BMJ Open Association of sleep duration and quality with blood lipids: a systematic review and meta-analysis of prospective studies

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ABSTRACT

Objectives To assess the longitudinal evidence of the relationships between sleep disturbances (of quantity and quality) and dyslipidaemia in the general population and to quantify such relationships.

Setting Systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Methods We performed a systematic search of PubMed and Embase (up to 9 September 2017), complemented with manual searches, of prospective population studies describing the association between sleep duration and quality and the incidence of dyslipidaemias. Relative risks (95% CIs) were extracted and pooled using a random effects model. Subgroup analyses by lipid type were performed. Heterogeneity and publication bias were also assessed. Quality was assessed with Downs and Black score.

Participants Studies were included if they were prospective, had measured sleep quantity and/or quality at baseline and either incident cases of dyslipidaemia or changes in blood lipid fractions assessed prospectively.

Primary outcome measures Incidence of dyslipidaemia and changes in lipid fractions. Dyslipidaemia was defined as a high total cholesterol, triglycerides, low-density lipoprotein cholesterol or low high-density lipoprotein cholesterol compared with the reference group.

Results Thirteen studies were identified (eight using sleep duration, four sleep quality and one both). There was heterogeneity in the sleep quality aspects and types of lipids assessed. Classification of sleep duration (per hour/groups) also varied widely. In the pooled analysis of sleep duration (6 studies, 16 cohort samples; 30 033 participants; follow-up 2.6–10 years), short sleep was associated with a risk of 1.01 (95% CI 0.93 to 1.10) of developing dyslipidaemia, with moderate heterogeneity ($I^2=56\%$, $P=0.003$) and publication bias ($P=0.035$). Long sleep was associated with a risk of 0.98 (95% CI 0.87 to 1.10) for dyslipidaemia, with heterogeneity ($I^2=63\%$, $P<0.001$) and no significant publication bias ($P=0.248$).

Conclusion The present analysis was unable to find supportive evidence of a significant relationship between sleep duration and the development of dyslipidaemia. However, heterogeneity and small number of studies limit the interpretation.

PROSPERO registration number CRD42016045242.

Strengths and limitations of this study

- This is the first study evaluating the collective prospective evidence of the association between sleep duration and biomarkers of lipid metabolism.
- Strengths of this review include the broad search strategy and in-depth quality assessment of studies.
- Limitations to interpretation are: heterogeneity of exposure and outcome measurements and small number of studies.
- The results can only be representative of published and included studies.

BACKGROUND

Research into sleep and its effects on health has increased in recent years. This has been accompanied by public health concerns about the declining quality and quantity of sleep in modern society.¹ Both short and long sleep duration are consistently associated with mortality and serious chronic diseases, such as diabetes and cardiovascular disease (CVD).^{2–4} Similarly, poor sleep quality has been associated with mortality and CVD.^{4 5} CVD is the leading cause of non-communicable disease deaths globally and deaths by CVD have risen by 12.5% between 2005 and 2015.⁶ There is still debate about whether the association between sleep and CVD is causal or whether sleep disturbances are merely symptoms or risk markers of disease.⁷ Understanding the possible mechanisms through which sleep affects CVD can provide important supportive evidence for a causative link.

U-shaped relationships between duration of sleep and risk factors for CVD, such as hypertension and metabolic syndrome have been observed.^{8 9} For obesity, the longitudinal association is most clear in paediatric populations, in which shorter sleep is associated with an increased risk of obesity.¹⁰ Fewer studies have been performed on sleep quality,

Figure 1 PRISMA flow diagram of study selection. HDL, high-density lipoprotein; LDL, low-density lipoprotein; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TC, total cholesterol; TG, triglyceride.

but poor sleep quality has also been associated with an increased risk of hypertension,¹¹ metabolic syndrome¹² and diabetes.²

An unfavourable blood lipid profile, including high total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), is a well-established risk factor for CVD.¹³ Circulating lipids are influenced by lifestyle factors such as diet, smoking and physical activity.¹⁴ Whether sleep duration and quality are associated with blood lipids remains to be ascertained.

Systematic reviews of observational studies suggest a lack of consistency in the association between sleep duration and lipid profiles, with a large heterogeneity in the classification of exposure and outcome and the

type of analysis. Furthermore, these were mainly based on cross-sectional evidence—hence unable to establish a temporal relationship between exposure and outcome—and did not evaluate sleep quality as a potential exposure of interest.^{15 16} In recent years, new prospective studies that include measures on sleep and blood lipids have emerged. Nadeem *et al*¹⁷ performed a meta-analysis of 64 observational studies involving 18 116 patients on obstructive sleep apnoea (OSA) and the blood lipid profile. They found that OSA was associated with a significantly higher risk of dyslipidaemia, for example, high TC and LDL-C, high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C). However, this meta-analysis was performed in a specific patient group, did not include

sleep duration as an exposure and was based on cross-sectional studies.

To the best of our knowledge, a meta-analysis of prospective studies on sleep quality and duration, and blood lipids in the general population without diagnosed sleep disorders has not yet been published. We set out to systematically evaluate prospective studies for an association between sleep duration and quality, and blood lipids in the general population and to pool the evidence in a meta-analysis.

DATA AND METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁸ PROSPERO registration number: CRD42016045242, available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016045242.

Search strategy

The electronic databases, PubMed (from 1996) and EMBASE (from 1947), were searched on 9 September 2017 using keywords related to exposure (sleep duration and quality), outcome (blood lipids) and design (prospective). Abbreviations, plural forms and alternate spellings (American-English) of keywords were searched. The search was restricted to human research and published journal articles. No language restriction was applied. In addition, a manual check of reference lists was performed using (1) previous review articles on the subject, (2) relevant review articles identified in the search and (3) articles included in the present study. Additional searches were performed into the studies that measured lipids at baseline and follow-up, but did not report on lipids, to see if additional publications were available which did report on the outcome of interest.

Study selection

After title and abstract scanning, full-text articles were retrieved. Prospective articles were evaluated for inclusion by two of three investigators (MK, WR and FPC) according to the following criteria set a priori: (A) original published article, (B) observational prospective design, (C) a baseline assessment of exposures (sleep duration or sleep quality) and (D) one of the following outcomes: (1) a change in serum lipids over time or (2) a relative risk of developing dyslipidaemia in short or long sleepers compared with the reference sleep category. Studies were excluded if (A) exposure was napping or shift work, (B) population had a diagnosed sleep disorder like OSAS or pre-existing cardiovascular or metabolic disease, (C) it was a case-control study. No sample size, age or duration of follow-up restriction was applied. Disagreement on inclusion was resolved by discussion and consensus among the three investigators. Authors were contacted for additional data.

Data extraction

Data from each study was extracted independently by two investigators (MK and FPC). Extracted data included: first author, year of publication, country of origin of the population, recruitment year of cohort, age (at sleep assessment), sex, duration of follow-up, number of participants included, methods of assessment of both exposure and outcome, definitions of sleep categories, relative risks (RR), HR, OR, regression coefficients (β) representing changes in lipid levels, 95% CI, SE and adjustment for covariates. SEs were derived from CI if not reported (online supplementary appendix table A1). The most adjusted estimates were used for analysis. When data were reported for men and women separately, they were entered for analysis as two separate cohorts. When data from the same cohort was published in separate papers, only one estimate was used (usually the longer follow-up or the largest dataset). Differences in extracted information were resolved by discussion and consensus among two of the investigators.

Risk of bias assessment

The quality of the included studies was assessed using the Downs and Black Quality Index Score.¹⁹ This checklist includes items for measuring a study's reporting quality, external validity, bias, confounding and power. The maximum score for prospective studies is 20.

Statistical analysis

A random effects model with inverse-variance weighting was used to pool HRs, ORs and RRs into RRs for developing high TC, low HDL-C, TC/HDL-C ratio ≥ 5 and high TG in short sleepers and long sleepers compared with the reference category. Ratio measures and standard errors were transformed into natural logarithms for analysis. For a detailed overview and examples of data transformations performed, see online supplementary appendix table A2. Changes in lipid levels over time were meta-analysed using a random effects model when at least two cohorts with a similar exposure and outcome measurement were available. Due to heterogeneity in sleep quality aspects and types of outcomes reported, we were unable to meta-analyse the studies on sleep quality. Publication bias was assessed with examination of funnel plot symmetry and Egger's regression test for small study effects when the number of cohorts available was greater than 2. Heterogeneity was investigated with Q test statistic and quantified by I^2 statistics. The following thresholds for I^2 interpretation from Cochrane Reviews were used: '0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity'.²⁰ The influence of individual studies was investigated by excluding one study at a time. A two-tailed P value <0.05 was considered statistically significant. Statistical analyses were performed with Stata V.14 (StataCorp, College Station, Texas, USA).

RESULTS

Identified studies

Searches yielded 1594 titles (figure 1). After title and abstract scanning, 157 full-text articles were retrieved. Twelve studies were identified in the search, seven concerned only sleep duration, one concerned only sleep quality and one concerned both. Searching the references of included studies yielded one additional study regarding sleep quality, yielding a total of 13 studies. Four authors were contacted^{21–24} for additional data of whom one could provide data.

Assessment and definition of exposures

Sleep duration was mostly self-reported, either by questionnaire^{21 24–28} or interview^{29 30} (table 1). Three studies used accelerometry to assess sleep duration.^{23 31 32} Sleep duration was analysed as a continuous measure in four studies, meaning a risk²⁹ or change in lipid levels per hour of sleep increase^{23 31 32} was reported. Two studies used qualitative groups^{27 28} and five used sleep duration groups for analysis. Short sleep was defined as ≤ 6 hours,^{21 <5 hours, 24 <6 hours 25 30} and < 7 hours.²⁶ Long sleep duration was defined as ≥ 9 hours,^{21 25} ≥ 7 hours²⁴ and ≥ 10 hours.^{26 33} Subjective aspects of sleep quality that have been evaluated by questionnaire include difficulty falling asleep,^{33 34} difficulty maintaining sleep,³³ unrefreshing or non-restorative sleep,^{33 34} presence or absence of sleep disorder,²⁸ frequency of sleep duration²⁷ and Pittsburgh Sleep Quality Index (PSQI) score.²³ Sleep fragmentation was objectively assessed with accelerometry in one study.²³

Change from protocol

In the original protocol submission to PROSPERO (CRD42016045242), the Outcome(s) section reads Primary outcomes: we expect most studies will have measured cholesterol. The expected primary outcomes are therefore changes in TC or the risk of developing hypercholesterolaemia. Secondary outcomes: the following outcomes will also be assessed: changes in serum levels HDL-C, LDL-C and TGs and the risk of developing dyslipidaemia (this can be hypercholesterolaemia, hypertriglyceridaemia, etc). The submission reflects the ‘a priori’ uncertainty on how the outcomes in prospective studies would look like. After the search, it became apparent that the most common form of outcome in prospective studies was indeed ‘incidence of dyslipidaemia’. We report all outcomes originally planned to avoid the risk of selective outcome reporting.

Assessment and definition of outcome

For an overview of outcomes assessed, see table 1. To assess outcomes, 10 studies used a fasting blood samples,^{21 23–27 30–32} 2 self-report^{28 29} and 1 data register.³⁴ TC was assessed in six studies,^{23 24 26 27 29 32} HDL-C in seven studies,^{23–26 30 31 33} LDL-C in three studies,^{23 24 26} TG in eight studies,^{21 23–26 30 31 33} non-HDL-C in one study²⁴ and TC/HDL-C ratio in one study.²³ One study assessed changes in lipid levels,³¹ 10 studies reported a risk of dyslipidaemia

for one or more lipids or lipid fractions^{21 24 25 27–33} and 1 study reported on both.²³ Furthermore, one study assessed changes in lipid levels compared with a reference group.²⁶ Dyslipidaemia was defined as a high TC, TG, LDL-C or low HDL-C compared with the reference group as described in table 1.

Study characteristics

All identified publications were recent (2010–2017) (table 1). Ten studies were performed in adults,^{21 23–28 30 33 34} one in adolescents^{29 32} and one in children.³¹ Twelve studies recruited men and women,^{21 23 25–34} four of these reported on outcomes in men and women separately.^{23 25 29 32 34} One study recruited only men.²⁴ Follow-up ranged from 200 days to > 20 years. Four studies were performed in the USA,^{23 29 32 33} two in China^{25 26} and Finland,^{32 34} one in Canada,²¹ Denmark³¹, France,²⁸ Japan²⁴ and South Korea.³⁰

Sleep quality

In online supplementary appendix table A3, an overview of the results reported in the individual studies for sleep quality is given. In general, studies reported both favourable and unfavourable associations of poor sleep quality with blood lipids. The associations reported differed by lipid type and aspects of sleep quality assessed. Only Haaramo *et al*³⁴ reported significant associations. Those occasionally or frequently suffering from insomnia symptoms had a significantly increased risk of dyslipidaemia medication compared with those without insomnia symptoms.

Sleep duration and dyslipidaemia risk

The quality of studies included in the meta-analyses ranged from 12 to 18 out of a maximum score of 20 (see online supplementary appendix table A4). All studies scored high on items of reporting and bias. Studies scored less well on items of external validity and confounding. All studies lacked in adequate confounder adjustment by not adjusting for at least one of the following factors: baseline lipid levels, dyslipidaemia medication, other sleep variables or depression. Meta-analyses included three cohorts with high TC (21 453 participants), four cohorts with low HDL-C (11 851 participants), two cohorts with high TC/HDL-C ratio (503 participants) and five cohorts with high TG (11 450 participants). Meta-analyses of short sleep duration by different lipids fractions are shown in figure 2. In an overall pooled analysis of sleep duration (6 studies, 16 cohort samples; 30 033 participants; follow-up 2.6–10 years), short sleep was associated with a risk of 1.01 (95% CI 0.93 to 1.10) of developing any dyslipidaemia, with moderate heterogeneity ($I^2=56\%$, $P=0.003$) and publication bias ($P=0.035$). Short sleep was associated with a non-significant increased risk of developing high TC (RR=1.10; 95% CI 0.99 to 1.22; $P=0.07$; no heterogeneity and publication bias). There were not enough observations to perform an Egger’s test for the risk of TC/HDL-C ratio ≥ 5 , there was no evidence for

Table 1 Characteristics of studies included in systematic review

Author	Year of publication	Country	Cohort	Quality	Recruitment year	Age at baseline sleep measurement	Follow-up	Gender	n*	Exposure(s) assessed	Exposure assessment method	Exposure categories	Outcomes assessed	Outcome assessment method	Variables adjusted for
Gangwisch <i>et al</i> ²⁹	2010	USA	Add Health (National Longitudinal Study of Adolescent Health)	14	1994–1995	Grade 7–12	Max 8 years	Men and women (separately)	Women: 7318 Men: 6939	Habitual sleep duration (average of wave I and wave II, these were 1 year apart)	Self-reported (interview question)	Continuous (per hour increase)	OR hypercholesterolaemia†	Self-report (interview question)	Age, sex, race/ethnicity, alcohol consumption, cigarette smoking, physical activity, physical inactivity, emotional distress, body weight
Troxel <i>et al</i> ³³	2010	USA	Heart SCORE	12	2003‡	45–74	3 years	Men and women (combined)	HDL: 742, TG: 514	Insomnia symptoms: difficulty falling asleep and unrefreshing sleep	Self-reported (insomnia symptom questionnaire)	Ref: no insomnia symptoms	OR hypertriglyceridaemia (>150 mg/dL) OR low HDL-C (<50 mg/dL for women, <40 mg/dL for men)	Fasting blood sample	Age, sex, race, marital status, study randomization, smoking status, alcohol consumption, sedentary lifestyle and presence of clinically significant depressive symptoms
Chaput <i>et al</i> ⁴¹	2013	Canada	Quebec Family Study	12	1978	18–65 years	Mean (SD): 6.0 (0.9) years	Men and women (combined)	293	Average daily sleep duration	Self-reported (questionnaire)	Short: ≤6. Long: ≥9 Ref: 7–8	RR hypertriglyceridaemia: ≥1.7 mmol/L	Fasting blood sample	Age, sex, smoking habits, total annual family income, alcohol consumption, coffee intake, daily caloric intake and cardiorespiratory fitness
Petrov <i>et al</i> ²³	2013	USA	CARDIA Sleep Study, Chicago site	14	1985–1986	Mean: 39.9 SD: 3.7	Max 10 years	Men and women (separately)	503 men and women at baseline§	Sleep quality (fragmentation, PSQI) and quantity	Wrist actigraphy, self-reported (PSQI)	Continuous (per hour of sleep increase, per PSQI score increase of 1, per 10% sleep fragmentation increase)	10-year changes in TC, TG, HDL-C, LDL-C OR of high TC/HDL ratio (≥ 5)	Fasting blood sample	Age, race, income, education, BMI, alcohol use, smoking status, CES-D score, physical activity level, C reactive protein level, apnoea risk, presence of diabetes, thyroid problems or kidney problems. Additionally for women: oral contraceptive use, hormonal therapy use and menopausal status
Hjorth <i>et al</i> ³¹	2014	Denmark	OPUS (Optimal well-being, development and health for Danish children through a healthy New Nordic Diet)	15	2011	Mean: 10.0 SD: 0.6	Max 0.55 years (200 days)	Boys and girls (combined)	486	Night-time sleep duration (average comprised of week and weekend sleep)	Estimated by accelerometer, within window of sleep reported in logbooks by parents and children	Continuous (hours)	200-day changes in plasma TG and HDL-C	Fasting blood sample	Baseline age, sex, pubertal status, sex-pubertal status interaction, days of follow up, baseline sleep duration and baseline TG and HDL-C

Continued

Table 1 Continued

Author	Year of publication	Country	Cohort	Quality	Recruitment year	Age at baseline sleep measurement	Follow-up	Gender	n*	Exposure(s) assessed	Exposure assessment method	Exposure categories	Outcomes assessed	Outcome assessment method	Variables adjusted for
Haaramo <i>et al</i> ²⁴	2014	Finland	Helsinki Health Study	18	2000–2002	40–60 at baseline SD: 4.2	5 years	Men and women (separately)	Women: 5084 Men: 1393	Insomnia symptoms: difficulties in initiating and maintaining sleep and non-restorative sleep	Self-reported (Jenkins sleep questionnaire)	Rare: any of the symptoms one to three times in the previous 4 weeks occasional: 4 to 14 times frequent: at least 15 times Ref: no insomnia symptoms	OR dyslipidaemia	Register data on prescribed reimbursed dyslipidaemia medication	Age, prebaseline dyslipidaemia medication, heavy drinking, smoking, physical inactivity, fruit and vegetable consumption and BMI, SES, psychosocial job strain, shift work, working overtime, lifetime physician-diagnosed diabetes and mental disorders
Kinuhata <i>et al</i> ²⁴	2014	Japan	The Kansai Healthcare Study	12	2000–2001	Mean: 47.8 SD: 4.2	6-year observation period	Men only	Varying between 5941 and 7627 for the different analyses	Daily sleep duration	Self-reported (questionnaire)	5–7 ≥7 Ref: <5	HR for low HDL-C (<40 mg/dL), high LDL-C (≥160 mg/dL), high non-HDL-C (≥190 mg/dL), high TG (≥200 mg/dL) and high TC (≥240 mg/dL)	Fasting blood sample	Age, BMI, smoking habits, alcohol consumption, regular leisure time physical activity and hypertension. Multiple linear regression LDL cholesterol and TC additionally adjusted for log-e
Kim <i>et al</i> ²⁰	2015	South Korea	KoGes-ARIRANG	13	2005–2008	40–70 at baseline	Average: 2.6 years	Men and women (combined)	2579	Daily sleep duration (on average, including naps)	Self-reported (interview question)	<6, 8–9.9 ≥10 Ref: 6–7.9 hours	OR for hypertriglyceridaemia (serum TG concentration ≥ 150mg/dL). And low HDL-C (serum HDL cholesterol concentration < 40 mg/dL for men or <50 mg/dL for women)	Fasting blood sample	Age, sex, education, smoking, alcohol intake, total calorie intake, exercise
Li <i>et al</i> ²⁵	2015	China	Cohort study of chronic disease in Harbin	14	2008–2013	30–65 at baseline	Average: 4.4 years	Men and women (separately)	Women: 2278 Men: 2496	Night-time sleep duration	Self-reported (questionnaire)	<6 6–<7 8–<9 ≥9 Ref: 7–8	HR for hypertriglyceridaemia (serum TG ≥ 1.7 mmol/L) and reduced HDL-C (drug treatment or <1.0 mmol/L for men and <1.3 mmol/L for women).	Fasting blood sample	Age, SBP, smoking, alcohol use, physical activity level, education, psychological pressure, bad mood, stroke, cardiovascular disease, mental illness, insomnia, use of hypnotics, sleep quality, sleep in daytime, snoring, WC, FBG, TG, postmenopausal status (in women)
Yang <i>et al</i> ²⁶	2016	China	Dongfeng-Tongji cohort	14	2008–2010	Mean: 62.8	Max follow-up 5 years	Men and women (combined)	14 565	Usual night-time sleep duration	Self-reported (questionnaire)	<7 8–<9 9–<10 ≥10 ref: 7–8	5-year changes in TC, TG, HDL-C, LDL-C compared with ref group	Fasting blood sample	Age, sex, BMI, smoking status, drinking status, education, physical activity, lipid-lowering drugs, baseline lipids, midday napping

Continued

Table 1 Continued

Author	Year of publication	Country	Cohort	Quality	Recruitment year	Age at baseline sleep measurement	Follow-up	Gender	n*	Exposure(s) assessed	Exposure assessment method	Exposure categories	Outcomes assessed	Outcome assessment method	Variables adjusted for
Byrne <i>et al</i> ⁶⁷	2016	USA	'Go for the Gold' programme—Vanderbilt	16	2003	Mean: 41.2 SD: 10.8	Max 9 years	Men and women (combined)	Women: 6975 Men: 3273	How often sleeping 7–8 hours per night	Self-reported (questionnaire)	Seldom/never (ref) < Half the time Most of the time Always	OR hypercholesterolaemia	Fasting blood sample	Age and sex
Meneton <i>et al</i> ²⁸	2016	France	GAZEL prospective cohort	15	1989	35–50 years	>20 years	Men and women (combined)	Women: 2723 Men: 8013	Sleep disorders	Self-administered questionnaire	Yes/no (ref)	OR of dyslipidaemia	Blood sample	
Kuula <i>et al</i> ³²	2016	Finland	Urban community-based cohort	17	2006	8 years Mean: 8.1 SD: 0.3	4 years	Boys and girls (separately)	Girls: 101 Boys: 89	Sleep duration and quality	Actigraphy	Continuous (hours)	Regression coefficient	Fasting blood sample	Age, BMI, physical activity, pubertal development, SES

*N is given for the specific analysis when available.

†Assumption that diagnosis of high cholesterol at wave III are incident cases due to young age of subjects at wave I.

‡From Bambs *et al*⁵⁹

\$Due to model used. GEE, exact number of unique people included in analysis was unavailable.

BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; CES-D, Center for Epidemiological Studies—Depression Scale; FBG, fasting blood glucose; GAZEL, GAZandElectricité study; GEE, generalised estimating equations; HDL-C, high-density lipoprotein cholesterol; KoGES-ARIRANG, Korean Genome and Epidemiology Study on Atherosclerosis Risk of Rural Areas in the Korean General Population; LDL-C, low-density lipoprotein; PSQI, Pittsburgh Sleep Quality Index; SBP, systolic blood pressure; SCORE, Strategies Concentrating on Risk Evaluation; SES, socioeconomic status; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

publication bias for the remaining lipid types (see online supplementary appendix figures A1 a–c).

Meta-analyses of long sleep duration by different lipid fractions are shown in figure 3. In an overall pooled analysis, the risk of any dyslipidaemia among long sleepers was 0.98 (95% CI 0.87 to 1.10), with heterogeneity ($I^2=63\%$, $P<0.001$) and no significant publication bias ($P=0.248$). There were not enough observations to perform an Egger's test for the risk of TC/HDL-C ratio ≥ 5 , there was no evidence for publication bias for the remaining lipid types (see online supplementary appendix figure A1 d–f).

Sleep duration and lipid changes over time

There were too few studies to draw any meaningful conclusions from this analysis. (table 2). An increase in sleep duration was not associated with a change in HDL cholesterol. Furthermore, Yang *et al*³² report changes in lipid levels in short and long sleepers compared with a 7–8 hours reference group. None of these associations reached significance, except for an 0.085 mmol/L (95% CI 0.014–0.156, P unreported) increase in TG for those sleeping ≥ 10 hours compared with those sleeping 7–<8 hours.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis of the current prospective evidence on the relation between sleep quality, sleep duration and blood lipids in the general population. The results were not influenced by age, study quality, follow-up duration, gender or sleep assessment method. The analysis was carried out by separate lipid fractions. The risk of the development of dyslipidaemia varied among short and long sleepers and by lipid type.

Like Abreu *et al*,¹⁶ we found that studies often adjusted for factors such as diet and body mass index, without exploring potential mediation, while the influence of other sleep variables are ignored. Sleep disordered breathing was not taken into account in any of the included studies, even though it has been associated with an increased risk of dyslipidaemia.¹⁸ Another factor that was inconsistently taken into account was stress, which can be a determinant of both poor sleep and increased stress levels. In the Whitehall II study, cortisol secretion was raised in those reporting short sleep duration and high sleep disturbance.³⁵

Polysomnography is the gold standard for objective assessment of sleep quality and quantity, but objective sleep assessment is often not feasible in large cohort studies. Sleep quality and quantity were assessed subjectively by questionnaire or interview in most included studies. Moderate correlation between assessment of sleep duration by self-report and more objective actigraphy assessment have been observed in the Coronary Artery Risk Development in Young Adults study.³⁶ Similarly, the Pittsburgh Sleep Quality Index and Epworth Sleepiness scale, two often used subjective measures of

Figure 2 Forest plot of risk of dyslipidaemia in short sleepers. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

sleep quality, do not correlate well with objective sleep measures.³⁷ In all included studies, a single measurement of sleep was taken at baseline, which may not represent the full sustained effect of sleep duration.

In previous systematic reviews, both long and short sleep duration were strongly associated with health outcomes, including cardiovascular disease.^{1,4} No such effects were found in this meta-analysis. It is possible that the effects of sleep duration on cardiovascular health are not mediated through blood lipids,³⁸ but through other pathways such as obesity, hypertension and inflammation.^{10,39–41} However, an effect of sleep duration on blood lipids would be biologically plausible. Sleep restriction is associated with an altered secretion of metabolic and hunger hormones, such as growth hormone, cortisol, leptin and ghrelin.^{42–44} Furthermore, sleep can influence eating behaviour and physical activity. Short sleep time and non-restorative sleep have been associated with a dietary alterations reflecting a higher intake of energy and fat.^{45–47} Sleep loss has also been shown to decrease physical activity in free-living conditions,⁴⁸ and insufficient sleep could undermine dietary efforts to reduce adiposity.⁴⁹ Several short-term experimental studies also suggest an effect of sleep restriction on blood lipid levels.^{50,51} Since it is difficult to have people sleep for long periods of time, mechanisms for the effects of long sleep duration on health have been less investigated and remain mostly speculative. It is possible that the observed

relationship between long sleep duration and cardiovascular outcomes reflects long sleep duration being a risk marker or symptom of disease rather than a cause.⁷

Strengths and limitations

Strengths of this review include the broad search strategy and in-depth quality assessment of studies. The high heterogeneity of exposure and outcome measurements encountered in this review limited the scope of the meta-analysis. We were unable to perform a meta-analysis for sleep quality. The results can only be representative of published and included studies and the interpretation is limited by the small number of studies and some publication bias. Other limitations include the inability to directly adjust for confounding with study level meta-analysis and the fact that the quality of the meta-analysis cannot go beyond the quality of the included studies.

Perspectives

We do not yet have the strength of evidence needed to inform public health policy on the relation between sleep quality and duration and blood lipid profiles. In future research, individual patient data meta-analysis could provide possibilities to analyse data in a more homogeneous way. Furthermore, this review and meta-analysis focused on the general healthy population only. There are indications for an association between sleep and blood lipids in patients with diabetes⁵² and mental illness.⁵³

Figure 3 Forest plot of risk of dyslipidaemia in long sleepers. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Other potential areas for future research are sleep timing and circadian disruption. Cross-sectional evidence indicates sleep timing and patterns may be associated with

unfavourable lipid profiles,⁵⁴ although causality cannot be implied from those studies. Disruptions in the circadian rhythm have also been shown to be associated with metabolic alterations.⁵⁵ Sleep disturbances are important to consider in the light of other CVD risk factors, such as obesity, hypertension and diabetes. randomised controlled trials that evaluate the effect of improved sleep habits on obesity and cardiovascular health are now becoming available.^{56–58}

CONCLUSION

The present analysis was unable to find supportive evidence of a relationship between sleep duration and the development of dyslipidaemia. However, heterogeneity and small number of studies limit the interpretation. Further prospective studies are needed.

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Contributors MK set the search, reviewed part of the search output, extracted data, set up the database, drafted methods and results, contributed to analysis and discussion of results. WR contributed to the design of the search, reviewed part of the search output, contributed to the arbitration for data extraction, contributed to discussion of results. CJ carried out statistical analysis and contributed to the interpretation and discussion of results. MAM and JMG contributed to study design, interpretation and discussion of results. FPC developed the idea, contributed to study design, extracted data, supervised the analysis and drafted the final version

Table 2 Meta-analytical results for continuous outcomes

Blood lipid fraction	No of studies and cohorts	n	Publication bias	Change in lipid levels per hour of sleep
Total cholesterol	One study, two cohorts	503	—	0.14 (0.06 to 0.23), $P=0.001$, $I^2=0.0$
HDL cholesterol	Two studies, three cohorts	989	$P=0.020$	0.00 (−0.02 to 0.03), $P=0.719$, $I^2=0.0$
LDL cholesterol	One study, two cohorts	503	—	0.09 (0.01 to 0.17), $P=0.033$, $I^2=0.0$
Triglycerides	Two studies, three cohorts	989	$P=0.450$	0.01 (0.01 to 0.01), $P<0.001$, $I^2=0.0$

Values are reported in millimole per litre with 95% CI.
HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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