Sleep Duration and Metabolic Syndrome

An Updated Dose–Risk Metaanalysis

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Abstract

Rationale: Several studies have reported that both short and long sleep durations are associated with the metabolic syndrome, but whether a dose–response relationship exists is unclear.

Objectives: We performed a metaanalysis to study the magnitude of the association between the different durations of sleep and metabolic syndrome.

Methods: We searched in the databases of PubMed, Web of Science, and Ovid (all Journals@Ovid) from inception to October 4, 2014 for cross-sectional studies where an association between metabolic syndrome and sleep duration was analyzed.

Measurements and Main Results: Eighteen studies with 75,657 participants were included. Daily sleep duration of 7 to 8 hours was

used as the reference group. The odds ratio (OR) of having metabolic syndrome for short (<7 h) sleep was 1.23 (95% CI, 1.11–1.37; $P < 0.001$; I^2 , 71%). The ORs for less than 5 hours, 5 to 6 hours, and 6 to 7 hours of sleep were 1.51 (95% CI, 1.10–2.08; $P = 0.01$), 1.28 (95% CI, 1.11–1.48; $P < 0.001$), and 1.16 (95% CI, 1.02–1.31; $P = 0.02$), respectively. The coefficient of sleep duration on log of ORs was -0.06 ± 0.02 ($P = 0.02$). The OR for long sleep duration was 1.13 (95% CI, 0.97–1.32; $P = 0.10$; I^2 , 89%).

Conclusions: A dose–response relationship exists between short sleep duration and metabolic syndrome. Those who report a sleep duration of less than 5 hours have a 1.5 higher odds of having metabolic syndrome. Our study does not support the notion that long sleep is associated with metabolic syndrome.

Keywords: sleep duration; metabolic syndrome; metaanalysis

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Short sleep duration is a growing public health epidemic. About one-third of the adult population in the United States reports obtaining less than 7 hours of sleep daily (1, 2). Insufficient sleep is associated with motor vehicle crashes, industrial disasters, and occupational errors (3). Habitual short sleep duration is also associated with a host of chronic health conditions such as hypertension, diabetes, depression, obesity, certain cancers, and increased mortality (4–9). On the other hand, long sleep duration has also been

associated with chronic health problems such as obesity, diabetes, heart disease, and stroke (10–16). In fact, in several studies, the association between long sleep duration and health problems is even stronger than that found with short sleep duration (12, 17, 18).

Conflicting information has been published regarding the association between sleep duration and metabolic syndrome (MetS). On the association of MetS with the short and long sleep duration, two recent metaanalyses (19, 20) have reported different

results. Although one (19) reported a U-shaped association between extremes of sleep duration and MetS, the other (20) did not show a significant association between long sleep duration and MetS. Since the publication of these two metaanalyses, several other studies have been published in this regard. However, still, the exact relations, including whether a dose–response association exists, are currently unclear.

Defining which categories of short and long sleep durations are strongly associated

with MetS is important in shaping public health recommendations about optimal sleep duration. Therefore, we performed an updated metaanalysis to study the magnitude of the association between the different durations of sleep and MetS in a large group of participants of different ethnic backgrounds and also to determine whether a dose–response association exists.

Methods

Data Sources

We searched in the databases of PubMed, Web of Science, and Ovid (all Journals@Ovid) from inception to October 4, 2014 for all eligible studies. We also searched through the meeting abstracts of Associated Professional Societies of Sleep, American Thoracic Society, and American College of Chest Physicians.

Search Strategy and Selection Criteria

We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Metaanalyses) guidelines for all stages of the design, implementation, and reporting of this metaanalysis (*see* Table E1 in the online supplement for checklist).

For inclusion in our metaanalysis, we considered cross-sectional studies or studies in which datasets were cross-sectionally analyzed from survey datasets and in which an association between sleep duration and MetS was reported as the odds ratio (OR) in adults (aged ≥ 18 yr). We used the following search terms: “sleep,” “duration,” and “metabolic syndrome.” Table E2 lists the search terms used in databases, and Figure 1 shows the study selection process. Only one abstract was found relevant to our inclusion criteria (obtained from Associated Professional Societies of Sleep) (21). However, due to incomplete data, this abstract was excluded. After reviewing abstracts of all citations obtained from different databases, only 14 were found to be relevant for inclusion in this metaanalysis.

Full manuscripts of these 14 studies were obtained. These were divided among the investigators for review using the inclusion criteria (stated above). All excluded studies were then reviewed for a second time by one of the investigators (I.H.I.). Eight studies were further identified through bibliographic search of articles already screened. After exclusion of 4 studies from the final list,

a total of 18 studies were finally included in the metaanalysis (Figure 1). Full manuscripts of these studies were reviewed by all investigators. There were no disagreements between the authors on the inclusion or exclusion of a study.

Data Abstraction

For all metaanalyses, an investigator (I.H.I.) extracted from each paper the first author’s name, year of publication, number of participants, country of origin, and demographics, including number of participants, mean age, sex distribution,

different methods used to measure sleep duration, criteria used to classify patients into MetS, and different covariates used to adjust the reported OR. All investigators independently verified the extracted data. Quality ratings for each study were assigned by each investigator using predefined quality assessment criteria (Table E3).

Quantitative Data Synthesis

We abstracted the OR for the association of MetS with different durations of sleep from all included studies. Different categories of sleep duration included: less than 5 hours,

Figure 1. Selection process of studies included in metaanalysis.

5 to 6 hours, 6 to 7 hours, 8 to 9 hours, and more than 9 hours. From each study, we selected the OR that was maximally adjusted for the covariates and compared with the referent (7–8 h sleep duration) group. OR estimates were pooled across all studies for each category of sleep duration. Random effects method was used to account for variance between the studies as well as within the studies. This was decided *a priori*, as the study population to be analyzed in our metaanalysis was heterogeneous.

Additionally, the heterogeneity was separately assessed by I^2 statistics. In analyses where I^2 greater than 35% was observed, we explored possible sources of heterogeneity by subgroup analyses based on different definitions of MetS used, geographic distribution, and different durations of sleep.

Sensitivity analyses were conducted for all analyses, to evaluate the effects of each

selected study on the overall results of the metaanalysis. Using metaregression with random effects method, we assessed the trend of association of MetS across the spectrum of different sleep duration categories.

Finally, publication bias was assessed with the construction of a funnel plot and further assessed by the Begg and Mazumdar rank correlation test. A P value of less than 0.05 on these tests was considered statistically significant for evidence of publication bias. Publication bias assessment was conducted for the analysis with the greatest number of studies included—analysis for the short sleep duration.

Results

A total of 18 studies (22–39) were selected for inclusion in this metaanalysis. Table E4 outlines the characteristics of study

participants. About 51% of the participants were men. Age of the participants ranged from 18 to 96 years. Most of the studies reported ORs adjusted for different confounders (Table E4). The most commonly adjusted confounders included, age, sex, smoking, and alcohol intake. Altogether, the included studies enrolled a total population of 75,657 participants. The majority of the studies were from the Far East (22, 24, 26–28, 31, 32, 36, 37, 39), six were from North America (23, 25, 29, 33, 34, 38), one was from the Middle East (30), and one was from Europe (35).

Four studies (28–30, 35) reported MetS using the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III) (40). Three studies (24, 37, 39) reported MetS using the NCEP/ATP III

Table 1. Metabolic syndrome definitions used in studies

	Waist Circumference (cm)	Triglycerides	HDL	Blood Pressure (mm Hg)	Fasting Plasma Glucose
NCEP/ATP II,I 2002 (40)	>102 in men >88 in women	≥150 mg/dl (1.69 mmol/L)	<40 mg/dl (1.04 mmol/L) in men <50 mg/dl (1.29 mmol/L) in women	≥130/85	≥110 mg/dl (6.1 mmol/L)
NCEP/ATP III, 2002 (abdominal obesity assessed by Asian criteria–WHO criteria) (41)	>90 in men >80 in women	≥150 mg/dl (1.69 mmol/L)	<40 mg/dl (1.04 mmol/L) in men <50 mg/dl (1.29 mmol/L) in women	≥130/85	≥110 mg/dl (6.1 mmol/L)
AHA/NHLBI, 2005 (42)	>102 in men >88 in women	≥150 mg/dl (1.69 mmol/L) or on drug treatment	<40 mg/dl (1.04 mmol/L) in men <50 mg/dl (1.29 mmol/L) in women or on drug treatment	≥130/85 or on drug treatment	>110 mg/dl or on drug treatment
AHA/NHLBI, 2005 (modified: abdominal obesity assessed by Asian criteria–WHO criteria)	>90 in men >80 in women	≥150 mg/dl (1.69 mmol/L) or on drug treatment	<40 mg/dl (1.04 mmol/L) in men <50 mg/dl (1.29 mmol/L) in women or on drug treatment	≥130/85 or on drug treatment	>110 mg/dl or on drug treatment
AHA/NHLBI, 2009 (43)	Population- and country-specific definitions (Asian cut-off for waist circumference: >90 in men, >80 in women)	≥150 mg/dl (1.69 mmol/L) or on drug treatment	<40 mg/dl (1.04 mmol/L) in men <50 mg/dl (1.29 mmol/L) in women or on drug treatment	≥130/85 or on drug treatment	>100 mg/dl or on drug treatment
CEDSMS (44)	≥85 in men ≥90 in women	≥150 mg/dl (1.69 mmol/L) or on drug treatment	<40 mg/dl (1.04 mmol/L) or on drug treatment	≥130/85 or on drug treatment	≥110 mg/dl or on drug treatment
JASSO (27)	≥85 in men ≥90 in women	≥150 mg/dl (1.69 mmol/L)	<40 mg/dl (1.04 mmol/L)	≥130/85	≥110 mg/dl

Definition of abbreviations: AHA/NHLBI = American Heart Association/National Heart Lung and Blood Institute; CEDSMS = Committee for the Criteria of Metabolic Syndrome: definition and the diagnostic standard for metabolic syndrome–Committee to Evaluate Diagnostic Standards for Metabolic Syndrome; HDL = high-density lipoprotein; JASSO = Japan Society for the Study of Obesity; NCEP/ATP = Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; WHO = World Health Organization.

criteria but incorporated the Asian definition of abdominal obesity (41). Three studies (23, 25, 33) reported MetS using the American Heart Association/National Heart, Lung, and Blood Institute's (AHA/NHLBI) criteria published in 2005 (42). Two studies (26, 38) reported MetS using the 2005 AHA/NHLBI criteria but using the Asian definition of abdominal obesity. Four studies (22, 31, 34, 36) reported MetS using the AHA/NHLBI criteria published in 2009 (43). Three (22, 31, 36) of these used the Asian-specific cut-off for waist circumference as specified in the 2009 AHA/NHLBI guidelines. Two studies (27, 32) from Japan used their country-specific criteria (27, 44). The different definitions of MetS differed mostly in their waist circumference limits (Table 1).

Association of Metabolic Syndrome with Short Sleep Duration

The pooled estimate of the OR for short sleep based on 17 studies (22–38) was 1.23 (95% CI, 1.11–1.37; $P < 0.001$; I^2 , 71%) (Figure 2). Subgroup analyses to explore

heterogeneity showed that the heterogeneity was explained mostly by the different definitions of MetS used (Table E5).

Subgroup analyses based on different durations of short sleep revealed a dose-response relationship. Duration of sleep less than 5 hours, 5 to 6 hours, and 6 to 7 hours had pooled ORs of 1.51 (95% CI, 1.10–2.08; $P = 0.01$; I^2 , 88%) (Figure 3A), 1.28 (95% CI, 1.11–1.48; $P < 0.001$; I^2 , 67%) (Figure 3B), and 1.16 (95% CI, 1.02–1.31; $P = 0.02$; I^2 , 81%) (Figure 3C), respectively.

Association of Metabolic Syndrome with Long Sleep Duration

The pooled estimate of OR for long sleep duration based on 15 studies (22–26, 28, 30, 31, 33–39) was 1.13 (95% CI, 0.97–1.32; $P = 0.10$; I^2 , 89%) (Figure 4). Subgroup analyses to explore heterogeneity showed that the heterogeneity was explained mostly by the different definitions of MetS used (Table E5).

Pooled estimates of the ORs for long sleep duration groups (8–9 h and >9 h)

were 1.09 (95% CI, 0.94–1.27; $P = 0.24$; I^2 , 85%; $P < 0.001$) (Figure 5A) and 1.21 (95% CI, 0.99–1.46; $P = 0.052$; I^2 , 85%; $P < 0.001$) (Figure 5B), respectively.

Figure 6 shows a summary plot comparing pooled ORs for different durations of sleep with metabolic syndrome.

Sensitivity Analyses

Systematic exclusion of individual studies in the analysis of short sleep duration and MetS did not alter the statistical significance of the pooled estimate. However, in the analyses of long sleep duration and MetS, two studies (30, 33) were identified as outliers, the systematic exclusion of which led to an overall statistically significant pooled OR.

Post hoc, we performed sensitivity analyses of the pooled odds ratios by excluding studies that adjusted for body mass index (Table E6) and separately for the pooled ORs using the least adjusted covariates that were mostly similar across all studies (Table E7). The overall trend of

Figure 2. Association of short sleep duration (<7 h) with metabolic syndrome. The squares represent individual studies. Diamond represents the pooled estimate.

Figure 3. (A) Association of short sleep duration (<5 h) with metabolic syndrome. The *squares* represent individual studies. *Diamond* represents the pooled estimate. (B) Association of short sleep duration (5–6 h) with metabolic syndrome. The *squares* represent individual studies. *Diamond* represents the pooled estimate. (C) Association of short sleep duration (6–7 h) with metabolic syndrome. The *squares* represent individual studies. *Diamond* represents the pooled estimate.

dose–risk relationship across different categories of sleep duration was not changed. A similar trend was seen in a *post hoc* sensitivity analysis that included only studies from Asian countries (Table E8).

Metaregression

A summary metaregression of sleep duration (in hours) on log of calculated ORs (obtained from subgroup analyses based on different durations of short or long sleep)

showed regression coefficient of -0.05 (SE, 0.03; $P = 0.13$) (Figure E1). The regression slope was nonlinear, suggesting an inflection point at sleep duration greater than 9 hours. To explore the nonlinearity further, *post hoc*, we conducted a metaregression of sleep duration (in hours) on log of ORs (reported in individual studies for each duration of sleep). This showed a regression coefficient of -0.03 (SE, 0.02; $P = 0.06$). In conducting a sensitivity analysis of this metaregression plot, we found that excluding the data for sleep duration greater than 9 hours resulted in a regression coefficient of -0.06 (SE, 0.02; $P = 0.02$).

Publication Bias

The Begg test showed no statistical evidence of publication bias (Kendall's tau b [corrected for ties, if any] was 0.16, with a one-tailed P value [recommended] of 0.17). Visual inspection, however, did reveal bias (as evidenced by *closed circles* in the funnel plot; Figure E2). Of note, only 17 studies out of the 18 selected and analyzed in the entire metaanalysis are shown (as *open circles*) in the funnel plot.

Discussion

The results of our metaanalysis show that short sleep duration is significantly associated with MetS. However, the association of long sleep duration with MetS was not statistically significant. Our metaanalysis did not show the classic U-shaped association between sleep duration and MetS.

Several studies have reported a U-shaped association between sleep duration and various medical comorbidities, such as hypertension (45), coronary vascular disease (12), and even mortality (14). However, the data on the U-shaped association between MetS and sleep duration have been rather conflicting. Although a few studies have shown the U-shaped association between sleep duration and MetS (19, 24, 25, 31), a few (27, 37) have shown that the association only holds true for short sleep, and a recent study (22) shows the opposite relation. An earlier metaanalysis by Ju and Choi (19) on 12 cross-sectional studies, however, does prove the classic U-shaped association.

Our updated metaanalysis, which includes 18 studies on 75,657 participants, clearly shows that the association holds true

Figure 4. Association of long sleep duration (>8 h) with metabolic syndrome. The *squares* represent individual studies. *Diamond* represents the pooled estimate.

only for short sleep. Our metaanalysis expands on the findings of the metaanalysis by Xi and colleagues (20), in which 10 studies were analyzed comparing essentially two categories of sleep duration: less than or equal to 6 hours of sleep with greater than or equal to 8 hours of sleep—the former found more strongly associated with MetS than the latter. However, because most studies in the metaanalysis by Xi and colleagues (20) were done in Asia, the results cannot be considered generalizable.

Our metaanalysis takes the evidence further by including 18 studies and analyzing the association of different categories of short sleep (<5, 5–6, and 6–7 h) duration as well as long sleep (8–9 and >9 h) with MetS. In fact, results of our metaregression sensitivity analysis show that exclusion of the data for greater than 9 hours of sleep duration from the rest of the different durations of sleep (<5, 5–6, 6–7, 8–9), predicts a dose-dependent response, a finding not shown in prior metaanalyses (19, 20, 46). In other words, every 1 hour decrease in sleep duration corresponds to a 0.06 increase in the OR of having MetS.

Several pathophysiologic mechanisms link short sleep duration and MetS. Alterations in the leptin-to-ghrelin ratio have been proposed as a mechanism (47, 48). Leptin is a satiety hormone and ghrelin

is an appetite-stimulating hormone. Reduced leptin and increased ghrelin levels correlate with increases in subjective hunger when individuals are sleep restricted (49). In experimental studies (48, 50, 51), sleep restriction resulted in decreased leptin and increased ghrelin, which was associated with increased hunger and appetite specifically for carbohydrate-dense food (51). In other short-term experimental studies on healthy participants, induced sleep debt was found to be associated with increase in IL-6 (52), tumor necrosis factor- α (52), and cortisol (47) levels, which could also partially explain insulin resistance, a central feature of MetS.

With an accrual of 14 hours of sleep debt over 4 days in healthy individuals associated with a 30% decline in insulin sensitivity in abdominal adipocytes, Broussard and colleagues' study (53) provided a direct link between sleep restriction and alteration of a molecular metabolic pathway. Although mechanisms such as this are biologically relevant, it is unclear if these sustain over long periods of time with less severe sleep restriction. Similarly, there is a relative paucity of longitudinal studies on the association of MetS and sleep duration, and as such association studies preclude establishing a cause-and-effect relationship.

Our metaanalysis has several strengths. We analyzed a total of 75,657 participants in 18 different studies. The results are generalizable for the most part, as the study participants are from different ethnic backgrounds with age ranging from 18 to 92 years, with studies done in countries from Far East Asia to North America. Subgroup analyses (Table E5) based on geographic locations (Far East Asia or North America) did not change the overall conclusion of our metaanalysis. Using metaregression and sensitivity metaregression analyses, we were able to identify a dose-risk association between short duration of sleep and MetS. We also extensively searched possible sources of heterogeneity separately for each analysis (Table E5). Heterogeneity was mostly explained by different definitions used for MetS in different geographic locations. We also performed sensitivity analyses for the main analyses (short sleep and long sleep durations). In the analysis of the pooled OR for long sleep and MetS (Figure 4), we identified two studies (30, 33) as outliers. The study by Najafian and colleagues (30), with a total of 12,492 individuals, and that of Sabanayagam and colleagues (33), with a data of 10,914 participants from the NHANES (National Health and Nutrition Examination Survey) 2005 to 2006 databases, carried

Figure 5. (A) Association of long sleep duration (8–9 h) with metabolic syndrome. The *squares* represent individual studies. *Diamond* represents the pooled estimate. (B) Association of long sleep duration (>9 h) with metabolic syndrome. The *squares* represent individual studies. *Diamond* represents the pooled estimate.

significant weight on the overall analysis. The study by Najafian and colleagues (30) concluded that long sleep (>9 h) had a “protective” effect (OR, 0.79; 95% CI, 0.68–0.94). Similar estimates (OR, 0.97; 95% CI, 0.69–1.36), were found in the study by Sabanayagam and colleagues (33).

Our metaanalysis has several limitations. First, even though we selected the estimates of association that were maximally adjusted (for potential confounders) from the individual studies, as this is not an individual patient-data

metaanalysis, a uniform way of adjusting the data was not possible. Second, although the definitions of MetS were similar in most aspects, variations existed in defining abdominal obesity or waist circumference (Table 1), which could have resulted in significant heterogeneity of our results. Third, most of the studies reported sleep duration based on individual participant’s subjective perception of sleep over the preceding several weeks to months. Therefore, some element of subject recall bias cannot be entirely ruled out. On

a similar note, in the self-reported questionnaires (used by most studies) differentiation between weekend and weekday sleep and the inclusion of daytime napping in the overall reported sleep duration could have been unaccounted for. Fourth, visual inspection of the funnel plot did show publication bias. However, this needs to be interpreted with caution, as (1) there was no statistical evidence of publication bias with two different tests, and (2) the analysis chosen for conducting this assessment had 17 studies out of the

Figure 6. Summary forest plot with comparison of pooled odds ratios (ORs) for different durations of sleep with metabolic syndrome. The squares represent pooled ORs for different durations of sleep with metabolic syndrome. The red broken outline illustrating a nonlinear trend shows the absence of a U-shaped relationship.

total of 18 studies included in this metaanalysis, and a few studies were intentionally excluded (Figure 1). As no single analysis in our study was representative of all of the included 18 studies, we chose to use the analysis that had the highest number of studies (i.e., analysis of data for short sleep duration). Last, the nonsignificant association between long sleep duration

and MetS needs to be interpreted with caution due to high “between-study” heterogeneity.

In conclusion, the results of our metaanalysis reaffirm the strong association between MetS and short sleep duration and define those who report sleep duration of less than 5 hours as the ones with the highest risk of having MetS. Individuals with sleep duration of less than 5 hours have 1.5 higher

odds of having MetS. Considering the high prevalence of the adult population in the United States who report habitual short sleep duration, our metaanalysis supports the idea that increasing sleep hours may represent a simple modification that may prevent the development of MetS. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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