SLEEP DURATION AND WEIGHT

Meta-Analysis of Short Sleep Duration and Obesity in Children and Adults

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Background: Recent epidemiological studies suggest that short sleep duration may be associated with the development of obesity from childhood to adulthood.

Objectives: To assess whether the evidence supports the presence of a relationship between short sleep duration and obesity at different ages, and to obtain an estimate of the risk.

Methods: We performed a systematic search of publications using MEDLINE (1996-2007 wk 40), EMBASE (from 1988), AMED (from 1985), CINHAL (from 1982) and PsycINFO (from 1985) and manual searches without language restrictions. When necessary, authors were contacted. Criteria for inclusion were: report of duration of sleep as exposure, BMI as continuous outcome and prevalence of obesity as categorical outcome, number of participants, age, and gender. Results were pooled using a random effect model. Sensitivity analysis was performed, heterogeneity and publication bias were also checked. Results are expressed as pooled odds ratios (OR [95% confidence intervals, CIs]) and as pooled regression coefficients (β ; 95% CIs).

Results: Of 696 studies identified, 45 met the inclusion criteria (19 in

IN THE LAST FEW DECADES THERE HAS BEEN A SIG-NIFICANT INCREASE IN THE PREVALENCE OF OBESI-TY WORLDWIDE AND THE WORLD HEALTH organization has declared it a global epidemic.¹ Obesity in childhood is a cause of psychosocial problems including low self esteem,² and frequently continues into adulthood³ where it is a cause of major morbidity and mortality including cardiovascular disease and type 2 diabetes. At the same time there has been a reduction in sleep time. National surveys in USA have shown a decline in self-reported sleep duration over the past 50 years by 1.5 to 2 hours.⁴ This sleep curtailment has been attributed to lifestyle changes.

Several studies have reported associations between duration of sleep (short as well as long) and ill-health, including relationships with self-reported well-being,⁵ morbidity and mortality,⁶⁻¹² and with chronic conditions including type 2 diabetes, respiratory disorders, hypertension, and obesity.¹³⁻¹⁸ The associations between short duration of sleep and obesity, in particular, have stimulated

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children and 26 in adults) and 30 (12 and 18, respectively) were pooled in the meta-analysis for a total of 36 population samples. They included 634,511 participants (30,002 children and 604,509 adults) from around the world. Age ranged from 2 to 102 years and included boys, girls, men and women. In children the pooled OR for short duration of sleep and obesity was 1.89 (1.46 to 2.43; P < 0.0001). In adults the pooled OR was 1.55 (1.43 to 1.68; P < 0.0001). There was no evidence of publication bias. In adults, the pooled β for short sleep duration was -0.35 (-0.57 to -0.12) unit change in BMI per hour of sleep change.

Conclusions: Cross-sectional studies from around the world show a consistent increased risk of obesity amongst short sleepers in children and adults. Causal inference is difficult due to lack of control for important confounders and inconsistent evidence of temporal sequence in prospective studies.

Keywords: Sleep duration; obesity; meta-analysis

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a debate given the potential implications for children^{19,20} as well as adults.^{21,22} However, given the variety of studies and the large differences in the target populations, it is difficult to draw immediate conclusions on the consistency of the association, the direction of causality and the likely mechanisms involved. The aims of this article are to (i) systematically review published population-based studies, (ii) to carry out a meta-analysis to assess whether the evidence supports the presence of a relationship between short sleep duration and obesity at different ages, and (iii) to obtain a quantitative estimate of the risk in order to assess the consistency and potential public health relevance

METHODS

Literature Search

We performed a systematic search for publications using Medline (1996-2007 week 40), EMBASE (from 1988), AMED (from 1985), CINAHL (from 1982) Psychinfo (from 1985). Search strategies used subject headings and key words and did not use language restrictions. We (FMT, N-BK, AC, SS, MAM, and FPC) examined reference lists of the relevant reviews and all identified studies and reviewed the cited literature. Two reviewers (FMT and N-BK) independently extracted the data. Differences about inclusion of studies and interpretation of data were resolved by arbitration (FPC), and consensus was reached after discussion with all authors. Of a total of 696 studies identified from the search (Figure 1), 12 studies in children met the inclusion criteria and provided suitable data on 13 population samples to be included in the pooled analysis^{w1-w12} (Table 1). Seven studies^{w13-w19} were excluded, as they did not provide suf-



ficient data for inclusion (Table 2). In adults 26 studies met the inclusion criteria, and 18 provided suitable data on 23 population samples to be included in the pooled analysis^{w20-w37} (Table 3). Eight studies^{w38-w45} were excluded as they did not provide sufficient data for inclusion (Table 4). Note: All references beginning with a W are available in the website version of this paper on the *SLEEP* website at www.journalsleep.org

Inclusion Criteria

The main objective was to assess the relationship between sleep duration and either obesity or body mass index (BMI). No restriction was placed on populations included. When data were not readily available from the published reports, we wrote to authors to ask for raw data.

Meta-Analysis

Exposure: Sleep Duration

Both the nature and quantity of sleep in children is different from that of adults. There is a gradual change with age and by age 10, sleep is similar to that of adults but the total time is longer (10 h).²³ We analyzed the results of studies in children separately from those in adults. For children the definition of "short sleep" was <10 h or \leq 10 h per night unless stated otherwise in Table 1.

In most of the studies in adults, short sleep was defined as either <5 h or ≤5 h per night for either average total sleep time (TST) in 24 h, nighttime sleep, weekday sleep, or based on a weighted average TST on weekdays and weekends, unless stated otherwise in Table 3. For odds ratios, short sleepers were compared to both middle and long sleepers, although in some studies they were compared to the reference category of either 7 h or 8 h sleep per night.

Outcome: Obesity

Unless stated otherwise (Table 1), obesity in children was defined either as BMI >95th percentile according to local national growth charts or by international growth charts where the thresholds for obesity is defined as the percentile which passes through BMI >30 kg/m² at age 18 years.^{w46} Unless stated otherwise (Table 3), obesity in adults was defined as BMI \geq 30 kg/m².

 Table 1—Description of the Study Populations of Children Included in the Meta-Analyses (n=30,002)

Author	Year Country		Sample	Age
			size (n)	(years)
Locard w1	1992	France	1,031	5
Ben Slama w2 *	2002	Tunisia	167	6-10
Sekine w3	2002	Japan	8,941	2-4
Von Kries w4	2002	Germany	6,645	5-6
Agras ^{w5}	2004	USA	150	9.5
(sleep at 3-5)				
Giugliano ^{w6}	2004	Brazil	165	6-10
Padez w7	2005	Portugal	4,390	7-9
Reilly w8	2005	UK	6,426	7
(sleep at 2.5)				
Chaput (1) w9	2006	Canada	422	5-10
Chen w10 † #	2006	Taiwan	656	13-18
Seicean w11 § #	2007	USA	509	14-18
Yu (males) w12	2007	China	273	10-20
Yu (females) w12 ¶	2007	China	227	10-20

Short sleep: * < 8 h per day; $\dagger \le 6$ h per night or ≤ 3 h weekday per week; \$ < 5 h on school nights;

¶ average week night sleep in hours

overweight/obesity defined as >85th percentile

Note: All references beginning with a W are available in the website version of this paper on the *SLEEP* website at www. journalsleep.org

Confounders

Mean age of the populations, proportion of boys and girls, men and women, and sample size were collected and used in stratified analyses of heterogeneity, publication bias and sensitivity.

Statistical Analysis

To estimate the quantitative relation between short sleep duration and obesity, we obtained an estimate from each study of the unadjusted odds ratio (OR) with 95% confidence intervals (CIs) and the unadjusted regression coefficient β (95% CIs) for BMI as a continuous outcome. Some studies did not report the unadjusted OR and β for the relationship between short sleep duration and obesity. We requested from various authors the unadjusted OR (95% CIs) for <5 h sleep versus >5 h and obesity defined as BMI \geq 30 kg/m², its standard error (SE), and the exact sample size (N). We also requested the unadjusted β (95%) CIs) for BMI (as a continuous outcome) on sleep duration, its standard error (SE), and the exact sample size (N). If the SE of either the OR or β were not supplied, it was algebraically computed from the 95% CIs. We used a random effect model and calculated pooled effects (95% CIs) for both OR and β . A problem which occurs in observational studies is selection bias and confounding. Selection bias is a feature of the study design and the possibility of this can be assessed by examining the methods of the study. Confounding can be due to known or unknown factors involved in the etiology and are related to both exposure and outcome variables. We examined possible sources of heterogeneity between the studies using a meta-regression

Author	Year	Country	Study design and Popula- tion	Sample size (n)	Age (yr)	Definition of sleep and obesity	Outcome measures presented	Summary of find- ings	Reason for exclusion
Gupta ^{w13}	2002	USA	Cross-sectional Heartfelt Study	383	11-16	TST BMI >85th percentile for age and sex and % body fat ≥25% male or 30% female	Logistic regression	Obesity and TST β = -1.62 (0.28 SE) OR: 0.20 (0.11 to 0.34)	Logistic regression for OR and β only-adoles- cent study
Hui ^{w14}	2003	Hong Kong	Selected groups Student Health Service	343	6-7	Usual no. of h sleep BMI/overweight by HK reference categories	% short sleepers in 3 categories of BMI	Association be- tween short sleep and obesity (% obese increased in short sleepers and decreased in long sleepers)	Case-control analysis Selected by BMI group
Knutson ^{w15}	2005	USA	National Lon- gitudinal Study of Adolescent Health	4,555	grade 7-12 13-18	BMI and usual no. h sleep	β for sleep duration and BMI	Shorter sleep and obesity boys $\beta = -0.08$ (-0.12 to -0.03) girls $\beta = -0.02$ (-0.06 to 0.01)	OR from lo- gistic regres- sion only.
Eisen- mann ^{w16}	2006	Australia	Australian Health and Fit- ness survey	6,324	7-15	Sleep time in bed at night. BMI and Waist by sleep duration categories	OR _{adj} for age	Dose response relationship for short sleep and overweight in all age groups (from 7 to 16 yr) significant in boys but not girls.	$ \beta_{adj} \text{ and } OR_{adj} \\ for age $
Dieu ^{w17}	2007	Vietnam	Sample of 20 kindergartens in Ho Chi Minh City	670	4-6	Obesity by Cole IOTF definition. ^{w45} Night sleep time	Prevalence ratios with CI	Prevalence ratio 0.85 in univari- ate regression for duration of sleep and overweight. Children with longer night- time sleep had lower risk of obesity.	No OR or β available
Knutson ^{w18}	2007	USA	Cross-sectional Child De- velopment supplement of Panel Study of Income Dynamics	767 boys 779 girls	10-18	2-d time diary and self-reported TST. "Over- weight" >95th percentile ac- cording to CDC and prevention growth charts	OR _{adj} for self-report- ed 0.5 to 7 h sleep vs 9.2 to 19.0 h sleep and obesity.	Self reported short sleep duration vs longest sleep OR _{adj} = 0.88 (0.45 to 1.69). However signifi- cantly higher risk of overweight with midrange self-re- ported sleep duration compared to longest sleep.	Reported OR- _{adj.} No linear regression.
Snell ^{w19}	2007	USA	Longitudinal Panel Survey of Income Dynamics	1,441	3-17	Average nightly sleep, BMI and obesity by Cole et al. ^{w45}	Linear regression BMI, non- linear (% categories) and sleep and wake timings.	BMI at time 1 sig corr <8 h sleep	No OR for short sleep vs obesity or β for cross sectional analysis. Only mean BMI in sleep duration categories

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 Table 3—Description of the Study Populations of Adults Included

 in the Meta-Analyses (n=604,509)

Author	Year	Country	Sample	Age
V . w20	2000	с ·	size (n)	(years)
Vioque ^{w20}	2000	Spain	1,//2	15+
Shigeta ^{w21} * ¶	2001	Japan	437	43-63
Kripke ^{w22}	2002	USA	497,037	30-102
Cournot w23	2004	France	3,127	32-62
Hasler w24	2004	Switzerland	457	27
Bjorkelund w25	2005	Sweden	1,460	38-60
Gangwisch (1) w26	2005	USA	3,682	32-49
Gangwisch (2) w26	2005	USA	3,324	50-67
Gangwisch (3) w26	2005	USA	2,582	68-86
Singh ^{w27}	2005	USA	3,158	18-65
Moreno ^{w28} §	2006	Brazil	4,878	Mean 40
Vahtera ^{w29} † ‡	2006	Finland	26,468	Mean 45
Watari (men) w30 ‡	2006	Japan	19,894	20-54
Watari (women) w30 ‡	2006	Japan	5,418	20-54
Kohatsu ^{w31}	2006	USA	990	Mean 48.3
Bjorvatn ^{w32}	2007	Norway	8,860	40-45
Chaput (men) ^{w33} * ¶	2007	Canada	323	21-64
Chaput (women) ^{w33} * ¶	2007	Canada	417	21-64
Ko ^{w34} * #	2007	Hong Kong	4,793	17-83
Tuomilehto w35 *	2007	Finland	2,770	45-74
Fogelholm (men) w36 *	2007	Finland	3,377	30+
Fogelholm (women) w36 *	2007	Finland	4,264	30+
Stranges w37	2008	UK	5,021	44-69

Short sleep: * <6 h or \leq 6 h per day; † <6.5 h or \leq 6.5 h per night; § <8 h per night; Obesity: ¶ BMI \geq 25 kg/m²; # BMI \geq 25 kg/m² and/ or waist \geq 80 cm in women and \geq 90 cm in men; ‡ BMI \geq 27 kg/m² or \geq 26.4 kg/m²; Note: All references beginning with a W are available in the website version of this paper on the *SLEEP* website at www.journalsleep.org

technique. We performed the Breslow-Day test for homogeneity of ORs, Cochran-Mantel-Haenszel test for the null hypothesis of no effect (OR=1), and the Mantel-Haenszel common OR estimate. We assessed publication bias by using a funnel plot and Begg's^{w47} test to find out whether there was a bias towards publication of studies with positive results among the smaller studies. In order to avoid bias in selection of papers, we tried to obtain all population studies which had data on the relationship between sleep duration and obesity which had been published worldwide and conducted the searches in an unbiased way using the main medical databases and reference lists from recent reviews. We also examined the influence of individual studies, in which the meta-analysis estimates are derived omitting one study at a time to see the extent to which inferences depend on a particular study or group of studies.

RESULTS

Children

Thirteen population samples from 12 studies were included in the pooled analysis. They included 30,002 participants from France, Tunisia, Japan, Germany, USA (n = 2), Brazil, Portugal, United Kingdom, Canada, Taiwan, and China. Age ranged from 2 to 20 years and included boys and girls. Sample sizes ranged between 150 and 8,941. Data was extracted from the published



Figure 2—Forest plot of the associations between short duration of sleep and obesity in studies carried out in children. OR and 95 CI indicate odds ratio and 95% confidence intervals.



articles when available and authors were contacted to request unavailable data or analyses. Details of the studies are summarized in Table 1.

For the meta-analysis sleep exposure was dichotomized for all studies. Figure 2 shows the Forest plot of 11 observational studies of short sleep and obesity involving 29,502 children studied around the world. Seven of 11 studies reported a significant association between short duration of sleep and obesity. The pooled OR was 1.89 (1.46 to 2.43). Publication bias was not detected by the Begg's test (P = 0.12) (Figure 3a). The het-





erogeneity test was significant (Q = 46.6, df =10, P < 0.001). The sensitivity analysis indicated that the omission of any of the studies led to changes in estimates between 1.61 (1.33 to 1.96) and 2.07 (1.54 to 2.79) (Appendix 1).

Adults

Twenty-two population samples from 17 studies met the inclusion criteria and provided suitable data for pooled analyses. They included 604,509 participants from Spain, Japan (n = 2), USA (n = 5), France, Switzerland, Sweden, Brazil, Finland (n = 3), Norway, Canada, Hong Kong, and United Kingdom. Age ranged from 15 to 102 years and included men and women. Sample sizes ranged between 437 and 497,037. Data were extracted from the published articles when available and authors were contacted to request unavailable data or analyses. Details of the studies included in the meta-analysis are summarized in Table 3. For the meta-analysis sleep exposure was used in two ways: as dichotomized variable and as continuous variable regressed over BMI used as continuous variable. Figure 4 shows the forest plot of 22 population samples from 17 observational studies of short sleep and obesity involving 603,519 adults studied around the world. Seventeen population samples showed a significant association between short duration of sleep and obesity. The pooled OR was 1.55 (1.43 to 1.68). There was no evidence of publication bias (Begg's test P = 0.09) (Figure 3b). The heterogeneity test was significant (Q = 64.0, df = 21, P < 0.001). The sensitivity analysis indicated that the omission of any of the studies led to changes in estimates between 1.50 (1.39 to 1.61) and 1.59 (1.44 to 1.76) (Appendix 2).

Figure 5 shows the Forest plot of 7 studies in adults including 16,509 participants and reporting regression coefficients (β)



Figure 5—Forest plot of the associations between duration of sleep and body mass index in studies carried out in adults. β and 95 CI indicate regression coefficient and 95% confidence intervals.

between hours of sleep per night and BMI. Unlike studies in children, all studies in adults showed a consistent and significant negative association between hours of sleep and BMI. The pooled β was -0.35 (-0.57 to -0.12) unit of change in BMI per hour of sleep (P = 0.002; heterogeneity P < 0.001). The sensitivity analysis indicated that the omission of any of the studies led to changes in estimates between -0.30 (-0.51 to -0.09) and -0.41 (-0.53 to -0.28) (Appendix 3).

DISCUSSION

This study provides for the first time a systematic review of the literature and quantitative estimates of the cross-sectional associations between duration of sleep and obesity (or measures of obesity) in population-based studies of children and adults around

Author	Year	Country	Study design and Popula- tion	Sample size (n)	Age (yr)	Definition of sleep and obesity	Outcome measures presented	Summary of findings	Reason for exclusion
Heslop ^{w38}	2002	UK	Cross-sec- tional Employed men	6,022	<65	Self reported TST in 24 h and BMI	Mean BMI for sleep duration categories	Shortest sleepers had higher BMI. [25.4 (25.2- 25.6) for <7 h to 25.1(24.7-25.4) for >8 h; P for trend = 0.02].	No OR for short sleep vs obesity or β
Buraz- eri ^{w39}	2003	Israel	Cross-section- al analysis in cohort	1,842	50+	Night sleep duration >8 h and TST >8 h and obesity	Cross sectional analysis for both long night sleep duration and long total sleep duration and obesity	No significant association be- tween long sleep and obesity - no analysis with short sleep	No report of relation between short sleep and obesity–only looked at 8 h+ vs <8 h
Taheri ^{w40}	2004	USA	Cross-sec- tional Employ- ees with oversampling of habitual snorers.	1,024	30-60	Average nightly sleep from 6-d diary and BMI	β _{adj} for average nightly sleep and BMI.	Mean BMI with se for sleep dura- tion groups	No OR for short sleep vs obesity or β
Tama- koshi ^{w41}	2004	Japan	Japan Collab- orative Cohort Study	43,852 men 60,158 women	40-9	Average sleep duration on weekdays and BMI	BMI (SD) for each of 7 sleep duration categories from <4 h to 10 h+	No test for trend	No odds ratio for short sleep vs obesity or regression coef- ficient. Only mean BMI in sleep duration categories
Ohayon ^{w42}	2005	France	Telephone survey fol- lowed by interviews	1,026	60+	Self-reported sleep duration and height and weight	OR for risk of short sleep (≤4 h30) among obese people (BMI>27) compared to people with normal BMI	Obese people were more likely to have the short- est sleep. OR for risk of short sleep (≤ 4 h 30) among obese people compared to people with normal BMI. OR = 3.6 (1.0 to 13.1)	OR not compa- rable because analysis does not include full range of BMI as outcome.
Vorona ^{w43}	2005	USA	Primary care population	924	18-91	Self-reported TST in 24 h for weekday and w/ end weighted for number of days. Self-reported weight and height	BMI in 4 groups. ANOVA	Obese partici- pants slept less than individu- als who were overweight (P = 0.04) or had normal BMI (P = 0.004).	No OR for short sleep vs obesity or β
Patel w44	2006	USA	Nurses Health Study	68,183	30-55	BMI and self- reported h sleep in 24 h	BMI and SE for sleep dura- tion categories	Short sleep- ers had higher BMI; P for trend <0.000)	No OR for short sleep vs obesity or β.
Meis- inger w45	2007	Germany	MONICA cohort	3,508 men 3,388	45-74	BMI h nighttime sleep	BMI (SD) by 5 sleep duration	BMI higher for ≤ 5 h sleep and 6 h	No OR for short sleep vs obesity

the world. It shows a consistent pattern of increased odds of being short sleeper if you are obese, both in childhood and in adulthood. A pooled regression analysis in adults also suggests that a reduction in one hour of sleep per day would be associated with a 0.35 kg/m^2 increase in BMI. For a person approximately 178 cm tall it would be equivalent to approximately 1.4 kg in weight.

These results are of interest for several reasons. First, the association is consistent in different populations. Although the meta-analysis detected significant heterogeneity between studies, further sensitivity analyses and the exclusion of publication bias are in favor of a similar effect across the populations. Second, they indicate an effect size consistent across ages. The 60% to 80% increase in the odds of being short sleeper amongst obese was seen in both children and adults, even after some attenuation following sensitivity analyses. Third, the categorical results were corroborated by the meta-analysis of regression coefficients, at least in adults.

There are some limitations. First, the quality of the data cannot go beyond the quality of the individual studies included. Second a meta-analysis of observational studies is open to important fallacies in that it cannot directly control for confounding and therefore may be open to biased estimates. Third, the results can only be representative of the studies that have been included and are unable to provide a representative inference of all studies published. Nevertheless, these results are important in guiding the assessment of current evidence and the definition of future research strategies.

The pooled studies are cross-sectional and cannot, therefore, determine temporal sequence, hence, causality. They also cannot examine changes in sleeping habits with time. Moreover, all studies used sleep questionnaires to determine self-reported sleep duration within their populations. Self-reported duration of sleep has been validated against actigraphy.²⁴

The variety of methods for analyzing weight and obesity reflects our current poor understanding of what the most effective measuring scheme is. Many different methods were used to determine obesity, particularly in children, making the various studies more difficult to reconcile.

The studies varied in the degree of control for confounders such as age, gender, ethnic background, socioeconomic status, degree of energy intake, energy expenditure, frequency of snacking, and other health-related behaviors and nutritional habits. A confounding factor in the relationship between sleep duration and obesity in adults is psychiatric comorbidity, particularly depression.²⁵⁻²⁷ Chronic illness, physical disability, use of hypnotics, etc., would also be important confounders to consider. In the pooled analysis we used exclusively unadjusted estimates from the individual studies. The consistency of the pooled associations between children and adults suggests that it is unlikely that a differential bias due to common unaccounted confounders might have occurred in the two age categories.

The results of prospective studies do not provide consistency in support of the view that short sleep duration predicts the future development of obesity,^{22,28-31} with the exception of a very large study (n >60,000), carried out in women only, which shows a small effect (hazard ratio of 1.15 and 1.06 for those sleeping \leq 5 h and \leq 6 h per night, respectively).³² The relationship may be confounded by comorbidity, such as chronic mental illness, causing a decrease in the levels of physical activity and a reduction in sleep, or by physical illnesses associated with pain—hence disrupted sleep—and severe limitation in energy expenditure through limited physical activity. More recent studies have adjusted for these potential confounders and found no prospective association.²²

Our study does not allow us to study mechanism. However, it has been suggested that short sleep may lead to obesity through the activation of hormonal responses³³ leading to an increase in appetite and caloric intake. Short sleep is associated to reciprocal changes in leptin and ghrelin.³³ This in turn would increase appetite and contribute to the development of obesity. The evidence in humans comes from short-lived severe sleep deprivation experiments^{35,36} that cannot be extrapolated to long term effects in the population.

Activation of inflammatory pathways by short sleep may also be implicated in the development of obesity.³⁷ Finally, it is not inconceivable that short sleep is just a marker of unfavorable health status and of lifestyle characteristics.^{38,39}

The potential public health implications of a causal relationship between short duration of sleep and obesity have already been widely disseminated in the media. The findings of our analysis suggest that whilst sustained sleep curtailment and ensuing excessive daytime sleepiness are undoubtedly cause for concern, the link to obesity is of interest but still to be proven as a causal link. Many questions still need an answer to determine causality. Prospective studies in which weight, height, waist measurements. and adiposity are measured at baseline and again at subsequent data collection times together with more accurate objective measurement of sleep duration (including naps) and confounding factors or mediators such as depression are needed.

Further prospective studies with improved assessment of long-term exposure (repeated self-reported sleep duration or repeated actigraphy), more specific outcomes (including measures of adiposity) and better control for confounders are needed before causality can be determined.

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Authors' Contribution

FPC conceived the study aims and design, contributed to the data extraction, planned the analysis, interpreted the results and drafted the final version of the paper. FMT carried out the systematic review and contributed to data extraction and analysis. N-BK contributed to data extraction and carried out the statistical analysis. AC, SS and MAM contributed to the systematic review, analysis and interpretation. EP contributed to interpretation of results. All authors contributed to the revision of the manuscript.

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