT (baseline) **(B)**. Data are presented in values of Pearson coefficient of correlation (*r*) and 95% confidence intervals (95% CI). Total, direct, and indirect effect are presented in values of β (95% CI) estimated through the bootstrap resampling method and statistical significance ($P < .05$). Δ = absolute change between assessments of the study, Δ% = relative change between assessments of the study, CIMT = carotid intima-media thickness, FIMT = femoral intima-media thickness

thickness. With this in mind, the inflammatory process leading to an atherosclerotic arterial wall is not limited to the luminal side of the vessel,[24] bearing in mind that C-reactive protein is related to higher permeability of the endothelium for intake of lipoproteins through the subendothelial space.

Moreover, it is relevant to consider that poor sleep quality may interfere in the natural cycles of sleep waves at night, affecting metabolism functions,[25] and increasing the risk of deleterious responses, such as insulin resistance.[21] It is known that insulin resistance affects the redox state, decreasing the amount of nitric oxide available in the smooth muscle,[26] increasing oxidative stress and leading to proinflammatory pathways harmful to vessel structure.[21] Sauvet et al.[27] found that sleep deprivation can cause an increase in endothelin levels, a potent vasoconstrictor released by endothelial cells into smooth muscle through the Ras/Raf/MAP kinase pathway,[26] and its action on the vessel is increased due to insulin resistance.

Furthermore, it is interesting to note that the hypothesis that insulin resistance plays a relevant role in the interaction between sleep quality and arterial thickness is enhanced by the fact that TF had a positive relationship with both. Abdominal obesity severely affects the glucose metabolism, increasing the risk of insulin resistance on muscular tissue,[26] and this response is associated with high levels of proinflammatory cytokines that may play an important role in arterial thickness.[10] In the current study, it is not clear why the femoral artery seems more affected by sleep than the carotid artery. The response to this phenomenon might be supported by the fact that this artery presents greater oscillation in wall shear rates than other arteries,[28] leading to a higher risk of cardiovascular complications in this vascular bed.

This study has limitations that should be highlighted. First, the high dropout rate constitutes a limitation, especially since the statistical power to detect significant relationships is decreased. Similarly, we could not conduct analyses split by sex

due to the statistical power. Second, self-report of sleep quality is an outcome prone to biases (like any other questionnaire) and our questionnaire did not measure the time of sleep, a relevant component to clearly understand the effect of sleep on cardiovascular outcomes. Moreover, somatic maturation was estimated through the estimated peak of height velocity method, which can present bias, although our sample was inside the range of best prediction, especially for girls.[29] Finally, measurement of other metabolic agents (eg, insulin resistance and interleukin-6) would be helpful to better understand this phenomenon.

The strong points of this study include its longitudinal design, which is less usual than cross-sectional designs in research about this issue. Moreover, the use of more accurate methods to assess adipose tissue (dual-energy x-ray absorptiometry) and physical activity (pedometer) are relevant aspects of internal validity. Finally, few data are available in pediatric groups on the interaction between sleep quality and arterial thickening, a phenomenon mostly investigated in adults.[8] To the best of our knowledge this is the first longitudinal study to investigate the effects of sleep quality on CIMT and FIMT in adolescents. Our questionnaire assesses different components of sleep, including symptoms of both insomnia (difficulty in falling asleep, midsleep awakenings, early awakening in the morning, and hypnotic medication use) and obstructive sleep apnea (snoring, feeling tired upon awakening, excessive daytime sleepiness, and restless sleep). Therefore, it is not entirely clear which of these sleep components is the main one responsible for our findings, leading us to assume that more research about this issue is still necessary.

It is important to highlight the public health message from our results. "Health begins at home," and during adolescence, sleep quality has an important role in this phenomenon. It is necessary for parents and/or legal guardians to be aware of the time spent in sleep and also try to understand whether sleep quality is satisfactory in order to avoid health problems related to cardiovascular disease risk factors.

In conclusion, the findings of this longitudinal study hint that worse sleep quality was related to higher FIMT among adolescents, whereas physical activity and adiposity did not mediate this process. In addition, FIMT had a positive and independent relationship with TF, but not physical activity.

ABBREVIATIONS

Δ, absolute change
Δ%, relative change
CIMT, carotid intima-media thickness
FIMT, femoral intima-media thickness
MSQ, Mini Sleep Questionnaire
TF, trunk fat

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