A Systematic Review on Sleep Duration and Dyslipidemia in Adolescents: Understanding Inconsistencies

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Introduction

Although many questions about the role of sleep remain unanswered, it is known that sleep is not only a physiological function, but also performs an important role in promoting growth, maturation and general health of children and adolescents\(^1\), contributing significantly to cognitive, emotional functions and school performance\(^2\). Currently, there is a tendency for the young population to have irregular sleeping hours, with differences in bed and wake-up times between weekdays and weekends, especially as they get older\(^3-4\).

There is a growing interest about the impact of sleep and its disorders on regulation of inflammatory processes and morbidities, particularly in the context of metabolic and cardiovascular diseases (CVD) and their complications\(^5\). In children and adolescents, cross-sectional\(^6-7\) and prospective\(^8,9\) studies have shown an association between overweight or obesity and few hours of sleep. In adults, there is evidence supporting this association, as well as correlations with insulin resistance, diabetes and cardiovascular diseases\(^10-15\). Few hours of sleep can also play a role in the etiology of a key risk factor to CVD, dyslipidemia\(^12,14,15\). Physiologically, sleep reduction is associated with hormonal alterations that may promote the development of an atherogenic lipid profile, including increase of cortisol and ghrelin and reduction of leptin levels, in addition to sympathovagal responses\(^16-18\). In order to obtain more information about the association between lipid metabolism alterations and sleep duration specifically in adolescents, we have performed a systematic review of the literature.

Methods

This systematic review was based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement\(^19\).

The search was performed in the electronic databases Medline via Pubmed\(^20\) Lilacs\(^21\), Web of Science\(^22\), Scopus\(^23\) and Adolec\(^24\).

Selection of the descriptors used in the review process was made through MeSH (Pubmed’s Medical Subject Headings). The search was performed in English, using three concept blocks: the first with terms related to sleep (sleep); the second with terms related to adolescence (adoles\(^*\), teen\(^*\), student\(^*\), youth, young); and the third with terms related to lipids (lipid\(^*\), lipemia\(^*\), cholesterol, HDL, LDL, triglyceride\(^*\), lipoprotein\(^*\), hypercholesterolemia\(^*\), hypercholesteremia\(^*\), dyslipidemia\(^*\), dyslipoproteinemia\(^*\), hyperlipidemia\(^*\), hyperlipemia\(^*\), “high density lipoprotein cholesterol”, “low density lipoprotein cholesterol”). The Boolean operator “OR” was used for the combination of the descriptors within each block and the Boolean operator “AND” was used to combine the blocks amongst themselves. The truncation of terms was applied when necessary. No search limits were used for date, language, study design or sample size. The search was carried out in August 2014, contemplating articles published up to that date. Table 1 shows the search strategy used in each database.

Criteria for article inclusion in the systematic review were as follows: (a) studies on adolescents older than 10 years old; (b) studies that evaluated the association between sleep duration in hours and any lipid marker; (c) original research article. Articles evaluating any kind of sleep-related disorder, review studies, and experimental studies with animals were excluded. It was decided not to include theses, dissertations, and monographs. We reviewed the bibliographic references of reviews, systematic reviews, and meta-analyses that were found in the databases.

The articles were selected by two epidemiologists (GAA and LAB), initially based on title reading and then on abstract reading. Of the selected abstracts, the full articles were reviewed. In case of disagreement between the two reviewers with regard to the inclusion criteria, the title, and the abstract or the full article was maintained to be further evaluated. In case of disagreement with regard to the inclusion criteria, a third person was consulted.

Data from included articles were extracted independently, in duplicate (GAA and LAB), using a standard form. After extraction, data were compared and discussed. We extracted information about authorship, publication date, study place, population study, type of study, methods of sleep duration measurement and lipid profile assessment, sleep duration in hours, lipid markers, measure of association used to evaluate the correlation between hours of sleep and lipid profile, and variables used for adjustment of regression models.

We used an adaptation of the Newcastle-Ottawa (NOS) Quality Assessment Scale for Case-Control and Cohort Studies\(^25\), from the Ottawa Hospital Research Institute, to assess the quality of the longitudinal study included in this review. We also used the same scale adapted by Flynn et al\(^26\) to assess the quality of cross-sectional studies.

Keywords

Sleep; Dyslipidemias; Adolescent; Review.

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Manuscript received January 18, 2015; revised manuscript June 29, 2015;
accepted July 01, 2015.

DOI: 10.5935/abc.20150121
The longitudinal study showed a moderate risk of bias obtained four points out of six in the bias risk evaluation.

Table 3. Only two cross-sectional studies

| Table 1 – Search strategy used for each database |
|-----------------------------------------------|
| **Pubmed**                                    |
| (sleep OR Title/Abstract) AND (adoles OR teen OR student OR youth OR young) OR (lipid OR lipemia OR cholesterol OR HDL OR LDL OR VLDL OR triglyceride OR lipoprotein OR hypercholesterolemia OR hypercholesteremia OR dyslipidemia OR dyslipoproteinemia OR hyperlipidemia OR "high density lipoprotein cholesterol" OR "low density lipoprotein cholesterol") |
| OR sleep OR (adoles OR teen OR student OR youth OR young) AND (lipid OR lipemia OR cholesterol OR HDL OR LDL OR VLDL OR triglyceride OR lipoprotein OR hypercholesterolemia OR hypercholesteremia OR dyslipidemia OR dyslipoproteinemia OR hyperlipidemia OR "high density lipoprotein cholesterol" OR "low density lipoprotein cholesterol") |
| **Lilacs**                                    |
| (Topic=sleep) AND Topic(adoles OR teen OR student OR youth OR young) AND Topic(lipid OR lipemia OR cholesterol OR HDL OR LDL OR VLDL OR triglyceride OR lipoprotein OR hypercholesterolemia OR hypercholesteremia OR dyslipidemia OR dyslipoproteinemia OR hyperlipidemia OR "high density lipoprotein cholesterol" OR "low density lipoprotein cholesterol") |
| **Adolec**                                   |
| (TITLE-ABS-KEY(sleep) AND TITLE-ABS-KEY(adoles OR teen OR student OR youth OR young) AND TITLE-ABS-KEY(lipid OR lipemia OR cholesterol OR HDL OR LDL OR VLDL OR triglyceride OR lipoprotein OR hypercholesterolemia OR hypercholesteremia OR dyslipidemia OR dyslipoproteinemia OR hyperlipidemia OR "high density lipoprotein cholesterol" OR "low density lipoprotein cholesterol") |
| **Web of Science**                           |
| (sleep* [Title/Abstract] AND (adoles* OR teen* OR student* OR youth OR young* OR lipid* OR lipemia* OR cholesterol OR HDL OR LDL OR VLDL OR triglyceride OR lipoprotein OR hypercholesterolemia OR hypercholesteremia OR dyslipidemia OR dyslipoproteinemia OR hyperlipidemia OR "high density lipoprotein cholesterol" OR "low density lipoprotein cholesterol") [Words]) |
| **Scopus**                                   |
| (TITLE-ABS-KEY(sleep*) AND TITLE-ABS-KEY(adoles* OR teen* OR student* OR youth OR young*) AND TITLE-ABS-KEY(lipid* OR lipemia* OR cholesterol OR HDL OR LDL OR VLDL OR triglyceride* OR lipoprotein* OR hypercholesterolemia* OR hypercholesteremia* OR dyslipidemia* OR dyslipoproteinemia* OR hyperlipidemia* OR "high density lipoprotein cholesterol*" OR "low density lipoprotein cholesterol") [Words]) |

Due to the great amount of methodological heterogeneity observed between the assessed studies, a narrative approach to synthesize the results of studies included in the present systematic review was considered a better strategy.

Results

The flowchart showing the selection process is shown in Figure 1. By the end of the evaluation process, of the 859 articles chosen after the removal of duplicates, 25 were submitted to full evaluation. Seven articles met the inclusion criteria at the end of the process.

Table 2 shows the relevant characteristics of the selected studies. Of the seven studies included, only one is longitudinal. The other six studies are cross-sectional. Of the 7 studies, only one included students. Sample sizes varied considerably, from 699 in the study by Rey-López et al. to 14,267 adolescents in the study by Gangwisch et al.

All studies used questionnaires to obtain hours of sleep. The variable “sleep duration” was used as continuous in three studies, whereas the other studies used different categories to classify sleep duration.

To obtain the lipid profiles, five studies collected venous blood, one collected capillary blood, and another used self-reported information. Five studies measured total cholesterol and HDL-cholesterol, four measured triglycerides, and two evaluated LDL-cholesterol. Almost all studies controlled for gender and age, waist perimeter was adjusted for in two studies, physical activity in four, Tanner stage in two, and caloric intake in one study. The methodological quality assessment of the seven included studies is shown in Table 3. Only two cross-sectional studies obtained four points out of six in the bias risk evaluation. The longitudinal study showed a moderate risk of bias.

Table 4 shows the main results of the associations found and the control variables each study used. Considering the seven studies included, only in three an association was found between hours of sleep and lipid profile. Two studies found that shorter sleep duration was associated with a worse lipid profile (total cholesterol and LDL-cholesterol) and the results of the third one showed that long sleep duration was associated with high triglyceride levels. The other four studies did not find any association.

In four studies, the odds ratio was reported, whereas the other studies reported β coefficients from regression analysis.

Discussion

The present systematic review showed lack of consistent evidence regarding the association between sleep duration and lipid profile in adolescents. Few studies were found and some had methodological limitations. There was great heterogeneity regarding the classification and type of analysis of sleep duration and lipid metabolism markers, which probably contributed to the inconsistency of the observed results.

Concerning heterogeneity between studies, this systematic review included studies that evaluated the outcome using different methods (self-reported, capillary blood sample, venous blood sample) with different interval duration between the measure of exposition and the outcome.

Gangwisch et al. did not exclude adolescents with dyslipidemia at baseline, thus, the incidence of dyslipidemia in adolescents could not be ascertained. Moreover, as the outcome established was self-reported, and the diagnosis of dyslipidemia depends on access to medical care, a bias may have occurred if adolescents from different socioeconomic status have different sleep habits.
All studies included in this systematic review obtained information about sleep duration based on questionnaires, a method frequently used in sleep research because of its easy application and low cost. However, the validity of the information obtained through questionnaires is of concern, particularly when the tools have not been submitted to a validation process. Adolescents may report only socially desirable sleeping and waking up hours. Although all studies used questionnaires, sleep duration evaluation was also heterogeneous: one study asked the parents about the adolescent’s sleep duration, one used pre-defined categories of bedtime and waking-up time, while the others asked about sleep duration in an open question.

Objective methods for hours of sleep quantification in a population-based study are difficult to use, particularly in studies with relatively large samples. Kong et al. used actigraphy in only about 7% of their study sample (138 out of 2,053) and demonstrated a reasonable agreement between actigraphy and adolescents’ self-reports (intra-class correlation coefficient = 0.72, CI 95%: 0.61-0.80).

In the studies included in this review, duration of sleep was measured in two different ways, as a continuous or categorical variable. The lack of consensus about the best cut-off point to define short sleep duration makes it difficult to compare different studies, which would become easier if sleep duration were used as a continuous variable.

The present systematic review included a longitudinal study with important limitations and the cross-sectional studies showed associations in different directions. It was not possible to evaluate publication bias, due to the small number of studies identified. In summary, it is still uncertain whether there is an association between hours of sleep and lipid profile in adolescents. Heterogeneity regarding the way sleep hours were classified and analyzed, as well as the use of different lipids analytes may have contributed for the inconsistency of findings. More studies should be conducted on this issue to clarify the nature of this association and the involved biological mechanisms. These future studies must be longitudinal, use sleep duration as a continuous variable and consider the role of potential confounders or effect modifiers. Care must be taken to avoid over-adjustment, including variables that can be intermediary in the association between sleep duration and dyslipidemia such as BMI and food consumption.

Because of its strong association with cardiovascular disease in adults, it is important to identify and modify factors that are associated with lipid profile in adolescents. If short sleep duration is responsible for an unfavorable lipid profile, interventions that improve the quality and duration of sleep may contribute to decrease long-term cardiovascular risk.
| Reference/ Country          | Study design/ Collection date | Study population | Age | Method for obtaining hours of sleep | Exposure classification (hours of sleep) | Method for lipid profile evaluation | Outcome (alterations of lipids) |
|----------------------------|-------------------------------|------------------|-----|-----------------------------------|-----------------------------------------|-----------------------------------|----------------------------------|
| Gangwisch et al.27, 2010/ United States | Longitudinal Wave I: 1994-95 Wave II: 1996 Wave III 2001-02 | Students, with national representativeness n = 14,257 | 11-21 years boys ≥ 15.8 years old girls ≥ 15.9 years old | Questionnaire | Continuous | Questionnaire/ “Has any doctor ever (between the 1st and the 3rd wave) said you have high cholesterol?” | Dichotomous variable Yes/No |
| Kong et al28, 2011/ Hong Kong | Cross-sectional/ Collection date February 2007 – April 2008 | Students’ n = 1,274 | 12-20 years old | Questionnaire7 | <6.5h: 20% 6.5-8h: 40% >8h: 20% | Blood collection (TC, TG, HDL, LDL cholesterol) | Hypercholesterolemia |
| Narang et al29, 2012/ Canada | Cross-sectional/ Collection date 2009-2010 | Student n = 3,372 | ≥ 14.6 years old | Questionnaire27,28 | Continuous | Capillary blood collection without fasting (TC and HDL cholesterol) | TC Borderline: 4.4-5.1 mmol/L High: ≥ 5.2 mmol/L Non-HDL-cholesterol Borderline: > 3.10 to 3.75 mmol/L High: > 3.75 mmol/L |
| Azadbakht et al30, 2013/ Iran | Cross-sectional/ Collection date Data from CASPIAN III// | Students n = 5,528 | ≥ 14.69 (2.45) years old boys ≥ 14.7 (2.38) years old girls | Questionnaire | < 5h 5 to 8h > 8h | Blood collection (TC, TG and LDL cholesterol) | Abnormal serum lipids were defined as TC, LDL-C and or TG higher than the level corresponding to the age and gender-specific 95th percentile39 |
| Berentzen et al31, 2014/ Netherlands | Cross-sectional | General population n = 1,481 | Mean age at completion of the questionnaire 11.4 (± 0.3) years Mean age at the moment of medical examination 12.7 (± 0.4) years | Questionnaire | 7.5–9.5 h 10–10.5 h (ref. cat.) 11–12.5 h | Blood collection (TC and HDL cholesterol) | Continuous variable (mM) |
| Rey-López et al32, 2014/ Greece, Germany, Belgium, France, Hungary, Italy, Sweden, Austria, Spain | Cross-sectional/ Collection date 2006-2007 | Students n = 699 | ≥ 14.8 years old | Questionnaire | Continuous variable | Blood collection (TG, TC and HDL cholesterol) | Continuous variable (mg/dL) |
| Lee et al.33, 2014/ Republic of Korea | Cross-sectional/ Collection date 2007-2008 | General population n = 1,187 | = 15 years old | Questionnaire | ≤ 5h 6-7h 8-9h (ref. cat.) ≥ 10h | Blood collection (TG and HDL cholesterol) | Continuous variable (mg/dL) |

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total cholesterol; TG: Triglycerides; BMI: Body mass index.

1 number of adolescents evaluated; total number of individuals evaluated in the study is 2,053, including children and adolescents; 7 does not provide average age data or distribution by gender only for the adolescents’ group; 2 does not provide age group:

7 non-HDL cholesterol corresponds to total cholesterol minus HDL cholesterol; 27CASPIAN III – Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable disease.
### Table 3 – Evaluation of the risk of bias of the studies included

| Study                          | Kong et al\(^{27}\), 2011/Hong Kong | Narang et al\(^{28}\), 2012/Canada | Azadbakht et al\(^{29}\), 2013/Iran | Berentzen et al\(^{30}\), 2014/Netherlands | Rey-López et al\(^{31}\), 2014/Greece, Germany, Belgium, France, Hungary, Italy, Sweden, Austria, Spain | Lee et al\(^{32}\), 2014/Republic of Korea | Gangwisch et al\(^{33}\), 2010/United States |
|-------------------------------|------------------------------------------|------------------------------------|-------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|------------------------------------------------------------------|
| **Sample representativeness** | 0                                        | 0                                  | 1                                  | 0                                           | 1                                                                              | 0                                                              | 0                                                                  |
| **Definition of presenting condition** | 1                                        | 1                                  | 1                                  | 1                                           | 1                                                                              | 1                                                              | 0                                                                  |
| **Evaluation of exposure**    | 1                                        | 0                                  | 0                                  | 0                                           | 0                                                                              | 0                                                              | 0                                                                  |
| **Evaluation of outcome**     | 2                                        | 1                                  | 2                                  | 2                                           | 2                                                                              | 2                                                              | 0                                                                  |
| **Nonresponse rate**          | 0                                        | 0                                  | 0                                  | 0                                           | 0                                                                              | 0                                                              | 0                                                                  |
| **Representativeness of the exposed cohort** | 0                                        | 0                                  | 0                                  | 0                                           | 0                                                                              | 0                                                              | 1                                                                  |
| **Demonstration that outcome of interest was not present at start of study** | 0                                        | 0                                  | 0                                  | 0                                           | 0                                                                              | 0                                                              | 0                                                                  |
| **Comparability of cohorts**  | 0                                        | 0                                  | 0                                  | 0                                           | 0                                                                              | 0                                                              | 1                                                                  |
| **Assessment of outcome**     | 0                                        | 0                                  | 0                                  | 0                                           | 0                                                                              | 0                                                              | 0                                                                  |
| **Was follow-up long enough for outcomes to occur** | 0                                        | 0                                  | 0                                  | 0                                           | 0                                                                              | 0                                                              | 1                                                                  |
| **Adequacy of follow up of cohorts** | 0                                        | 0                                  | 0                                  | 0                                           | 0                                                                              | 0                                                              | 1                                                                  |
| **Total**                     | 4/6                                      | 2/6                                 | 4/6                                 | 3/6                                         | 3/6                                                                            | 3/6                                                            | 4/9                                                               |

Cross-sectional studies (maximum 6 points)
- Sample representativeness: yes (1); no (0); not informed (0)
- Definition of presenting condition: classification based on two or more lipid markers (1); on only one lipid marker (0)
- Evaluation of Exposure (hours of sleep): combination of questionnaire with another evaluation method (1); only questionnaire (0)
- Evaluation of Outcome (lipid profile): venous blood (2); capillary blood (1); self-reported (0)
- Nonresponse rate: non-respondents described (1); non-described (0)

Cohort studies (maximum 9 points)
- Evaluation of Exposure (hours of sleep): combination of questionnaire with another evaluation method (1); only questionnaire (0)
- Evaluation of Outcome (lipid profile): venous blood (2); capillary blood (1); self-reported (0)
- Representativeness of the exposed cohort (representative of the average): adequately addressed (1); not adequately addressed/not reported (0)
- Demonstration that outcome of interest was not present at start of study: adequately addressed (1); not adequately addressed/not reported (0)
- Comparability of cohorts on the basis of the design or analysis: adequately addressed (1); not adequately addressed/not reported (0)
- Assessment of outcome (independent blind assessment or record linkage): adequately addressed (1); not adequately addressed/not reported (0)
- Was follow-up long enough for outcomes to occur: adequately addressed (1); not adequately addressed/not reported (0)
- Adequacy of follow up of cohorts (complete follow up or subjects lost to follow up unlikely to introduce bias): adequately addressed (1); not adequately addressed/not reported (0)
| Variable          | Study                           | Total Control Variables Investigated                                                                 |
|-------------------|---------------------------------|-------------------------------------------------------------------------------------------------------|
| **Total cholesterol** |                                 |                                                                                                       |
| Gangwisch et al²⁷, 2010 | OR (CI 95%) Each hour: 0.87 (0.79-0.96) | Age/ gender/ race/ ethnic group/ alcohol/ smoke/ physical activity/ inactivity/ stress/ body weight |
| Kong et al³⁰, 2011 | β* = -0.160 (p-value = 0.023) OR (CI 95%) Each hour: 0.91 (0.79-1.05) | Age/ gender/ race/ ethnic group/ alcohol/ smoke/ physical activity/ inactivity/ stress/ body weight |
| Azadbakht et al¹¹, 2013 | --- | Age/ sex/ BMI/ waist perimeter/ Tanner stages (2-3 and 4-5) |
| Berentzen et al¹², 2014 | --- | Age at completion of the questionnaire/ age at medical examination/ height/ maternal level of education/ puberty and screen time |
| **LDL cholesterol** |                                 |                                                                                                       |
| Kong et al³⁰, 2011 | β* = -0.122 (p-value = 0.042) OR (CI 95%) Each hour: 0.87 (0.79-0.96) | Age/ gender/ race/ ethnic group/ alcohol/ smoke/ physical activity/ inactivity/ stress/ body weight |
| Azadbakht et al¹¹, 2013 | --- | Age/ sex/ BMI/ waist perimeter/ Tanner stages (2-3 and 4-5) |
| **HDL cholesterol** |                                 |                                                                                                       |
| Kong et al³⁰, 2011 | β* = -0.056 (p-value = 0.061) OR (CI 95%) Each hour: 0.87 (0.79-0.96) | Age/ gender/ race/ ethnic group/ alcohol/ smoke/ physical activity/ inactivity/ stress/ body weight |
| Berentzen et al¹², 2014 | --- | Age/ sex/ BMI/ waist perimeter/ Tanner stages (2-3 and 4-5) |
| Lee et al³³, 2014 | OR (95%CI) ≤ 5 h = 0.79 (0.40 - 1.53) 6-7 h = 0.86 (0.50 - 1.49) 8-9 h = 1 ≥ 10 h = 1.03 (0.44 - 2.40) | Age/ gender/ household income/ caloric intake/ physical activity |
| **TG** |                                 |                                                                                                       |
| Kong et al³⁰, 2011 | β* = 0.060 (p = 0.115) OR (CI 95%) Each hour: 0.87 (0.79-0.96) | Age/ gender/ socioeconomic status/ physical activity |
| Azadbakht et al¹¹, 2013 | --- | Age/ sex/ BMI/ waist perimeter/ Tanner stages (2-3 and 4-5) |
| Rey-López et al³⁵, 2014 | β (95%CI) School days: 0.26 (2.57; 3.09) Weekend: 0.69 (1.50; 2.88) OR (95%CI) ≤ 5 h = 1.85 (0.55 - 6.00) > 8 h = 2.17 (1.14 - 4.13) | Age/ gender/ socioeconomic status/ physical activity |
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Acknowledgments

We would like to thank Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) for providing a doctoral fellowship to GAA (process nº E26/100.332/2013), KVB (process nº 303594/2009-8) and MS process nº 302877/2009-6) were partially supported by CNPq.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Abreu GA, Barufaldi LA, Bloch KV, Szklo M; Acquisition of data: Abreu GA, Barufaldi LA; Writing of the manuscript: Abreu GA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of Doctoral submitted by Gabriela de Azevedo Abreu, from Universidade Federal do Rio de Janeiro.
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