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ORIGINAL ARTICLE

Sleep duration and metabolic syndrome in adult populations: a meta-analysis of observational studies

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OBJECTIVE: Epidemiological studies have repeatedly investigated the association between sleep duration and metabolic syndrome. However, the results have been inconsistent. This meta-analysis aimed to summarize the current evidence from cross-sectional and prospective cohort studies that evaluated this.

DATA SOURCES: Relevant studies were identified by systematically searching the PubMed, Cochrane CENTRAL, EMBASE and PsycINFO databases through November 2012 without language restriction.

STUDY SELECTION: We identified 12 cross-sectional studies with 76 027 participants including 14 404 cases of metabolic syndrome, and 3 cohort studies with 2055 participants and 283 incident cases of metabolic syndrome.

RESULTS: For short sleep durations (<5 to 6 h), the odds ratios (OR) was 1.27 (95% confidence interval (CI) = 1.10–1.48, $I^2 = 75.5\%$) in the 12 cross-sectional studies and 1.62 (95% CI = 0.74–3.55, $I^2 = 71.4\%$) in the 3 cohort studies; for long sleep durations (>8 to 10 h), the OR was 1.23 (95% CI = 1.02–1.49, $I^2 = 75.8\%$) in the 11 cross-sectional studies and 1.62 (95% CI = 0.86–3.04, $I^2 = 0.0\%$) in the 2 cohort studies.

CONCLUSIONS: Short and long sleep durations are risky behaviors for increasing the risk of metabolic syndrome and thus have important public health implications, as sleep habits are amenable to behavioral interventions. The available data are sparse, and further studies, especially longitudinal studies, are needed to facilitate a better understanding of these associations.

INTRODUCTION

The metabolic syndrome is characterized by abdominal adiposity, dyslipidemia, elevated glucose and blood pressure.[1] The metabolic syndrome is strongly linked to cardiovascular events,[2] cancer[3] and mortality.[4] Given that the metabolic syndrome is becoming a worldwide pandemic, with prevalence rates between 20 and 30% among the adult population,[5] the identification of modifiable risk factors associated with the development of metabolic syndrome is important to public health.

Sleep is a basic human need; it takes up more time in a day than any other activity. Too short or too long a duration of habitual sleep are currently thought to be important lifestyle risk factors for such metabolic diseases such as diabetes,[6–8] obesity[8–10] and cardiovascular disease, (and hypertension in particular[11,12]) and sleep duration may also be a significant predictor of all-cause mortality in prospective population studies.[13,14]

Several epidemiological studies have been conducted to investigate the association between length of sleep and metabolic syndrome, with inconsistent results. A number of studies in adults have demonstrated an association between short sleep duration and metabolic syndrome.[15–21] Conversely, some of these studies also showed that long sleep duration was associated with metabolic syndrome.[22,23] To our knowledge, there has been no published systematic literature review that has characterized the magnitude of these associations. Therefore, we have summarized published data from cross-sectional and prospective cohort studies, and performed a meta-analysis to obtain a quantitative estimate of the risk.

MATERIALS AND METHODS

We planned, conducted and reported this systematic review according to widely accepted standards of quality for reporting meta-analyses of observational studies in epidemiology (Supplementary Table 1).[24]

Literature search

A master's level medical librarian with experience in systematic reviews participated in designing the search strategy. We searched PubMed, Cochrane CENTRAL, PsycINFO and EMBASE via Elsevier from the date of inception until 26 November 2012. A PubMed search for studies on sleep and metabolic syndrome was conducted without restrictions by combining synonymous or related search terms for sleep and metabolic syndrome. The keywords used in the PubMed search were converted to search tags for Cochrane CENTRAL, PsycINFO and EMBASE (Supplementary Table 2). In addition, manual searches of the bibliographies of the relevant articles were performed to identify additional studies.

Study selection

Several criteria were used to identify relevant studies for the meta-analysis. The studies included had an observational design, including cross-sectional studies and cohort studies, and were conducted in human adults. The exposure of interest was sleep duration. The outcome of interest was metabolic syndrome. Finally, the adjusted relative risk estimates (odds ratios [OR] in cross-sectional studies) and their corresponding 95% confidence intervals (CI), or sufficient data to calculate these values, were reported. We selected full-length articles without language

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restriction. Disagreements between the reviewers were resolved by consensus. We also checked the reference lists of included publications using a cross-reference table.

Data extraction

Two reviewers (J-SY and C-WS) independently extracted the data from original reports. The adjusted risk estimates that reflected the most comprehensive control were extracted to avoid potential confounding variables. The following predictors of sleep duration were extracted: study characteristics (study name, authors, publication year, country of data collection, number of participants and follow-up years for cohort studies), participants' characteristics (age range or mean age and sex) and metabolic syndrome measures. The methodological quality of the eligible non-randomized studies reviewed in meta-analyses was assessed according to the seven domains proposed as being fundamental to the methodological quality of the included studies (Supplementary Table 3).[25,26]

Statistical analysis

We used adjusted relative risk or OR with the corresponding 95% CI for the meta-analysis. If OR estimates for an outcome were reported in a study, we selected the OR that was adjusted for most covariates in the study. Pooled OR estimates were obtained using a random-effect model. For consistency, we chose the group that slept 7 h per day as the reference category. When the reference category differed in each study, we used variances in the independent observations to obtain the CI of OR for each sleep category. When the variables X and Y were considered, the variance was as follows: $var(X − Y) = var(X) + var(Y) − 2 \times covariance(XY)$ or, in another formula: $var(X − Y) = var(X) + var(Y) − 2 \times correlation\ coefficient \times \sqrt{var(X) \times var(Y)}$. This correlation coefficient could only be assessed within the studies in which all individual data were presented. By comparing the variance with the reference sleep duration category, we estimated the pooled risk and 95% CI of metabolic syndrome for the short- and long-sleep categories separately. For the meta-analysis, the statistical heterogeneity between the studies was assessed using Q statistics.[27] For the Q statistics, heterogeneity was considered to be present if $P < 0.1$. We defined low, moderate and high heterogeneity as I^2 values of 25, 50 and 75%, respectively. Publication bias was evaluated using Egger's test and Begg's test. In the presence of publication bias, the P-values for Egger's test and Begg's test are less than 0.05. Subgroup meta-analyses were conducted according to the study design (cross-sectional study or cohort study), the different methods used to measure sleep duration, the definition of metabolic syndrome used and the subject's gender, age and geographic region. We also performed a two-stage random-effects dose-risk meta-analysis to examine a nonlinear dose–response relationship between length of sleep and metabolic syndrome. After modeling the length of sleep using restricted cubic splines with three knots at fixed percentiles (10, 50 and 90%) of the distribution,[28–30] we used a generalized least-squares method[31] and a multivariate maximum likelihood method to estimate a summary of nonlinear dose-risk relationship, taking into account random effects.[32] All statistical analyses were performed using Stata software Version 12.0 (Stata Corp, College Station, TX, USA).

RESULTS

Literature searches and study selection

Figure 1 shows a flow diagram of the procedure used to identify the relevant studies. Briefly, we identified 36 potentially relevant articles on sleep duration in relation to metabolic syndrome after an initial screening of titles and abstracts. After we examined the 36 assembled articles, 24 articles were excluded (Supplementary Table 4). Finally, we identified 12 articles including 15 studies that investigated the association between sleep duration and metabolic syndrome risk; 3 articles reported separate results for stratification by gender.[15,20,23] No additional studies were identified via cross-referencing.

Study characteristics

Most of studies used multivariate logistic regression to adjust for potential confounders. The 12 cross-sectional[17,19–23,33–36] studies,

with 76 027 participants, including 14 404 metabolic syndrome patients and the three cohort[15,18] studies, with 2055 participants, are represented in Table 1. A total of 283 metabolic syndrome cases occurred during follow-up in the three cohort studies. Three studies[23,34,35] defined metabolic syndrome 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).[1] Four studies[15,20,22,33] assessed metabolic syndrome using the modified NCEP ATP-III. Two studies[19,36] used the American Heart Association/National Heart Lung and Blood Institute's (AHA/NHLBI) criteria.[37] One study[21] used the modified criteria of the AHA/NHLBI and assessed abdominal obesity according to the World Health Organization's definition. Two studies[17,18] used the Japanese criteria for metabolic syndrome. Eight studies[17–21,23,33,34] assessed sleep duration using a questionnaire and four studies[15,22,35,36] used an interview. Of the included studies, five were conducted in men,[15,18,20,23,35] four in women[15,20,23,35] and eight in both genders;[17,19,21,22,33–36] seven were conducted in Asia,[15,17,18,20,22,33,35] four in the United States[19,21,34,36] and one in Europe.[23] All of the studies were published in the 2000s. The study periods ranged from 1 to 7 years. The patients' age ranged from $\geqslant 18$ to $\geqslant 50$ years. The study quality was high in 10 of the 15 included studies (3 cohort and 12 cross-sectional studies).

Short duration of sleep

Short duration of sleep was significantly associated with a greater risk of developing metabolic syndrome in four of the twelve cross-sectional studies and two of the three cohort studies. The pooled OR between short sleep and metabolic syndrome was 1.27 (95% CI = 1.10–1.48, $I^2 = 75.5\%$) in the 12 cross-sectional studies and 1.62 (95% CI = 0.74–3.55, $I^2 = 71.4\%$) in the 3 cohort studies (Figure 2). Significant heterogeneity was observed ($P < 0.1$). No publication bias was detected with Egger's test ($P = 0.17$) or Begg's test ($P = 0.92$) (Figure 3).

Subgroup analyses of the cross-sectional studies are shown in Table 2. There were significant differences in the mean age, cohort-based group, definition of metabolic syndrome, quality of study and sleeping measure (P for heterogeneity < 0.1). No significant group difference was found for gender or location.

Long duration of sleep

Long duration of sleep was associated with a greater risk of developing metabolic syndrome in five of the eleven cross-sectional studies and none of the two cohort studies. The pooled OR between long sleep and metabolic syndrome was 1.23 (95% CI = 1.02–1.49, $I^2 = 75.8\%$) in the 11 cross-sectional studies and 1.62 (95% CI = 0.86–3.04, $I^2 = 0.0\%$) in the 2 cohort studies. Significant heterogeneity was observed between the 11 cross-sectional studies ($P < 0.1$). No publication bias was detected with Egger's test ($P = 1.33$) or Begg's test ($P = 0.95$) (Figure 3).

Subgroup analyses of the cross-sectional studies are shown in Table 2. There were significant differences in location, definition of metabolic syndrome, quality of study and sleeping measure (P for heterogeneity < 0.1). No significant group difference was found for gender, age or cohort-based group.

Dose–response relationship

When we assessed the dose–response relationship between sleep duration and metabolic syndrome, we found some evidence of a statistically significant departure from linearity ($P < 0.001$; Figure 4). Among the shorter and longer sleepers, the risk of metabolic syndrome might increase gradually compared with individuals who report sleeping 7 h per day. Compared with the reference level, the combined odds ratios of metabolic syndrome were 1.33 (95% CI = 1.07–1.65) for $\leqslant 5$ h per day, 1.21

1990 Articles identified from databases using the PICO:
1607 EMBASE, 562 PubMed, 192 PsycINFO, and14 Cochrane CENTRAL

14 Update on 10th December 2012

108 Duplicate articles excluded by program of reference manager and manual

1860 Articles excluded after the initial screening on the basis of the title or abstract

    1802 No relevant study

      36 No original article

      20 No adult study

       2 No human study

36 Potentially relevant articles reviewed in full-text

24 Articles excluded

    13 No association between sleep duration and metabolic syndrome

      6 review,commentary , case report

      4 Data no available

      1 Same cohort used in other publication

12 Articles included in dose-response analysis with 15 studies
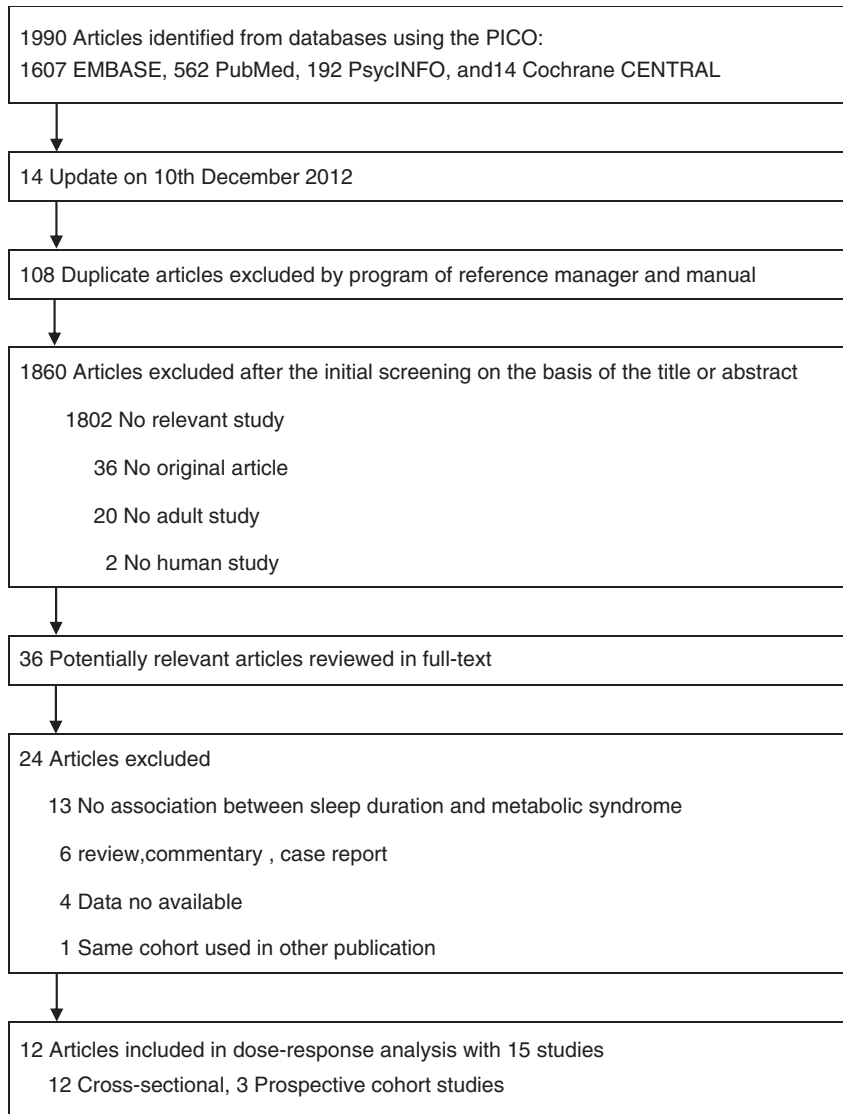   12 Cross-sectional, 3 Prospective cohort studies

Figure 1. Flow diagram for search strategy and study selection process.

(95% CI = 1.04–1.41) for 5.5 h per day, 1.11 (95% CI = 1.02–1.21) for 6 h per day, 1.04 (95% CI = 1.00–1.07) for 6.5 h per day, 1.07 (95% CI = 1.00–1.13) for 8 h per day, 1.15 (95% CI = 1.03–1.28) for 8.5 h per day, 1.26 (95% CI = 1.07–1.49) for 9 h per day and 1.38 (95% CI = 1.10–1.74) for $\geqslant$ 9.5 h per day in the eight cross-sectional studies.[17,19,22,23,33,35,36] There was significant between-study heterogeneity among study-specific trends defined by the coefficient of the first and second spline transformations of sleep duration ($P < 0.1$).

Sensitivity analyses in the cross-sectional studies
We included five studies of healthy populations and participants not taking antihypertensive medication for our sensitivity analyses.[17,20,22,36] The sensitivity meta-analyses yield somewhat weakened summary ORs of 1.22 (95% CI = 0.96–1.54) for short sleep durations and 1.14 (95% CI = 0.98–1.32) for long sleep durations. There was heterogeneity for short sleep ($I^2 = 33\%$, $P = 0.20$) and long sleep ($I^2 = 84.6\%$, $P < 0.1$). We also excluded two studies from our sensitivity analyses, as they reported the association between sleep duration and metabolic syndrome in police officers. The sensitivity meta-analyses yielded nearly identical summary ORs of 1.25 (95% CI = 1.07–1.46; $I^2 = 78.6\%$)

for short sleep and 1.22 (95% CI = 1.22–1.48; $I^2 = 77.9\%$) for long sleep.

DISCUSSION
To our knowledge, this is the first quantitative systematic review of observational studies investigating the effect of sleep duration on the risk of metabolic syndrome using data from cross-sectional and cohort studies. This study shows a significant increased risk of metabolic syndrome on either end of the distribution of sleep duration in the cross-sectional studies, but not in the cohort studies. Pooled analyses of cross-sectional studies indicate that short sleepers have a greater risk of metabolic syndrome compared with those who sleep 7–8 h per night. Longer sleepers also show an increased risk for metabolic syndrome, confirming the presence of a U-shaped association in the cross-sectional studies. There was some heterogeneity between studies, no publication bias and no differences between men and women. Furthermore, compared with the 7-h sleep duration, U-shaped associations between sleep duration and the risk of metabolic syndrome were observed in a dose–response meta-analysis of eight cross-sectional studies. This complementary investigation may strengthen the plausibility of a causal association, and allow

Table 1. Characteristics of cross-sectional and cohort studies included in the meta-analysis

Author study name	Country observation period	No. of participants	No. of cases	Age range mean (s.d.)	Gender population	Metabolic syndrome assessment	Sleeping assessment	Sleep (h)	Odds ratio (95% CI)	Adjusted covariates
Cross-sectional studies										
Santos et al.[23]	Portugal 1999–2003	832	96	18–92	Men	NCEP ATP-III	Questionnaire	≤6	1.40 (0.76–2.60)	1, 3, 4, 5
			216					7	1.00 (Reference)	
			214					8	1.10 (0.73–1.70)	
			227					≥9	1.50 (0.90–2.60)	
		1332	153		Women			≤6	0.92 (0.55–1.50)	
			270					7	1.00 (Reference)	
			401					8	1.20 (0.80–1.70)	
			388					≥9	2.00 (1.30–3.00)	
Choi et al.[33] KNHNS, 2001	Korea 2001	633	217	44.1 (0.4)	Both	Modified NCEP ATP-III	Questionnaire	≤5	1.20 (0.87–1.60)	1, 2, 3, 4, 5, 6, 12
		1056	293					6	1.10 (0.85–1.30)	
		1182	274					7	1.00 (Reference)	
		1056	293					8	1.30 (1.00–1.70)	
		296	94					≥9	1.70 (1.20–2.50)	
Hall et al.[36] AHAB	USA	187	58	30–54	Both	AHA/NHLBI	Interview	<6	1.80 (1.20–2.80)	1, 2, 4, 8, 9, 10, 14
		402	101					6–6.99	1.50 (1.10–2.10)	
		525	100					7–8	1.00 (Reference)	
		100	25					>8	1.80 (1.00–3.10)	
					Not taking antihypertensive medication			<6	1.80 (1.10–2.70)	
								6–6.99	1.50 (1.00–2.10)	
								7–8	1.00 (Reference)	
								>8	1.60 (0.91–3.00)	
Arora et al.[22] GBCS	China	1142	329	50–96	Both	Modified NCEP ATP-III	Interview	<6	0.97 (0.88–1.10)	1, 2, 3, 4, 5, 8, 11
		2020	570					6–7	1.00 (Reference)	
		2303	603					7–8	1.20 (1.10–1.30)	
		1995	575					8–9	1.20 (1.10–1.30)	
		762	226					≥9	0.93 (0.84–1.00)	
					Healthy			<6	0.98 (0.90–1.10)	
								6–7	1.00 (Reference)	
								7–8	1.10 (1.10–1.20)	
								8–9	1.20 (1.10–1.30)	
					Middle age			<6	1.10 (0.91–1.20)	
				51–61				6–7	1.00 (Reference)	
								7–8	1.20 (1.10–1.30)	
								8–9	1.10 (1.00–1.30)	
								≥9	1.30 (1.20–1.50)	
					Old age			<6	0.93 (0.83–1.10)	
				>61				6–7	0.98 (0.89–1.10)	
								7–8	1.00 (Reference)	
								8–9	1.20 (1.10–1.30)	
								≥9	1.10 (0.95–1.30)	
Kobayashi et al.[17]	Japan 2008	7295	641	44.8 (12.8)	Both	JASSO	Questionnaire	<6	1.40 (1.20–1.60)	1, 2, 4, 6, 13
		11355	905					6–6.99	1.10 (0.95–1.30)	
		6732	592					7–7.99	1.00 (Reference)	
		2410	233					≥8	0.98 (0.83–1.20)	
Najafian et al.[35] IHHP	Iran 1999–2006	1447	485	38.89 (14.93)	Both	NCEP ATP-III	Interview	≤5	1.50 (1.30–1.70)	1, 2
		2336	575					6	1.20 (1.10–1.40)	
		7622	1654					7–8	1.00 (Reference)	
		1089	223					≥9	0.79 (0.68–0.94)	
		5976			Men			≤5	1.30 (0.99–1.60)	1
								6	1.10 (0.89–1.30)	
								7–8	1.00 (Reference)	
								≥9	0.77 (0.55–1.10)	
		6320			Women			≤5	1.70 (1.40–2.00)	
								6	1.30 (1.10–1.50)	
								7–8	1.00 (Reference)	
								≥9	0.81 (0.67–0.98)	
		10699		<60	Both			≤5	1.70 (1.50–2.00)	2
								6	1.20 (1.10–1.40)	
								7–8	1.00 (Reference)	

Table 1. (Continued)

Author study name	Country observation period	No. of participants	No. of cases	Age range mean (s.d.)	Gender population	Metabolic syndrome assessment	Sleeping assessment	Sleep (h)	Odds ratio (95% CI)	Adjusted covariates
		1597		>60	Both			≥9	0.84 (0.70–1.00)	1, 2, 3, 4, 5, 8, 10
								≤5	1.10 (0.84–1.40)	
								6	1.10 (0.79–1.40)	
								7–8	1.00 (Reference)	
Sabanayagam et al.[19] NHANES	USA 2005–2008	935	377	44.63 (0.46)	Both	AHA-NHLBI	Questionnaire	≥9	0.61 (0.40–0.92)	
		1412	548					≤5	1.20 (0.98–1.60)	
		1777	650					6	1.10 (0.93–1.30)	
		1621	579					7	1.00 (Reference)	
		377	135					8	0.92 (0.76–1.10)	
McCanlies et al.[34]	USA	28	7	39.61	Both Police	NCEP ATP-III	Questionnaire	≥9	0.97 (0.69–1.40)	1, 2, 3, 4
		70	7					<6	2.30 (0.81–6.50)	
								≥6	1.00 (Reference)	
Wu et al.[20]	Taiwan 2006–2009	954	198	47.1 (12.0)	Men	Modified NCEP ATP-III	Questionnaire	<6	1.30 (1.00–1.60)	1, 3, 4, 5, 7
		3202	535	44.8 (11.1)				6–8	1.00 (Reference)	
		142	27	52.3 (12.2)				>8	1.40 (0.82–2.50)	
		794	94		Women			<6	1.40 (0.72–1.50)	
		1909	172					6–8	1.00 (Reference)	
		99	9					>8	0.90 (0.32–2.50)	
Yoo et al.[21]	USA	32	10	22–60	Both Police	Modified AHA-NHLBI	Questionnaire	≤6	2.30 (0.71–7.50)	1, 2, 4, 8, 17
		53	13					>6–<8	1.00 (Reference)	
		21	12					≥8	1.90 (1.30–18.0)	
Cohort studies										
Choi et al.[15] KGRC	Korea 2005–2009	27	5	40–70	Men	Modified NCEP ATP-III	Interview	<6	0.62 (0.24–1.60)	1, 4, 5, 7, 8
		209	49					6–7.9	1.00 (Reference)	
		132	23					8–8.9	0.74 (0.44–1.20)	
		18	5					≥10	1.60 (0.61–4.00)	
		68	20		Women			<6	1.80 (1.10–3.00)	1, 4, 5, 7, 8, 15
		403	61					6–7.9	1.00 (Reference)	
		226	34					8–8.9	0.91 (0.59–1.40)	
		24	7					≥10	1.70 (0.71–3.90)	
Otsuka et al.[18]	Japan 2005–2009	120	20	35–63	Men	The Japanese criteria	Questionnaire	≤5	3.20 (1.50–6.60)	1, 4, 5, 6, 16
		559	46					5–6	1.80 (0.96–3.50)	
		269	13					>6	1.00 (Reference)	

Abbreviations: AHA-NHLBI, American Heart Association/National Heart Lung and Blood Institute; AHAB, Adult Health and Behavior; CES-D, Center for Epidemiological Studies Depression Scale; CI, confidence interval; GBCS, The Guangzhou Biobank Cohort Study; IHHP, Isfahan Healthy Heart Program; JASSO, Japan Society for the Study of Obesity; KGRC, The Korean Genomic Rural Cohort; KNHNS, Korean National Health and Nutrition Survey; NCEP ATP-III, National Cholesterol Education Adult Treatment Panel III; PSS, Perceived Stress Scale; 1, age; 2, sex; 3, education; 4, smoke; 5, alcohol; 6, exercise; 7, body mass index; 8, physical activity; 9, race; 10, depression; 11, diagnosed mental illness, insomnia, use of hypnotics, daytime sleepiness, snoring, mean systolic pressure, glucose, total cholesterol and triglycerides; 12, family history of hypertension or diabetes, residential area and monthly income; 13, myocardial infarction and cerebral infarction; 14, low-density lipoprotein cholesterol; 15, menopause; 16, frequency of vegetable intake, frequency of oily food intake and frequency of salty food intake; 17, burnout, Center for Epidemiological Studies Depression Scale and Perceived Stress Scale.
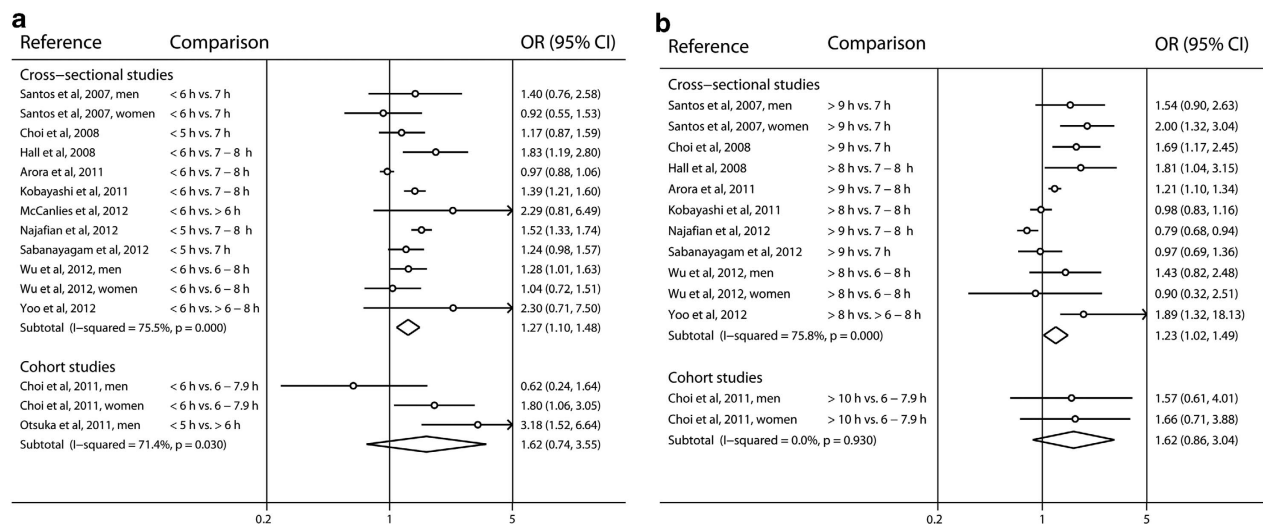
Figure 2. Forest plots of the risk of metabolic syndrome associated with (**a**) short duration of sleep compared with the reference group, and (**b**) long duration of sleep compared with the reference group. The results are expressed as odds ratio (relative risk in cohort studies) and 95% confidence intervals.
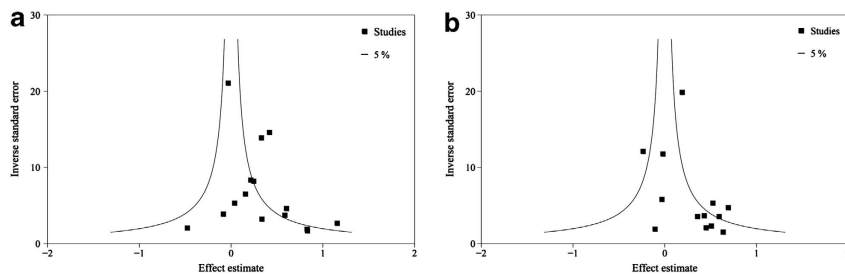

Figure 3. Inverse funnel plot with 95% CIs of the odds ratio of metabolic syndrome according to (**a**) short duration of sleep compared with the reference group (Egger's test, $P = 0.17$; Begg's test, $P = 0.92$), and (**b**) long duration of sleep compared with the reference group (Egger's test, $P = 1.33$; Begg's test, $P = 0.95$).

us to draw an overview of the nonlinear relationship between sleep duration and metabolic syndrome risk.

Causal mechanisms relating the short duration of sleep to adverse health outcomes include changes in circulating levels of leptin and ghrelin, which in turn would increase appetite and calorie intake, reduce energy expenditure and impair glycemic control.[38,39] Increased cortisol secretion and altered growth hormone metabolism have also been implicated.[40] Low-grade inflammation is also activated during short sleep.[41] Conversely, the association between a long duration of sleep and metabolic syndrome may be explained by residual confounding factors and comorbidity. Unrecognized confounders such as sleep fragmentation, fatigue and depression[42] could lead to both metabolic syndrome and an increased need for sleep.[43] Long sleepers have less waking time to undertake physical activity, which may contribute to this association.[44] Lifestyle interventions that aim to reduce weight and physical activity may ameliorate the risk of diabetes in long sleepers.[45] Furthermore, obesity itself is regarded as a chronic inflammatory condition. The elevated levels of proinflammatory cytokines have been considered as factors that contribute to increased sleep durations,[46] which promotes insulin resistance.

There are several possible reasons for the risk of metabolic syndrome according to sleep duration. Hypothalamic–pituitary–adrenal hyperactivity has a role in the pathogenesis of the metabolic syndrome,[47] and activation of the hypothalamic–pituitary–adrenal axis can lead to sleeplessness.[14] Sleep fragmentation or restriction leads to insulin resistance,[48] which

appears to have a key role in the pathophysiology of metabolic syndrome.[49] In addition, longer sleep could be associated with circadian and hormonal alternations.[50] A previous report suggested that the nocturnal intervals of high plasma melatonin levels, increasing cortisol levels, low body temperature and increasing sleepiness are longer in long sleepers (>9 h) than short sleepers (<6 h).[51] However, the mechanisms that underline these associations are not fully understood. An investigation reporting an association between variants of the human *CLOCK* gene and sleep duration may prove fruitful in this regard.[52] Some evidence has suggested that the covariation among sleep parameters and clusters of metabolic syndrome may be partially related to genetic influences. For example, disruptions of the core *CLOCK* genes that regulate endogenous circadian rhythmicity are linked to perturbations in glucose metabolism, adipocyte and vascular function,[53] obesity and metabolic syndrome.[54] Thus, it is possible that short and long sleep are linked to metabolic syndrome risk through different pathways.

There were significant differences in the relationship between sleep duration and metabolic syndrome in different groups based on age, location, type of cross-sectional study (community based or hospital based), sleep measure, quality of study and definition of metabolic syndrome. However, due to the limited number of studies within several groups, these results should be interpreted cautiously. For short duration of sleep, a significant 33% increase in metabolic syndrome was observed in hospital-based studies. Not surprisingly, hospital-based samples of patients suffering from disease are at a higher risk of developing metabolic

Table 2. Subgroup meta-analyses of cross-sectional studies to explore sources of heterogeneity

Subgroups	Short sleep		Long sleep	
	No.of studies	OR (95% CI) P for heterogeneity	No. of studies	OR (95% CI) P for heterogeneity
Gender				
Men	3	1.27 (1.08, 1.49)	3	1.03 (0.80, 1.33)
Women	3	1.49 (1.29, 1.72)	3	0.94 (0.80, 1.12)
		P = 0.156		P = 0.588
Mean age (years)				
[a]Middle	5	1.34 (1.21, 1.48)	4	1.15 (1.04, 1.28)
[b]Elderly	2	0.96 (0.86, 1.06)	2	1.03 (0.90, 1.18)
		P < 0.1		P = 0.210
Location				
Asia	6	1.18 (1.11, 1.26)	6	1.08 (1.01, 1.16)
Europe	2	1.09 (0.74, 1.61)	2	1.81 (1.30, 2.52)
USA	4	1.40 (1.15, 1.72)	3	1.18 (0.89, 1.56)
		P = 0.237		P < 0.1
Cohorts-based				
Community	6	1.15 (1.07, 1.23)	6	1.12 (1.03, 1.21)
Hospital	3	1.33 (1.18, 1.49)	3	1.01 (0.86, 1.18)
		P < 0.1		P = 0.263
Measure of sleeping				
Interview	3	1.14 (1.06, 1.23)	3	1.09 (1.00, 1.19)
Questionnaire	9	1.29 (1.18, 1.42)	8	1.16 (1.03, 1.31)
		P < 0.1		P < 0.1
Metabolic syndrome				
NCEP ATP-III	4	1.48 (1.30, 1.68)	4	0.93 (0.80, 1.07)
Modified NCEP ATP-III	4	1.02 (0.94, 1.11)	4	1.24 (1.13, 1.36)
AHA-NHLBI	2	1.36 (1.10, 1.67)	2	1.15 (0.86, 1.54)
Modified AHA-NHLBI	1	2.30 (0.71, 7.50)	1	1.89 (0.51, 7.00)
JASSO	1	1.39 (1.21, 1.60)	1	0.98 (0.83, 1.16)
		P < 0.1		P < 0.1
Quality of study				
High	7	1.06 (0.99, 1.15)	6	1.23 (1.13, 1.34)
Low	5	1.44 (1.31, 1.58)	5	0.96 (0.86, 1.07)
		P < 0.1		P < 0.1

Abbreviations: AHA-NHLBI, American Heart Association/National Heart Lung and Blood Institute; CI, confidence interval; JASSO, Japan Society for the Study of Obesity; NCEP ATP-III, National Cholesterol Education Adult Treatment Panel III; OR, odds ratios. [a]Middle, <60 or ⩽61. [b]Elderly, >60 or ⩾61.
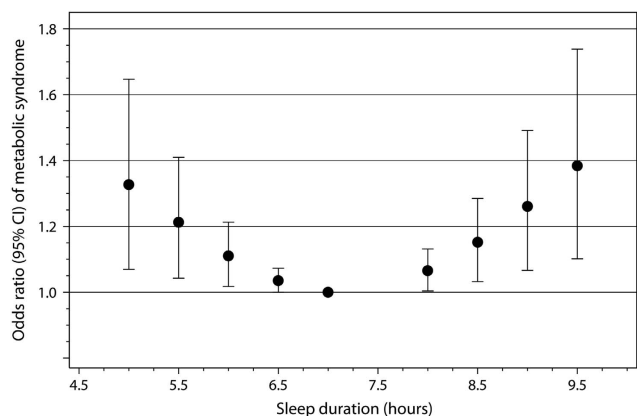
Figure 4. The odds ratio (filled circle) with 95% CI (solid longitudinal line) for the dose–response relationship between sleep duration and the risk of metabolic syndrome in the cross-sectional studies. The reference duration of 7 h per day was used to estimate all odds ratios. The eight cross-sectional studies (out of 12) with at least four levels of sleep categories were used in a restricted cubic spline random-effects meta-analysis.

syndrome, as metabolic syndrome itself is a cluster of risk factors of metabolic abnormalities, and short sleep duration is a risk behavior for the development of chronic disease, particularly stroke and cancer,[55] which can strengthen the relationship between short sleep and metabolic syndrome.

We found that the association was stronger for both long and short sleep in cross-sectional studies that identified habitual sleep duration using questionnaires rather than interviews. One possible explanation is that the cross-sectional studies could contain sources of bias, such as recall bias. Therefore, overestimation or underestimation of sleep duration per night may be caused by a single self-reported survey item that may not capture the subject's actual amount of sleep per night. For short sleep, there was a significant association with middle age. This finding may be explained by the distribution of weekly averaged sleep duration. Sleep duration decreases steadily in both genders from the end of adolescence to the age of menopause. From that age on, sleep duration increases slightly with age.[52] This distribution would implicitly allow the inclusion of many people with short sleep. Thus, the inclusion of only middle-aged people may have led to the stronger estimates.

Although our meta-analysis included only multivariable adjusted ORs, there is evidence of heterogeneity across the studies in both study designs. This heterogeneity may be attributable to differences in study design, sample size, analytic strategies, participant characteristics, the diagnostic criteria for metabolic syndrome, study quality and the measurement of sleep duration. To account for this heterogeneity, we used random-effects models of the meta-analyses, and conducted subgroup analyses using fixed-effects models; however, the results were not significantly changed.

This meta-analysis has several strengths and limitations. The primary strength is that this is the first meta-analysis that examines the relationship between sleep duration and metabolic syndrome based on a comprehensive literature search. In addition, a dose–response meta-analysis using restricted cubic splines revealed a U-shaped relationship between sleep duration and the risk of metabolic syndrome, despite the heterogeneous categorization of sleep duration in the individual studies. A limitation of this approach is that it depends on means, median or midpoints of the sleep-duration categories. The estimates of risk in this approach are therefore slightly less accurate than in the individual patient data meta-analyses. We found no publication bias in any of the analyses. Despite the calculation of risk estimates that reflected the greatest degrees of controlling for potential confounders, some limitations must be considered when interpreting the meta-analyses results. As it is impossible to completely adjust for general health status, residual confounders must always be considered while interpreting results from observational studies. Finally, a major limitation was the evidence of heterogeneity across the studies, especially that resulting from heterogeneous sleep-measure methods, quality of study and variations in the definition of metabolic syndrome. Thus, the results of this analysis should be interpreted cautiously.

In this systemic review and meta-analysis of epidemiological studies of the association between sleep duration and metabolic syndrome, both short sleepers and long sleepers are at risk of metabolic syndrome in cross-sectional studies, but not in cohort studies; this is consistent with the results from an analysis using nonlinear dose–response method in the cross-sectional studies. Therefore, short and long sleep durations are risky behaviors for increasing the risk of metabolic syndrome and thus have important public health implications, as sleep habits are amenable to behavioral interventions. However, the available data are sparse, and further studies, especially longitudinal studies, are needed to enable more in-depth analyses, more precise and stable estimates of the association and a better understanding of the potential role of sleep duration in metabolic

syndrome risk. Further studies could also shed light on possible sources of heterogeneity across the studies included in this meta-analysis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: Ju, Choi. Acquirement of the data: Ju, Choi. Analysis and interpretation of the data: Ju. Drafting the manuscript: Ju. Critical revision of the manuscript for important intellectual content: Choi. Statistical analyses: Ju. Obtaining of funds: Choi. Providing of administrative, technical, or material support: Ju and Choi. Supervision of the study: Choi.

DISCLAIMER

The funding sources had no role in the design or execution of the study; the collection, management, analysis or interpretation of the data; or the preparation, review or approval of the manuscript.

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