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ORIGINAL RESEARCH

Association Between Sleep Time and Pro- and Anti-Inflammatory Biomarkers Is Mediated by Abdominal Obesity Among Adolescents

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Objectives: Movement behaviors and abdominal obesity are associated with higher inflammatory biomarkers. However, the role of waist circumference as a mediating factor is still unknown. Thus, our aims were to (1) test the associations between 24-hour movement behavior variables (physical activity, sedentary behavior, and sleep), abdominal obesity, and pro- and anti-inflammatory biomarkers; and (2) investigate whether abdominal obesity had a mediating effect between the investigated associations. ***Methods:*** This multicenter cross-sectional study included 3591 adolescents (aged 12–17 y) from 4 Brazilian cities. Waist circumference (in centimeters; at half the distance between the iliac crest and at the lower costal margin), 24-hour movement behaviors (validated questionnaire), high-sensitive C-reactive protein, and adiponectin (serum plasma) were evaluated. We used multiple mediation regression models (95% confidence interval) to determine if waist circumference mediated the association between 24-hour movement behaviors and pro- and anti-inflammatory biomarkers. ***Results:*** The results revealed that screen time and moderate to vigorous physical activity were not associated with pro- or anti-inflammatory biomarkers. However, sleep duration (in hours per day) was negatively associated with pro- (C-reactive protein, $\beta = -0.08$; 95% confidence interval, −0.38 to −0.02) and anti- (adiponectin, $\beta = -0.31$; 95% confidence interval, −2.13 to −0.12) inflammatory biomarkers. Our results also showed that waist circumference mediated the association between sleep duration and high-sensitive C-reactive protein (2.7%), and adiponectin (2.8%). ***Conclusion:*** Sleep duration was inversely associated with pro- and anti-inflammatory biomarkers, and these relations were mediated by abdominal obesity. Therefore, adolescents having healthy sleep can have implications for reducing waist circumference and inflammatory indicators.

Keywords: life styles, waist circumference, inflammatory

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Behaviors related to energy expenditure (physical activity, sedentary behavior, and sleep time) in adolescents are associated with several health outcomes, such as impaired cognition,[1] behavioral difficulties (eg, aggression, difficulties in emotion regulation),[2] reduced academic performance,[3] and increased risk of developing obesity[4] and cardiometabolic derangements (eg, impaired glucose).[5–7]

More specifically, an association between short (≥7 h/d) and long (≥11 h/d) sleep duration, low levels of physical activity, and high levels of sedentary behavior with obesity in adolescents has been previously shown,[8,9] with specific combinations of these behaviors increasing the likelihood of developing obesity by up to 80%. Obesity interferes not only with the individual's weight, but also alters the immune system function, generating inflammation as a result of the high amount of adipose tissue, which in turn, can play a causative role in insulin resistance development.[10,11]

Several studies have explored the association between behaviors related to energy expenditure independently and high-sensitive C-reactive protein (hs-CRP),[1] adjusting for adiposity

indicators.[12] However, the existing literature to examine the associations between the aggregation of movement behaviors (sleep time, screen time, physical activity, and 24-h movement behavior score) on levels of adiponectin is inconclusive.[13,14] Additionally, no study has focused on whether there is an association between movement behaviors (sleep time, screen time, physical activity, and 24-h movement behavior score) and pro- and anti-inflammatory biomarkers and if abdominal adiposity may mediate this association. Therefore, the objective of this study was to reexamine the relationship between 24-hour movement behaviors and health outcomes (such as inflammatory biomarkers) by adequately considering the compositional nature of daily time data. Given the existing evidence, we hypothesized that there is a negative association between a 24-hour movement behavior and hs-CRP (pro-inflammatory) and adiponectin (anti-inflammatory); and that this association would be partially mediated by anthropometric indicators of adiposity.

Methods

Study Sample

The present study is part of the Study of Cardiovascular Risk Factors in Adolescents ("ERICA") Study, a multicenter cross-sectional, school-based study. ERICA's main objective was to estimate the prevalence of metabolic syndrome and other cardiovascular risk factors in adolescents (aged 12–17 y) from public and private schools in Brazilian cities with more than 100,000 inhabitants.[15]

The present study analyzed a fasting blood sample from a subsample of 3591 adolescents who attended morning classes in 4 different latitudes: Fortaleza, Rio de Janeiro, Brasília, and Porto Alegre.[16] These cities were selected due to their location and having maintained biorepositories during the study. Sample selection for hs-CRP and adiponectin analysis was performed by proportional random allocation to ensure a distribution of gender, age, race, and a season of data collection, a proxy for sun exposure. Blood samples were drawn at school and sent to research centers in the 4 participating cities for processing and storage at −80 °C.[17]

Data Collection

Trained observers performed all measurements (anthropometrics and questionnaires). The questionnaire for adolescent participants was self-reported using an electronic data collector or the personal digital assistant, model LG GM750Q, and contained 115 questions. The adolescents were asked to answer all the questions, so if participants did not answer a question, they still needed to answer the subsequent related questions. However, in the present study, only questionnaires with complete responses by adolescents were used in the analyses. Data collection occurred between February 2013 and November 2014. The study was conducted in accordance with the principles of the Declaration of Helsinki. The Research Ethics Committee of the Federal University of Rio de Janeiro approved the study on January 2009. For each of the 26 states and the Federal District, approval was obtained from the respective Ethics Committees. Permission to carry out the study was obtained from all state and local departments of education and at all schools. Written informed consent was obtained from each student and from their legal guardians. During the data collection, care was taken to guarantee the student's privacy and confidentiality, such as when using folding screens for anthropometric measurements. ERICA sampling, design, and data collection details can be obtained from previous publications.[15,17]

Exposure Variables

The results obtained from the questionnaire were used to assess movement behaviors (sleep time, screen time, physical activity, and 24-h movement behavior score) and covariates.

Sleep Time

Within the questionnaire, there were 4 questions related to sleep. The participant selected the time they usually slept and woke up on a typical weekday and weekend. The answers were closed, with 24 responses (ie, 1 for each hour of the day). Weekly average sleep duration was calculated as the weighted average hour of sleep during the week and at the weekend, using the following formula: (weekly sleep duration × 5 + weekend sleep duration × 2)/7, which considered the corrections made at bedtime and waking up times.[18]

Physical Activity

To determine participant's level of physical activity, we used an adaptation of the Self-Administered Physical Activity Checklist. This tool consisted of a list of 24 modalities and allowed participants to report the frequency (days) and time (hours and minutes) that they participated in moderate to vigorous physical activity (MVPA) over the past week. This questionnaire has been used in other studies within Brazil and the version used in ERICA was validated for use with Brazilian adolescents.[19]

Screen Time

Screen time was assessed using questions about screen time: "During an ordinary weekday, how many hours do you spend watching television, using the computer, or playing videogames?" The alternatives allow response in hours (range between 0 [do not do these activities] and ≥7 h/d or option "do not report/do not remember").[20]

24-Hour Movement Behaviors

We considered exposure in this study as the composition (mix) of 24-hour movement behaviors: MVPA (mean = 65.3 min/d), sedentary behavior (mean = 10.8 h/d), and sleep duration (mean = 6.9 h/d) (Supplementary Table S1 [available online]). In the following sections, we describe the measurement methods and classification criteria according to the 24-hour movement guideline.[18] We selected theoretical definitions of the constructs of interest (physical activity, sedentary behavior, and sleep time).[17] In the design phase, we applied the international classification of activities for time-use statistics assumptions (coded participants' daily activities over a 24-hour period per day from 0:00 to 23:59 h)[21] to operationalize variables for physical activity (moderate and vigorous), sedentary behavior (TV watching, playing games, computer use, studying or reading, and passive commuting), and sleep duration (essential and incidental). Guidelines recommend ≥60 minutes per day of MVPA, ≤2 hours per day of screen time, and 9 to 12 hours per day of sleep for individuals aged 6–12 years (8–10 h for those aged 13–17 y). Using the operationalized variables, we applied the compositional data analysis to summarize the behaviors[22] and further classified the variables into 4 groups: no behaviors meet the criteria, 1 behavior meets the criteria, 2 behaviors meet the criteria, and 3 behaviors meet the criteria, according to the 24-hour movement guideline.[23]

Mediator

Abdominal Obesity

Anthropometric measurements were performed by trained staff. Waist circumference was measured as a *proxy* for abdominal adiposity.[24] Wait circumference was measured to the nearest 1 mm using a fiberglass anthropometric tape, with millimeter resolution and 1.5 m in length (Sanny) at the end of gentle expiration. The measurement was taken horizontally, at half the distance between the iliac crest and at the lower costal margin. Measurements were taken in duplicate for quality control purposes. A maximum variation of 1 cm between the 2 measurements was allowed.[15]

Outcomes

Inflammatory Serum Biomarkers

Blood samples were analyzed at the reference laboratory, and quality control was based on the criteria from the Clinical Pathology Society.[25] A full description of the blood sampling is available elsewhere.[26] In brief, blood samples were drawn after at least

Table 1 Demographic, Behavioral Characteristics, Anthropometrics, and Biomarkers Status Data of Adolescents From 4 Capitals Included in the ERICA Study (Mean or Percentage Values and 95% CIs)

Variable	n = 3591	Mean or %	95% CI	
City				
Fortaleza	709	19.7	18.5%	21.1%
Rio de Janeiro	886	24.7	23.3%	26.1%
Brasilia	1221	34.0	32.5%	35.6%
Porto Alegre	775	21.6	20.3%	23.0%
Type of school				
Public	2508	69.8	50.9%	71.6%
Private	1083	30.2	28.4%	49.1%
Age, y	3591	14.5	14.4	14.7
Biological sex				
Female	2237	62.3	60.7%	63.9%
Male	1354	37.7	36.1%	39.3%
Maternal education[a]				
Never studies	37	1.03	0.6%	1.4%
Secondary school or less	821	22.86	17.5%	23.7%
High school, incomplete	269	7.49	5.6%	8.5%
High school complete or incomplete college	1033	28.77	24.0%	30.2%
Graduate degree	785	21.86	17.4%	29.0%
Weight, kg	3591	58.4	57.5	59.3
Height, cm	3591	163.6	163.2	164.0
Waist circumference, cm	3591	73.0	72.1	73.8
Screen time				
>2 h/d	2323	64.7	60.2%	65.0%
≤2 h/d	1268	35.3	35.0%	39.8%
Sleep time				
<8 or >10 h/night	2408	67.1	61.6%	67.6%
8–10 h/night	1183	32.9	32.4%	38.4%
MVPA				
<60 min/d	2402	66.9	62.5%	67.2%
≥60 min/d	1189	33.1	32.8%	37.5%
Score 24 h				
0 healthy behavior	1143	31.8	27.7%	32.0%
1 healthy behavior	1449	40.4	36.5%	40.8%
2 healthy behaviors	806	22.5	23.4%	28.0%
3 healthy behaviors	193	5.4	4.9%	7.3%
C-reactive protein, mg/dL	3591	1.98	1.51	2.45
Adiponectin, mg/L	3591	14.71	13.92	15.50

Abbreviations: CI, confidence interval; MVPA, moderate to vigorous physical activity.
[a]n = 646 no information responses (18.0% of missing data).

12 hours of fasting. To confirm the compliance, a preexamination questionnaire was administered, including questions about time of last food intake, bedtime, and wake-up time on the day before the data collection and if any food or liquid was ingested. The use of any medication on the day before data collection (water and medications were allowed) was completed by each participant. For those who did not comply with the 12-hour fast, a new attempt to collect the blood sample was scheduled appropriately. Additionally, in some specific cases, a direct collection at the local laboratory was offered.

All participants were informed about the procedures before blood samples were drawn and could withdraw from the study at any point. First, correct identification was verified with the participant. Collection was performed using a vacuum needle for multiple collections, after asepsis of the collection site with alcohol, and a garroting time of less than 1 minute. After finishing the blood collection, all participants received a snack. All participants provided 6 tubes (4 mL of blood per tube).

C-Reactive Protein (hs-CRP)

The hs-CRP measurements were performed in the 2 laboratories using the same techniques (immunoturbidimetry—Kit Bio Systems), equipment brand, and model (Siemens, ADVIA 2400 chemistry analyzer). The concordance between local and reference laboratories in the quality control analyses of hs-CRP was high (0.94 [Bland–Altman test]) and when categorized, 3 mg/L κ it was .86.

Adiponectin

Serum total adiponectin concentrations (µg/mL) were measured using an enzyme-linked immunosorbent assay kit from Invitrogen (KHP0041) with a sensitivity of 0.001 µg/mL. Intra- and interassay coefficients of variation were <5%, following the manufacturer's instructions. Laboratory analyses were performed by a single laboratory using frozen serum (−80 °C) and following a standardized protocol.[26]

Statistics Analyses

The descriptive analyses were presented as means (continuous variables), percentages (categorical variables), and 95% confidence intervals. Multilevel nonparametric Kernel effects regression models were used to analyze the associations between each biomarker and independent variables,[27] considering 2 levels of data organization: (1) individual factors and (2) potential confounders (biological sex, age, type of school, and maternal education). We used the school (public/private) and study centers (Brasília, Fortaleza, Porto Alegre, and Rio de Janeiro) as the clustering variable. Representing 10% modification in the β of any variable already in the model was considered significant. If a variables had P values <.20 in the univariate analysis,[28] they were included as a variable in the multivariate multilevel models (Supplementary Figure S1 [available online]).

To assess mediation effects within the observed associations, we followed the methodology of Baron and Kenny. There was a mediation effect if the total effect (path c) between biomarker and the abdominal obesity was significant, and when this association was attenuated (path $c' <$ path c; partial mediation), or if path c' reached no statistical significance when the mediator was included in the regression model (complete mediation). As we observed no significant total effects, the Sobel test was used to test the joint significance for the indirect effects.[29] Subsequently, we considered the indirect effects when the product of coefficients was significant, and the total association was attenuated (path $c' <$ path c) when the mediator was included in the regression model. The mediated proportions were calculated by dividing the indirect by the total effect ($[a \times b]/c$), but only when mediation was established.[30,31]

Stata (version 15, Stata Corp) was used for all statistical analyses. All analyses were adjusted for the pooled nature of the sample using the "svy" command set. We did not stratify the analysis by biological sex because the interactions between biological sex and the variables studied were not observed.

Table 2 Adjusted[a] Nonparametric Regression Analysis Evaluating the Association Among the Outcomes and Independent Variables in Adolescents From the ERICA Study

	C-reactive protein, mg/dL (mean estimate = 1.76)		Adiponectin, mg/dL (mean estimate = 15.18)	
Outcomes	**Effect**	**95% CI**	**Effect**	**95% CI**
Independent variables				
Waist circumference, cm	**0.08**	**0.07 to 0.10**	**−0.15**	**−0.07 to −0.12**
Screen time, h/d	−0.08	−0.37 to 0.23	−0.02	−0.63 to 0.57
Sleep time, h/night	**−0.08**	**−0.38** to **−0.02**	**−0.31**	**−2.13** to **−0.12**
Physical activity, min/d	−0.002	−0.003 to 0.002	−0.001	−0.003 to 0.001
Score 24 h[b]				
0 healthy behaviors		**Ref**		**Ref**
1 healthy behavior	−0.01	−0.39 to 0.36	−0.11	−0.80 to 0.59
2 healthy behaviors	0.11	−0.37 to 0.59	−0.28	−0.71 to 1.26
3 healthy behaviors	−0.21	−1.00 to 0.59	−1.53	**−2.77** to **−0.30**

Abbreviation: CI, confidence interval. Note: Beta coefficient and their respective CIs 95%. Significant associations are in bold. [a]This analysis was adjusted for potential confounders: *city, type of school, age, sex, and maternal education.* [b]Sum of the 3 variables (screen time + sleep duration + physical activity) to estimate the degree of healthy behaviors (0, 1, 2, or 3) existing in the adolescent.

Table 3 Multiple Mediation Analyses of the Association Between 24-Hour Movement Behaviors and Inflammatory Biomarkers, Mediated by Waist Circumference in Adolescents Aged Between 12 and 17 Years (ERICA Study)

Dependent variable (y)	Mediator (*M*)	*X* effect on *M* (path *a*, *X* → *M*)		*M* effect on *Y* (path *b*, *M* → *Y*)		Indirect effect (*a* × *b*)		Direct effect (path *c'*)		% Mediated (*a* × *b*/*c*)
		β	95% CI	*β*	95% CI	*β*	95% CI	*β*	95% CI	%
Screen time, h/d										
C-reactive protein	Waist circumference	–0.01	–0.02 to 0.01	**0.08**	**0.07 to 0.11**	**0.08**	**0.07 to 0.10**	0.01	0.01 to 0.02	0.6
Adiponectin	Waist circumference	–0.01	–0.03 to 0.05	**−0.14**	**−0.17 to −0.11**	0.01	–0.01 to 0.03	0.005	–0.01 to 0.02	0.5
Sleep time, h/night										
C-reactive protein	Waist circumference	**−0.40**	**−0.65 to −0.16**	**0.09**	**0.07 to 0.10**	**−0.03**	**−0.06 to −0.01**	**−0.05**	**−0.07 to −0.01**	**2.7**
Adiponectin	Waist circumference	**−0.37**	**−0.61 to −0.13**	**−0.13**	**−0.16 to −0.10**	**0.05**	**0.02 to 0.08**	**−0.14**	**−0.39 to −0.09**	**2.8**
MVPA, min/d										
C-reactive protein	Waist circumference	**0.13**	**4.10 to 0.01**	**0.08**	**0.07 to 0.10**	0.01	–0.01 to 0.02	0.001	–0.101 to 0.02	0.08
Adiponectin	Waist circumference	**0.002**	**0.001 to 0.003**	**−0.14**	**−0.17 to −0.11**	–0.001	–0.004 to 0.01	–0.01	–0.05 to 0.02	1.3
Score 24 h[a]										
C-reactive protein	Waist circumference	–0.20	–0.56 to 0.17	**0.08**	**0.07 to 0.10**	–0.02	–0.05 to 0.02	–0.13	–0.20 to 0.17	3.0
Adiponectin	Waist circumference	–0.17	–0.53 to 0.19	**−0.14**	**−0.17 to −0.11**	0.02	–0.03 to 0.07	–0.11	–0.48 to 0.26	0.3

Abbreviations: CI, confidence interval; MVPA, moderate to vigorous physical activity.

[a]Sum of the 3 variables (screen time + sleep duration + physical activity) to estimate the degree of healthy behavior (0, 1, 2, or 3 healthy behaviors) existing in the adolescent.

Bold indicates significant associations ($P < .05$).

Results

We evaluated 3591 Brazilian adolescents from 4 state capitals, and their characteristics are presented in Table 1. The sample consisted of mostly females, attending public schools. One-third of the sample (n = 1189) did not engage in 60 minutes of more of MVPA per day and two-thirds (n = 2403) did not engage in adequate sleep duration (add definition).

Table 2 presents the associations between inflammatory biomarkers, waist circumference, and the independent and combined 24-hour movement behaviors (screen time, sleep time, and physical activity). MVPA and screen time did not show significant associations with either outcomes. However, hs-CRP showed a positive association with waist circumference and a negative association with sleep duration. Furthermore, there is an inverse relationship between adiponectin and waist circumference, sleep duration, and the combination of three healthy behaviors.

The mediation analyses are presented in Table 3. Waist circumference was a significant mediator in the association between sleep duration and inflammatory biomarkers, showing the largest magnitude in the association between sleep duration and adiponectin.

Discussion

Our study revealed that waist circumference mediated the association between sleep duration and hs-CRP and adiponectin. However, we observed that screen time and MVPA were not significantly associated with either inflammatory biomarkers (CRP and adiponectin). This was the first study to find the mediation effect of waist circumference on the association between sleep duration and inflammatory biomarkers in adolescents. Recent studies (epidemiological and animal) suggested that sleep plays an important role in energy homeostasis,[32] and also that sleep disturbances increase the risk for obesity[33] by modulating the clock genes (eg, CLOCK, BMAL1, RORa, REV-ERBα) of the circadian rhythm.[34] Therefore, poor sleep quality could lead obesity for adolescents because these genes generate a complex network of interlocking feedback loops that fine-tune the clock and coordinate metabolic processes with the daily cycles of sleep/wakefulness and fasting/feeding.[35]

Our results support studies evaluating the association between obesity × sleep and sleep × inflammatory biomarkers among adults. Several physiological mechanisms may explain the negative effects of sleep duration and adipose tissue induced on inflammatory biomarkers. There is strong evidence that short-duration sleepers modify the expression of REV-ERBα gene in favor of visceral fat accumulation.[36,37] Thus, obesity leads not only to increased circulating concentration of CRP,[12] but also to increased expression of its receptors, which, in turn, could result in increased adipogenesis, leading to a vicious circle. Although the physiological mechanism of these diurnal variations is still unknown, studies have demonstrated[38,39] that disruption of the normal sleep–wake cycle via sleep deprivation can significantly affect immune system function. Consequently, this decrease in sleep duration and quality generates inflammatory markers such as hs-CRP.[38,39]

We also found that waist circumference mediated the association between sleep duration and adiponectin. We expected sleep duration to present a positive association with adiponectin; however, waist circumference changed this hypothesized effect. There are several possible physiological mechanisms by which waist circumference (proxies for visceral adipose depot mass) may contribute to decreased adiponectin serum levels.[40] First, adiponectin production by visceral adipose tissue decreases with fat accumulation.[41] Second, a previous study showed that an increase in adiposity is positively associated with cytokines, which are one of the primary mediators that stimulate the hypothalamic–pituitary–adrenal axis during inflammatory stress generated by sleep deprivation.[42] Our findings offer some further insight into the inconsistency in the literature[43] about the role of sleep duration in the inflammation process.

A limitation of this study is that it was a cross-sectional design; consequently, causality cannot be established. Furthermore, we used questionnaires to assess 24-hour movement behaviors, which may be subject to recall bias and hinder the internal validity of these findings. By contrast, the diverse geographic origin of the samples, the use high-quality control of 2 serum inflammatory biomarkers, and multilevel adjusted analysis are some of the main strengths of our study. Therefore, adolescents having healthy sleep can have implications for reducing waist circumference and inflammatory indicators.

Conclusion

In conclusion, this study revealed that sleep duration is inversely associated with pro- and anti-inflammatory biomarkers, and these relations were mediated by abdominal obesity in Brazilian adolescents. Furthermore, abdominal obesity is positively associated with CRP and inversely associated with adiponectin in these adolescents. Although abdominal obesity is associated with inflammatory biomarkers, abdominal obesity does not mediate the association between screen time and MVPA and pro- and anti-inflammatory biomarkers in adolescents.

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