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CLINICAL REVIEW

Sleep disturbances compared to traditional risk factors for diabetes development: Systematic review and meta-analysis

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SUMMARY

Sleep disturbances [short (<6 h) and long (>8 h) sleeping time, insomnia (initiating or maintaining sleep), obstructive sleep apnea (OSA) and abnormal sleep timing] have been associated with increased diabetes risk but the effect size relative to that of traditional risk factors is unknown. We conducted a systematic review and meta-analysis to compare the risk associated with sleep disturbances to traditional risk factors. Studies were identified from Medline and Scopus. Cohort studies measuring the association between sleep disturbances and incident diabetes were eligible. For traditional risk factors (i.e., overweight, family history, and physical inactivity), systematic reviews with or without meta-analysis were included. Thirty-six studies (1,061,555 participants) were included. Pooled relative risks (RRs) of sleep variables were estimated using a random-effect model. Pooled RRs of sleeping ≤5 h, 6 h, and ≥9 h/d were respectively 1.48 (95%CI:1.25,1.76), 1.18 (1.10,1.26) and 1.36 (1.12,1.65). Poor sleep quality, OSA and shift work were associated with diabetes with a pooled RR of 1.40 (1.21,1.63), 2.02 (1.57, 2.61) and 1.40 (1.18,1.66), respectively. The pooled RRs of being overweight, having a family history of diabetes, and being physically inactive were 2.99 (2.42,3.72), 2.33 (1.79,2.79), and 1.20 (1.11,1.32), respectively. In conclusion, the risk of developing diabetes associated with sleep disturbances is comparable to that of traditional risk factors. Sleep disturbances should be considered in clinical guidelines for type 2 diabetes screening.

Introduction

Sleep is affected by demographic variables, behaviors (including those dictated by social pressures) and pathological conditions. According to the National Heart, Lung and Blood Institute, "sleep deficiency" occurs when an individual has insufficient sleep, poor sleep, a diagnosed sleep disorder or abnormal timing of sleep [1]. Multiple reviews [2–4] have elected to use the term "sleep disturbances" to designate insufficient or excessive sleep duration, poor self-reported sleep quality, or a diagnosed sleep disorder such as obstructive sleep apnea (OSA). There is increasing evidence linking these very common types of sleep disturbances to abnormal glucose metabolism and elevated diabetes risk.

Findings from laboratory studies manipulating sleep duration and/or quality in healthy adults indicate that a few days of sleep restriction and/or fragmentation are sufficient to cause a marked reduction of insulin sensitivity, without adequate compensation by increased insulin release, resulting in decreased glucose tolerance [5–7]. These findings are consistent with the results of prospective cohort studies that revealed that short sleep (generally ≤6 h/d) and poor sleep quality are both associated with an increased risk of incident diabetes after adjusting for confounders [8–12]. In addition, there is evidence that individuals who report being long sleepers (i.e., ≥9 h/night) are also at increased risk of developing diabetes [13]. It is important to note that the amount of sleep that

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Abbreviations

AHI	apnea hypopnea index
BMI	body mass index
CPAP	continuous positive airway pressure
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5th edition
FPG	fasting plasma glucose
GAD Ab	glutamate decarboxylase antibody
HbA1c	hemoglobin A1c
ODI	oxygen desaturation index
OGTT	oral glucose tolerance test
OSA	obstructive sleep apnea
PSG	polysomnography
RDI	respiratory disturbance index
RR	relative risk

optimizes physical and mental health is an individual characteristic that tends to decrease with age. However, it is generally considered that 7–8 h of sleep nightly is adequate for most adults [14].

OSA is a complex sleep disorder characterized by repetitive episodes of upper airway closures or partial collapse during sleep, resulting in intermittent hypoxia, fragmented sleep, and generally reduced total sleep time. Experimental intermittent hypoxia during the daytime in fully awake healthy volunteers results in a reduction in insulin sensitivity without simultaneous increase in insulin secretion [15,16]. Longitudinal studies indicate that the presence of OSA is associated with an increased risk of developing diabetes, even after adjusting for adiposity [17,18].

Shift workers generally have eating and sleeping schedules that are not synchronized with their own internal circadian rhythms, a condition called “circadian misalignment”. In well-controlled laboratory studies in healthy adults, experimentally induced circadian misalignment between eight days to five weeks resulted in elevated glucose levels, insulin resistance and increased systemic inflammation [19–21]. These metabolic derangements returned to baseline levels after a period of sleep recovery [20]. In agreement with these findings, several cohort studies revealed that shift work was associated with increased risk for incident diabetes [22,23], although the findings were not entirely consistent [24].

Despite the increasing body of evidence linking sleep disturbances with an adverse effect on glucose tolerance, they are not yet recognized by the medical community as novel risk factors for type 2 diabetes. Clinical practice recommendations issued yearly by the American Diabetes Association recommend screening for diabetes in all adults who are overweight (body mass index [BMI] $\geq$ 25 kg/m^2) with additional risk factors (e.g., hypertension, dyslipidemia, physical inactivity or a family history of diabetes) [25] without considering sleep disturbances as additional risk factors. The International Diabetes Federation recognizes a similar set of risk factors, but also includes unhealthy diet, ethnicity and poor nutrition during pregnancy [26]. The centers for disease control and prevention (CDC) also list advanced age (65 y or older) as a risk factor for prediabetes, in addition to other factors [27]. None of the 94 diabetes risk scores developed by multiple international groups of investigators have included sleep in their models of diabetes prediction [28]. With diabetes estimated to affect 387 million people around the world in 2014, 29 million of whom residing in the United States (9.3% of the US population), it has become a major chronic disease with significant morbidity (micro and macrovascular complications) and mortality, along with increased health care costs [29,30]. Diabetes was the 7th leading cause of death in the US in 2013 and cost 245 billion dollars in 2012 [29]. It is therefore crucial that we understand diabetes risk factors, especially the modifiable ones, in order to properly screen and attempt to prevent or reduce the severity and complications of this important disease.

We hypothesized that the impact of sleep disturbances on diabetes risk may be comparable to that of well-recognized traditional risk factors. We therefore conducted a systematic review and meta-analysis aiming to compare the diabetes risk imparted by different types of sleep disturbances to those considered as well-accepted traditional risk factors. For traditional risk factors, we have chosen family history of diabetes, overweight and physical inactivity to represent a set of universally accepted non-modifiable and modifiable risk factors. Our selection of overweight and physical inactivity was guided by the fact that intensive lifestyle modifications focusing on weight loss and exercise have resulted in clear reductions in diabetes risk [31].

Methods

Data sources and searches

Investigators identified relevant studies from searches of Medline and Scopus databases since their inception through November 2013. Reference lists of included studies were explored for identifying additional relevant studies. Search terms and search strategies are described in Appendix 1 and 2, respectively.

Study selection

Two reviewers (T.A., S.R.) independently selected studies. Disagreements between the two reviewers were resolved by discussion and consultation with a senior advisor (A.T.).

For sleep variables, cohort studies published in English were eligible if they met all of the following criteria: participants were 18 y or older; studied variables were any of the following: sleep duration, sleep quality (presence of an insomnia symptom as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) criteria [32] versus absence), OSA (presence or absence), shift work versus non-shift work; incidence of diabetes was the outcome of interest; and reported data were sufficient for extraction.

For traditional risk factors for diabetes, we focused on family history (yes versus no), overweight (BMI 25.0–29.9 kg/m^2 versus normal weight), and physical inactivity (inactive versus active) in adult subjects. Reviews with or without meta-analysis published in English were selected if they provided pooled effects of at least one of these risk factors.

Data extraction

Two reviewers independently extracted the data using a standardized data record form. Discrepancies were resolved by discussion and consensus with a third party (A.T.). The corresponding authors were contacted if there were missing data.

Sleep variables

These included sleep duration, sleep quality, OSA and shift work. Sleep duration was obtained by self-report and was categorized into short ($\leq$5 or = 6 h/d), normal (7–8 h/d), and long ($\geq$9 h/d). The studies by Kita [33] and Mallon [34] had classified sleep durations of 7 h and 6–8 h/d as normal, respectively. Thus, these sleep

durations were considered as "normal" when combined with the other studies.

For sleep quality, we focused on symptoms of insomnia according to the DSM-V criteria [32] including difficulty initiating sleep, difficulty maintaining sleep or early-morning awakening with inability to return to sleep, or report/diagnosis of insomnia. For studies reporting both difficulty initiating sleep and difficulty maintaining sleep, only difficulty initiating sleep was used in pooling effects for overall sleep quality.

The presence of OSA was classified according to the original studies. This included an apnea hypopnea index (AHI) $\geq$ 5 (the current definition of OSA adopted by the American Academy of Sleep Medicine), an AHI $\geq$ 8 [18,35,36], a respiratory disturbance index (RDI) $\geq$ 5 [37], a 3% oxygen desaturation index (ODI) $\geq$ 5 events/h [17], a 4% ODI $\geq$ 30 events/night [38], or a self-reported diagnosis of OSA [10].

Shift work was classified as in the original studies as rotating shift work, which included alternating shift work, and non-specified shift work when there was no specification of the work schedule.

Traditional risk factors

These included being overweight, having a family history of diabetes, and being physically inactive. We included reviews with or without meta-analysis and extracted their characteristics (period covered by the review, study design, number of included studies, total sample size), pooled risk ratios (RR) and their 95% confidence intervals (CI).

Outcome of interest

The outcome of interest was incident diabetes, diagnosed according to the original studies by self-report, and/or medical chart review, and/or blood tests [fasting plasma glucose (FPG), hemoglobin A1c (HbA1c) or oral glucose tolerance test (OGTT)].

Quality assessment

Assessment of risk of bias was performed using the modified Newcastle–Ottawa scale [39]. Five domains were assessed, i.e., representativeness of cohorts, ascertainment of exposure and outcome, adjustment for confounders, and duration of follow-up. The risk of bias in each domain was classified as low risk, high risk, or unclear (Appendix 3).

Data synthesis and analysis

For sleep duration, a summary of cross-tabulated data for short, long, and normal sleep duration versus diabetes groups was expanded to individual-patient data, using the 'mvmeta_make' command in STATA program. We pooled effects of short and long versus normal sleep as follows: First, effect size (i.e., log (relative risk, RR) along with its standard error of each individual study was estimated using Poisson regression. Second, a multivariate random effect meta-analysis was applied for pooling RRs across studies using mvmeta command, in which within subject–study correlation was accounted for using Riley's method [40,41]. A degree of heterogeneity (I^2) was estimated for each pooling. Sensitivity analysis was performed excluding two studies [33,34] with differently defined normal sleep durations.

For sleep quality, OSA and shift work, we used a random-effect (i.e., DerSimonian & Laird) model for pooling the crude RRs if heterogeneity between studies existed, otherwise the inverse variance method was used. Q test and I^2 statistic were applied to assess heterogeneity between studies. If heterogeneity existed (Q test $<$ 0.10 or $I^2 >$ 25%), the sources were explored by fitting covariates (i.e., sex, age, BMI, current smoking and family history of diabetes) one by one in a meta-regression. For sleep quality, a subgroup analysis was performed on studies reporting difficulty initiating and maintaining sleep. For OSA, a subgroup analysis was performed on studies using AHI $\geq$ 5 from a polysomnography as a cutoff. Potential publication bias was examined using the Egger test, a funnel and a contour-enhanced funnel if required. In addition, adjusted RRs, which were mostly adjusted for age, gender, and BMI, were pooled using the same methods. The results were compared to pooled crude RRs.

For traditional risk factors for which more than one meta-analysis was available, their pooled RRs were combined using the method described previously. All statistical analyses were performed using STATA version 12. A P-value $<$ 0.05 was considered as statistical significance for all tests, except for the heterogeneity test in which a P-value $<$ 0.10 was used.

Results

Sleep variables

We identified 1318 studies from Medline and 783 from Scopus. Thirty-six studies (37 cohorts) with a total of 1,061,555 participants met our inclusion criteria (Fig. 1). Summary characteristics are listed in Table 1. Thirty-four of the 37 cohorts were prospective and three [22,42,43] were retrospective. Sixteen studies specified type 2 diabetes as an outcome [8,9,12,17,18,24,35,42,44–51], 19 studies did not specify the diabetes sub-type [10,11,22,23,33,34,36–38,43,52–60], and one specified either prediabetes or type 2 diabetes [61]. Twenty-eight of the 36 studies utilized blood tests and/or chart review to verify diabetes diagnosis, and eight used only self-reported diagnosis (including two studies where all participants were nurses). Sleep variables included sleep duration (n = 14), sleep quality (n = 11), OSA (n = 8) and shift work (n = 10). Comorbidities are listed in Appendix Table 1. These ranged from 3% to 65% for hypertension, 8%–42% for dyslipidemia, 6%–64% for current smoking and 21%–74% for alcohol consumption. All except three studies [33,59,61] provided adjusted RR for relevant covariates for all sleep variables of interest (Appendix Tables 2–5). These included age, sex and BMI with the exception of four studies that adjusted for only one or two of these covariates [22,24,42,55]. In addition, multiple covariates were considered in most studies including race/ethnicity (n = 6), family history of diabetes (n = 10), smoking (n = 24), physical activity (n = 19), hypertension (n = 16), dyslipidemia (n = 9), waist circumference (n = 6), dietary pattern such as calorie, alcohol or coffee consumption (n = 21), socioeconomic status (n = 21), psychological factors (n = 7) and other health status (n = 13) (Appendix Tables 2–5).

Sleep duration

The risk imparted by short or long sleep duration, all based on self-report, on the incidence of diabetes was reported in 14 studies (583,263 participants) [8–11,33,34,44–47,52,53,59,61]. Number of participants and RR of diabetes for short and long sleep are given in Appendix Table 2. Pooled RRs were 1.48 (95% CI: 1.25, 1.76), 1.18 (95% CI: 1.10, 1.26), and 1.36 (95% CI: 1.12, 1.65) for sleep duration $\leq$5 h/d, 6 h/d, and $\geq$9 h/d, respectively (Fig. 2A). Pooling adjusted RRs were not much different, i.e., 1.45 (95% CI: 1.27, 1.65), 1.05 (95% CI: 1.01, 1.09), and 1.41 (95% CI: 1.18, 1.68) for sleep duration $\leq$ 5 h, 6 h, and $\geq$9 h, respectively.

Sensitivity analysis performed excluding two studies with differently defined normal sleep durations [33,34] revealed similar pooled RRs, i.e., 1.49 (95% CI: 1.25, 1.78), 1.19 (95% CI: 1.11, 1.27), and 1.35 (95% CI: 1.10, 1.67) for sleep duration $\leq$ 5 h, 6 h, and $\geq$9 h, respectively. There was moderate to high heterogeneity across

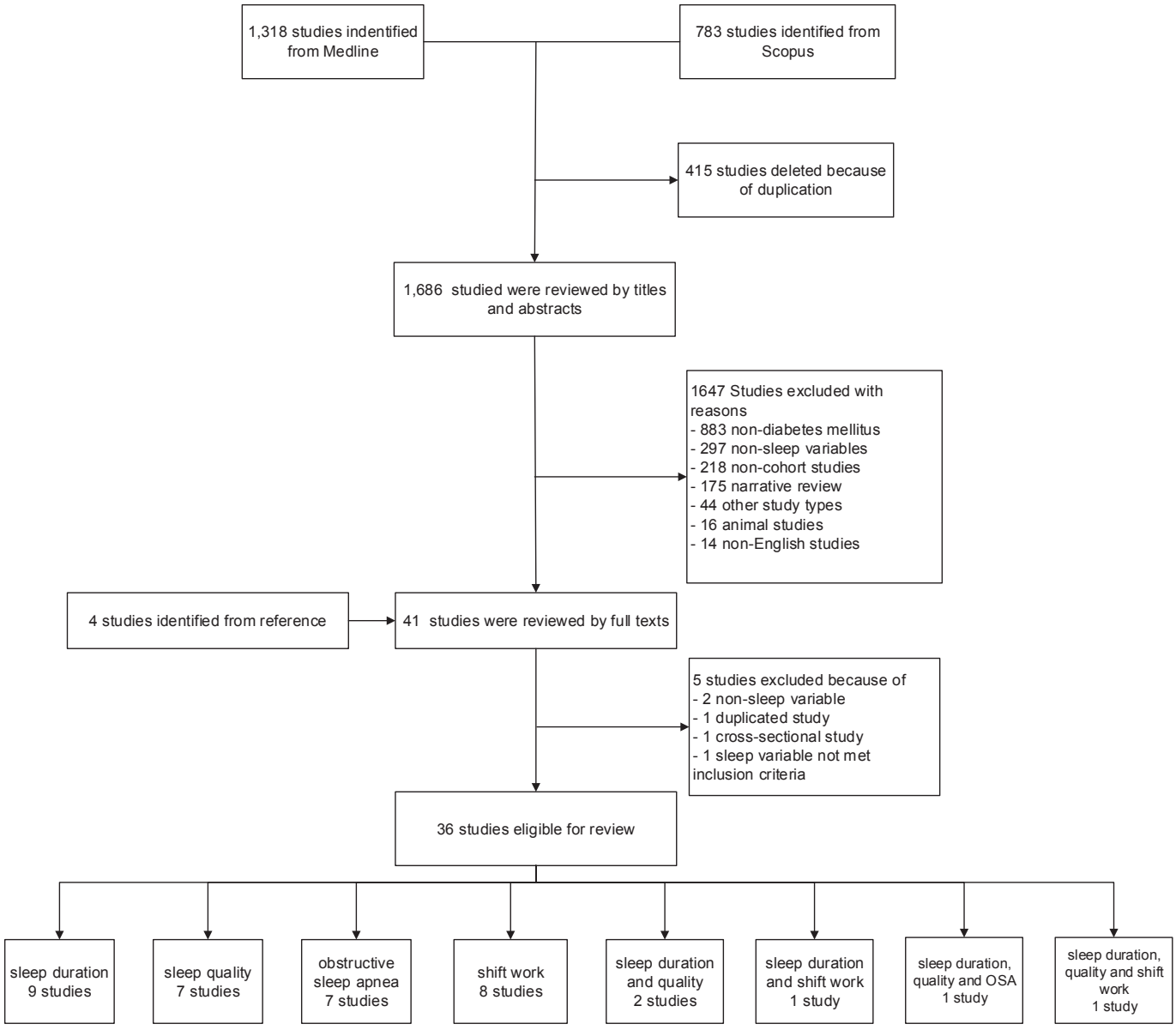

Fig. 1. Flow chart of study selection.

studies (i.e., I^2 of 81%, 55%, 86% for sleep ≤5, 6, and ≥9 h/d, respectively).

Sleep quality

Eleven studies (289,588 participants) were included (Table 1, Appendix Table 3) [8,10,12,33,34,42,48–50,54,55]. Methods utilized in capturing insomnia symptoms are listed in Table 1. The pooled RR for overall poor sleep quality was 1.40 (95% CI: 1.21, 1.63) (Fig. 2B). The adjusted RR was comparable, 1.38 (95% CI: 1.18, 1.62). The degree of heterogeneity was high ($I^2 = 83.6\%$), but explorations of the roles of sex, age, BMI, current smoking or family history of diabetes did not identify the source of heterogeneity.

Subgroup analysis for difficulty initiating sleep and difficulty maintaining sleep was performed by pooling six studies (40,649 participants) [8,33,34,49,50,55]. For difficulty initiating sleep, heterogeneity was low ($I^2 = 30.1\%$) and the pooled RR was 1.55 (95% CI: 1.21, 1.99) (Fig. 3A). For difficulty maintaining sleep, heterogeneity was moderate ($I^2 = 67.4\%$) and the pooled RR was 1.74 (95%CI: 1.30, 2.34) (Fig. 3B). The pooled adjusted-RRs were respectively: 1.55 (95% CI: 1.23, 1.95) and 1.72 (95% CI: 1.45, 2.05) for difficulty initiating and maintaining sleep, similar to the pooled crude-RRs.

Obstructive sleep apnea

Eight studies (63,647 participants) were included [10,17,18,35–38,60]. Methods utilized to identify OSA are listed in Table 1. For this sleep variable identified by objective recording criteria, the studies were moderately heterogeneous ($I^2 = 47.9\%$) with a pooled RR of 2.02 (95% CI:1.57, 2.61) (Fig. 2C and Appendix Table 4). A subgroup analysis performed on two studies using the current accepted diagnostic criteria (polysomnography with a cutoff AHI ≥ 5) [18,36,60] revealed a similar RR of 2.05 (95% CI: 1.17, 2.60).

After adjusting for age, sex, and BMI, the effect was diluted with the overall pooled adjusted RR of 1.49 (95% CI:1.27, 1.75). For the studies defining OSA as AHI ≥ 5, the adjusted RR was 1.42 (95% CI:1.02, 1.99).

Table 1
Baseline characteristics of all studies.

Authors, reference number	N	Setting	Mean age (y)	Mean BMI (kg/m^2)	Male (%)	Sleep assessment	Follow up (y)	Outcome and assessment
Sleep duration								
Ayas et al., 2003 [52]	70,026	U.S.	52.1	24.6	0.0	Self-reported sleep duration	10	• Diabetes mellitus • Questionnaire: symptoms of diabetes plus FPG ≥ 140 mg/dL or random glucose ≥200 mg/dl, two elevated glucose levels on two occasions (fasting or random), or use of hypoglycemic medication.
Beihl 2009 et al. [44]	900	U.S.	40–60	28.4	43.3	Self-reported sleep duration	5	• Type 2 diabetes mellitus • Report of using diabetes medications. • OGTT in those not taking diabetes medication. Diabetes defined as 2-h glucose value ≥ 200 mg/dL
Björkelund 2005 et al. [59]	1462	Sweden	46.8	24.1	0.0	Self-reported sleep duration	32	• Diabetes mellitus • Report of physician diagnosis of diabetes or use of medication or FPG ≥ 140 mg/dL on two separate occasions, or diagnosis documented in death certificate
Gangwisch 2007 et al. [53]	8992	U.S.	56.1	26.3		Self-reported sleep duration	8–10	• Diabetes mellitus • Report of diabetes diagnosis by physicians, chart review of hospital diagnosis or cause of death
Holliday 2013 et al. [9]	241,949	Australia	62.3		47.3	Self-reported sleep duration	2–3	• Type 2 diabetes mellitus • Hospital admissions data and mortality data
Tuomilehto 2009 et al. [45]	522	Finland	55.2	31.1	33.0	Self-reported sleep duration	7	• Type 2 diabetes mellitus • OGTT with FPG ≥140 mg/dL or 2-h glucose value ≥ 200 mg/dl
von Ruesten 2012 et al. [46]	23,620	Germany	49.3		38.6	Self-reported sleep duration	7.8	• Type 2 diabetes mellitus • Report of diabetes diagnosis verified by chart review
Xu 2010 et al. [11]	174,542	U.S.	62.5	26.4	56.8	Self-reported sleep duration	3–10	• Diabetes mellitus • Report of diabetes diagnosis by physicians
Yaggi 2006 et al. [47]	1139	U.S.	40–70			Self-reported sleep duration	15–16	• Type 2 diabetes mellitus • Report of diabetes diagnosis by physicians
Sleep quality								
Eriksson 2008 et al. [48]	5227	Sweden	47.0	25.3	40.7	Reported sometimes or frequently insomnia (for the last 12 mo)	8–10	• Type 2 diabetes mellitus • OGTT, FPG ≥126 mg/dL or 2-h value ≥ 200 mg/dL
Kawakami 2004 et al. [49]	2649	Japan			100.0	Reported difficulty initiating or maintaining sleep (for the past month)	8	• Type 2 diabetes mellitus • Medical checkup using World Health Organization criteria (FPG ≥140 mg/dL or 2 h-value after 75 gm OGTT ≥ 200 mg/dL)
Lai 2013 et al. [42]	136,626	Taiwan	50.6		36.1	Diagnosis of insomnia from diagnosis code	9	• Type 2 diabetes mellitus • Chart review
Meisinger 2005 et al. [50]	8269	Germany	47.1		50.0	Reported difficulty initiating or maintaining sleep	7.5	• Type 2 diabetes mellitus • Self-reported diabetes diagnosis and verified by chart review
Nilsson 2004 et al. [54]	6599	Sweden	44.5	24.5	100.0	Reported difficulty initiating sleep and regular use of hypnotic drugs	14.8	• Diabetes mellitus • Self-reported diabetes diagnosis or use of medication. A subgroup of 1551 subjects received fasting blood test (diabetes diagnosed when fasting whole blood glucose ≥ 6.1 mmol/l)
Olsson 2012 et al. [12]	53,394	Norway	43.5	25.0	46.1	Symptoms of insomnia per DSM IV criteria (for the past month)	11–22	• Type 2 diabetes mellitus • Report of diabetes diagnosis with verification by another interview on history and treatment • GAD Ab, c-peptide level
Rod 2011 et al. [55]	16,989	France	45.0		74.0	Questionnaire using Nottingham health profile (3 or more of the following currently present: I take tablet to help me sleep, I lie	19	• Diabetes mellitus • Report of diabetes diagnosis

(*continued on next page*)

Table 1 (*continued*)

Authors, reference number	N	Setting	Mean age (y)	Mean BMI (kg/m^2)	Male (%)	Sleep assessment	Follow up (y)	Outcome and assessment
						awake most of the night, I sleep badly at night, it takes me a long time to fall asleep or I wake up in the early hours of the morning)		
OSA								
Botros 2009 et al. [35]	1233	U.S.	61.5	33.2	93.4	AHI ≥ 8 events/h by a polysomnography	2.7	• Type 2 diabetes mellitus • FPG >126 mg/dL, ascertained by chart review
Celen 2010 et al. [38]	318	Sweden	48.2	26.6	81.6	4% ODI ≥30 events/ night using an oximetry, a nasal and oral airflow, and a respiration and body movement monitoring	16	• Diabetes mellitus • Report of diabetes diagnosis verified by chart review
Kendzerska 2014 et al. [60]	8678	Canada	48.0	28.4	62.0	AHI ≥5 events/h by polysomnography	5.6	• Diabetes mellitus • Diabetes diagnosis according to chart review (hospitalization records and physician service claims)
Lindberg 2012 et al. [36]	141	Sweden	57.5	26.9	100.0	AHI ≥5 events/h by polysomnography	11.3	• Diabetes mellitus • Self-reported diabetes diagnosis, verified by FPG ≥ 126 mg/dL
Marshall 2009 et al. [37]	399	Australia	53.1	26.6	41.3	RDI ≥5 events/h from a 4-channel home monitoring device (heart rate, oxygen saturation, snoring and body position)	4	• Diabetes mellitus • Self-reported diabetes diagnosis or use of medication or FPG ≥ 126 mg/dL
Muraki 2010 et al. [17]	4398	Japan	57.6	23.5	34.7	3% ODI ≥5 events/h a from pulse oximetry	3	• Type 2 diabetes mellitus • FPG ≥ 126 mg/dL or random glucose ≥ 200 mg/dL or use of diabetes medications/insulin
Reichmuth 2005 et al. [18]	1387	U.S.	49.0	28.9	56.0	AHI ≥5 events/h by a polysomnography	4	• Type 2 diabetes mellitus • Self-reported diabetes diagnosis or FPG ≥ 126 mg/dL
Shift work								
Eriksson 2013 et al. [24]	5432	Sweden	47.1		41.0	Shift work from questionnaire	8–10	• Type 2 diabetes mellitus • OGTT, FPG ≥ 126 mg/dL or 2-h value ≥ 200 mg/dL
Guo 2013 et al. [43]	26,463	China	63.6	23.9	44.7	Shift work from questionnaire	NA	• Diabetes mellitus • FPG ≥126 mg/dL or report of diabetes diagnosis or use of medication
Monk 2013 et al. [22]	1111	U.S.	75.4		57.1	Work overlap 12:00 –06:00 h, from questionnaire	NA	• Diabetes mellitus • Report of diabetes diagnosis
Morikawa 2005 et al. [23]	2860	Japan	34.3	22.6	100.0	Dayshift, rotating two or three shift, from questionnaire	8	• Diabetes mellitus • HbA1c ≥ 6.1% or report of diabetes diagnosis by physician
Oberlinner 2009 et al. [56]	31,346	Germany	38.1		100.0	Rotating shift, from work registry	11	• Diabetes mellitus Diabetes diagnosis according to chart review
Pan 2011 et al. [51]	69,269	U.S., NHS I	53.9	25.3	0.0	Rotating night shift, from questionnaire	18–20	• Type 2 diabetes mellitus • Report of diabetes diagnosis (participants were nurses)
Pan 2011 et al. [51]	107,915	U.S., NHS II	34.3	24.0	0.0	Rotating night shift, from questionnaire	18–20	• Type 2 diabetes mellitus • Report of diabetes diagnosis (participants were nurses)
Suwazono 2006 et al. [57]	5629	Japan	36.1	23.3	100.0	Alternating shift, from work registry	10	• Diabetes mellitus • Self-reported diabetes diagnosis by physicians, or HbA1c ≥ 6.0% (42 mmol/mol)
Teratani 2012 et al. [58]	8423	Japan	42.3	23.7	100.0	Daytime work, shift work from questionnaire	8	• Diabetes mellitus • Self-reported diabetes diagnosis by physicians, or HbA1c ≥ 6.1% (43 mmol/mol) or use of medication
Sleep duration and quality								
Hayashino 2007 et al. [8]	6509	Japan	38.2	22.7	78.4	Self-reported sleep duration, reported difficulty initiating or maintaining sleep	4.2	• Type 2 diabetes mellitus • Report of diabetes diagnosis or using medication or FPG ≥ 140 mg/dL or random glucose ≥ 200 mg/dL

Table 1 (*continued*)

Authors, reference number	N	Setting	Mean age (y)	Mean BMI (kg/m^2)	Male (%)	Sleep assessment	Follow up (y)	Outcome and assessment
Mallon 2005 et al. [34]	2663	Sweden	54.6	25.4	47.0	Self-reported sleep duration, difficulty initiating or maintaining sleep	12	• Diabetes mellitus • Questionnaire ascertained by using two questions
Sleep duration, quality and OSA								
Boyko 2013 et al. [10]	47,093	U.S.	36.7	26.3	25.3	Self-reported sleep duration, reported trouble falling asleep or staying asleep, reported physician diagnosis of OSA	6	• Diabetes mellitus • Report of diabetes diagnosis
Sleep duration, quality and shift work								
Kita 2012 et al. [33]	3570	Japan	46.4	23.4	78.6	Self-reported sleep duration, poor sleep quality (2 or more of the following: problems with sleep induction, awakening during the night, final awakening earlier than desired, insufficient sleep or overall poor sleep quality), shift work from questionnaire	3–5	• Diabetes mellitus • Having been prescribed diabetes medication or FPG $\geq$ 126 mg/dL
Sleep duration and shift work								
Chaput 2009 et al. [61]	276	Canada	38.6	25.6	42.4	Questionnaire on sleep duration and shift work	6	• Type 2 diabetes and impaired glucose tolerance (IGT) • Diabetes defined as FPG $\geq$ 126 mg/dL or 2-h value after OGTT $\geq$200 mg/dL, or use of insulin or oral hypoglycemic agents • Impaired glucose tolerance defined as 2-h value $\geq$ 140 mg/dL in those not meeting diabetes criteria

Shift work

Ten studies (262,294 participants) were included [22–24,33,43,51,56–58,61]. The publication by Pan et al. [51] included the two waves of the Nurses' Health Study (NHS I and NHS II), and these were considered separately (Appendix Table 5). Shift workers were 40% (pooled RR 1.40, 95% CI: 1.18, 1.66) more likely to develop diabetes than regular day workers (Fig. 2D). After adjusting for BMI and other covariates, the pooled RR was 1.15 (95% CI: 1.08, 1.22). However, the degree of heterogeneity between studies was high (I^2 = 95%) and did not seem to originate from differences in sex, age, BMI, current smoking or family history of diabetes.

A subgroup analysis indicated that both types of shift work significantly increased the risk of developing diabetes with a pooled RR of 1.60 (95% CI: 1.20, 2.14) for rotating shift work (I^2 = 97.3%) and 1.22 (95% CI: 1.03, 1.45) for non-specified shift work (I^2 = 69.4%). The corresponding adjusted pooled RRs were 1.15 (95% CI: 1.06, 1.25) and 1.25 (95% CI: 1.00, 1.55) respectively. This difference was not statistically significant (p = 0.399).

Publication bias

Publication bias for all sleep factors was explored using the Egger test and funnel plots (Appendix Figs. 1–3). There was no evidence of asymmetry of the funnel for sleep duration $\leq$5 h/d (p = 0.811), 6 h/d (p = 0.488), poor sleep quality (p = 0.661), OSA (p = 0.083) and shift work (p = 0.472). However, there was evidence of asymmetry for sleep duration $\geq$ 9 h/d (p = 0.016). A contour-enhanced funnel plot indicated that asymmetry was most likely due to heterogeneity (Appendix Fig. 1D). In addition, a funnel plot for shift work showed some asymmetry. A contour-enhanced funnel plot suggested that asymmetry resulted from heterogeneity between studies (Appendix Fig. 3B).

Quality assessment

Descriptions of the quality of the studies are presented in Appendix Table 6 (according to the classifications described in Appendix 3). All had a low risk of bias in the domain of adjustment for confounder. For the domains of representativeness of cohort, ascertainment of outcome, and duration of follow-up, most studies reported a low risk of bias with percentages of 63.8%, 83.3%, and 94.4%, respectively. Only 30.5% of studies had a low risk of ascertainment of exposure as most used subjective measurements of sleep variables.

Traditional risk factors

The characteristics of previous studies and flow charts of the study selections for traditional risk factors are listed in Appendix Table7, Appendix Figs. 4–6. For family history, we included four studies (18 cohorts) with a total of 81,499 participants [62–65]. Of these, diabetes in a first degree relative was specified in 11 cohorts (36,476 participants). The pooled RR was 2.33 (95%CI: 1.79, 2.79).

There was one meta-analysis study for overweight [66], which included 18 cohorts (590,251 participants), with a pooled RR of 2.99 (95%CI:2.42, 3.72). There was also one study for physical inactivity

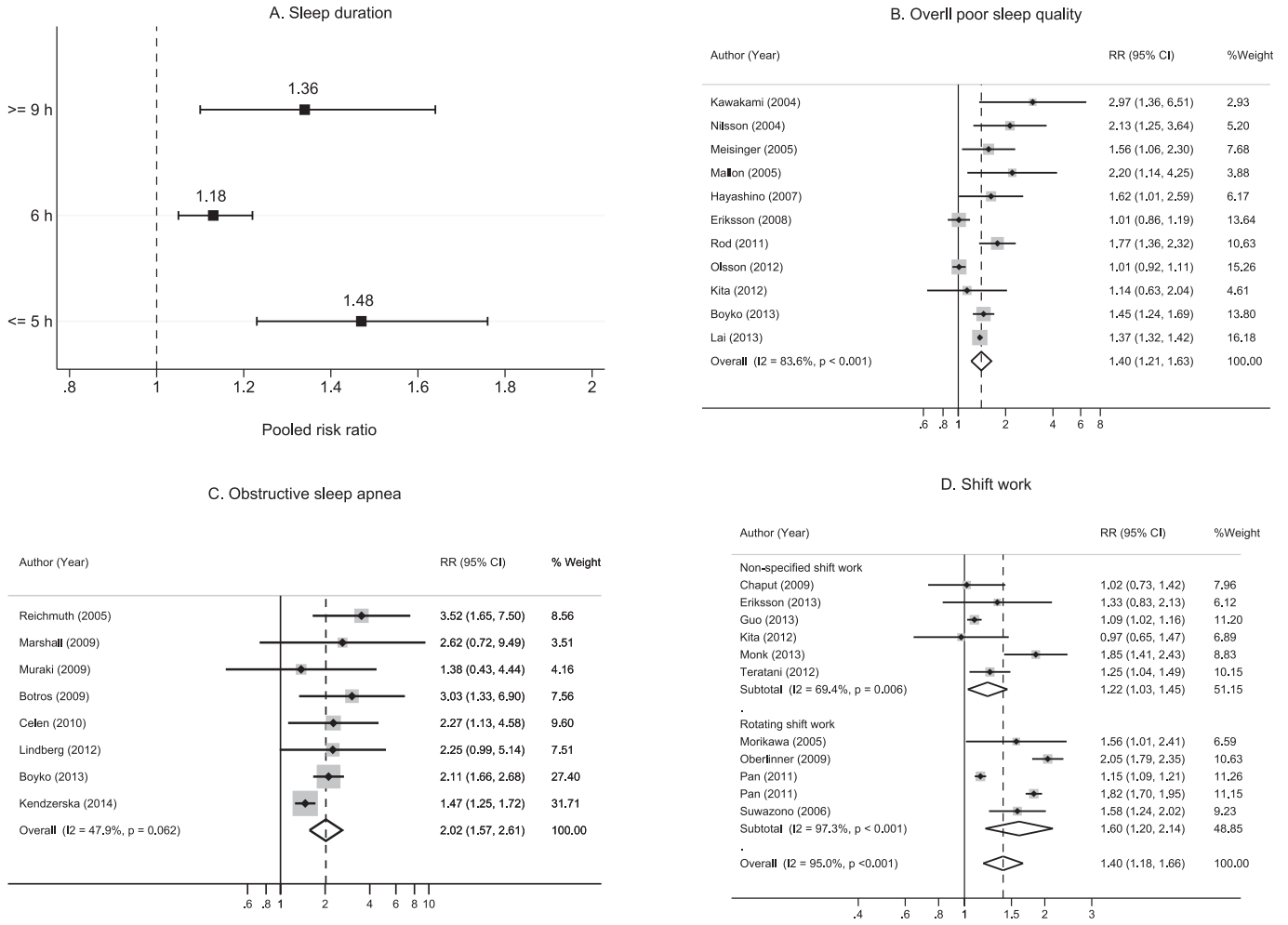

Fig. 2. Pooled relative risks of diabetes mellitus associated with sleep duration, sleep quality, obstructive sleep apnea and shift work. A: Sleep duration, B: Overall poor sleep quality increases diabetes risk by 40%, C: OSA is associated with two fold increase risk of developing diabetes. D: Shift work is associated with 40% increase in diabetes risk.

(10 cohorts, 301,221 participants) [67] with a pooled RR of 1.20 (95% CI:1.11, 1.32).

It is important to note that none of these studies examining these traditional risk factors included sleep factors in their analysis of diabetes risk. Of the 46 cohorts, 45 adjusted for age, 43 adjusted for sex or were single sex studies, and 27 of 28 studies of family history or physical inactivity adjusted for BMI. Other covariates considered included smoking (n = 22), hypertension (n = 21), dyslipidemia (n = 13), dietary pattern such as amount of calories, alcohol or coffee consumption (n = 17) and socioeconomic status (n = 23). None of the studies adjusted for the presence of sleep disturbances, not even OSA which is a very frequent co-morbidity of type 2 diabetes, affecting approximately 2 out of 3 patients [2].

Comparisons of sleep and traditional risk factors on diabetes risk

Fig. 4A, B and Appendix Table 8 compare the unadjusted and adjusted RRs of incident diabetes imparted by sleep disturbances to the RRs of traditional risk factors. In the unadjusted model, three factors represented high risk of diabetes (pooled RR > 2): overweight, a family history of diabetes, and OSA. However, the effect of OSA decreased in the adjusted model but still conferred a moderate diabetes risk (pooled RR approximately 1.5–2.0), similar to the effects of difficulty initiating and maintaining sleep, and higher than being physically inactive. The remainder of the factors, sleeping ≤5 h, 6 h and ≥9 h, overall poor sleep quality and shift work had significant but smaller effects (pooled RR < 1.5), ranging from 1.05 to 1.45, which were similar to being physically inactive.

Discussion

Our comprehensive meta-analysis and systematic review compared for the first time the risk of incident diabetes imparted by common sleep disturbances versus that of well-established risk factors listed in all guidelines for the screening of type 2 diabetes. For the sleep variables, data from more than 1,000,000 participants were included. OSA, difficulty initiating and maintaining sleep had the largest estimated impact on diabetes risk, with effect sizes only slightly smaller than having a family history of diabetes or being overweight but clearly larger than being physically inactive. The impact of short or long sleep duration, poor sleep quality and shift work on diabetes risk is comparable to that of being physically inactive. Importantly, almost all of the studies included in our meta-analysis of sleep disturbances had estimated the risk of incident diabetes after adjustment for age, sex, BMI as well as multiple other potential confounders. The studies of traditional risk factors also adjusted for similar covariates, but did not consider confounding effects of sleep disturbances. Thus, it is conceivable that the intrinsic effects of traditional risk factors

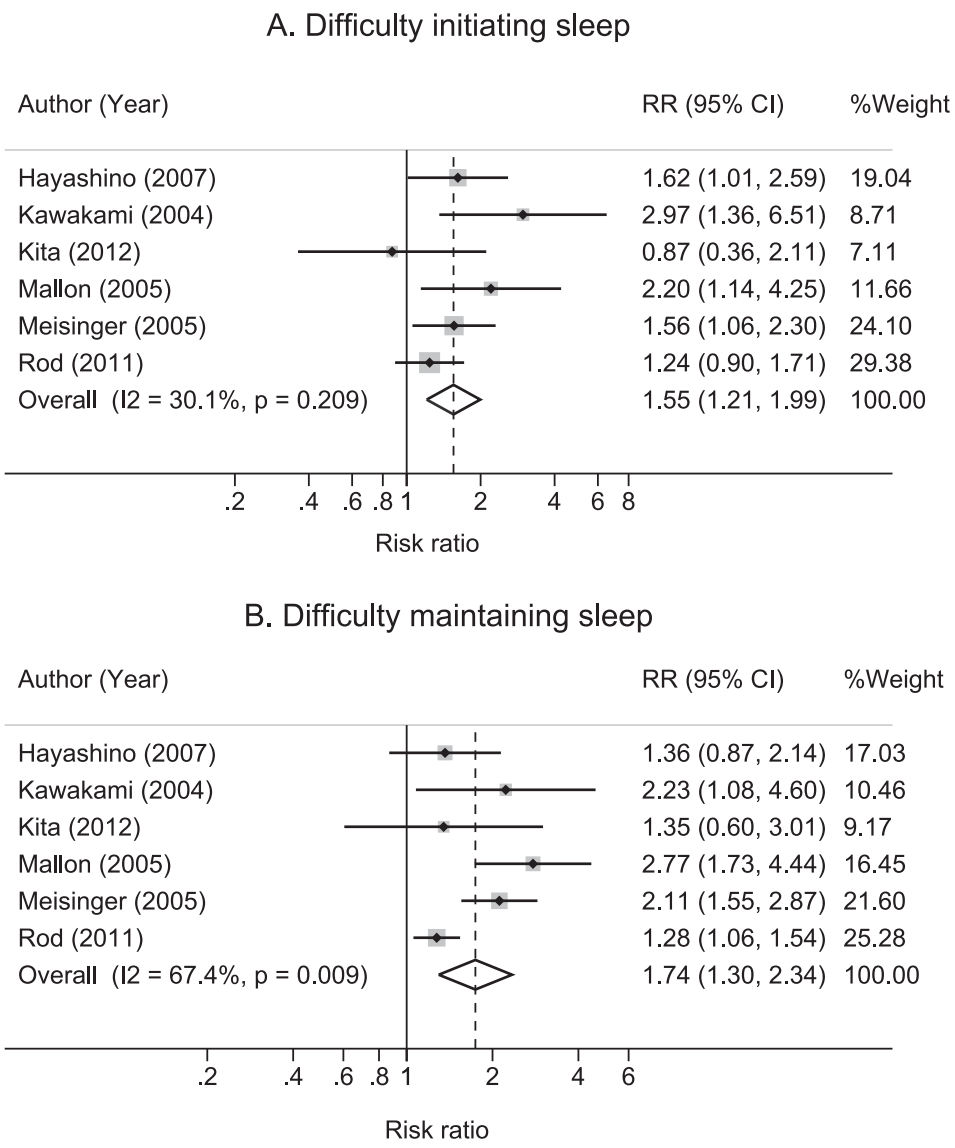

Fig. 3. Pooled crude relative risks of diabetes mellitus associated with difficulty initiating and maintaining sleep. A: Difficulty initiating sleep increases the diabetes risk by 55%, B: Difficulty maintaining sleep increases the diabetes risk by 74%.

could be lower than currently estimated if analyses had controlled for confounding effects of sleep disturbances. Our results thus provide strong evidence for an important role of sleep disturbances in the risk of developing diabetes. While the link between OSA and diabetes is occasionally mentioned in publications from organizations focusing on diabetes [68], the clinical recommendations for diabetes screening available to health professionals and the public rarely, if ever, include the word "sleep". There is thus a clear need to consider a revision of these clinical recommendations for diabetes screening and prevention, especially with the dramatic increase in the prevalence of OSA that has developed over the past two decades, reaching 33–77% in men and 11–46% in women [69]. Moreover, as both OSA and diabetes are risk factors for increased mortality and cardiovascular complications, such as stroke and coronary artery disease [70,71], the combination of OSA and diabetes involves greater health risks than either alone. More recently, OSA also emerged as a possible risk factor for microvascular complications including neuropathy and nephropathy in patients with diabetes [72–74]. Lastly, since the present meta-analysis shows that the diabetes risk associated with sleep disturbances tends to be larger than that associated with being physically inactive, it is possible that interventions to reduce sleep disturbances may have beneficial effects on diabetes prevention with an effect size similar to that seen in exercise interventions. For example, in a study of patients with impaired glucose tolerance, exercise intervention alone (without diet) resulted in a 39% reduction in the risk of developing diabetes over six years follow up [75]. Given the current diabetes epidemic, the role of sleep optimization in diabetes prevention needs to be urgently addressed.

Our results, using a much larger sample, confirmed the findings of the previous two meta-analyses that had examined the links between short or long sleep and incident diabetes, with similar effect size [9,13]. Experimental sleep restriction in several laboratory studies in healthy humans revealed a 16–24% reduction in insulin sensitivity without appropriate compensation by increased insulin release [6,76,77]. This adverse impact of insufficient sleep on both insulin secretion and beta-cell responsiveness is thought to be mediated by a combination of heightened sympathetic nervous system activity, increased evening levels of cortisol,

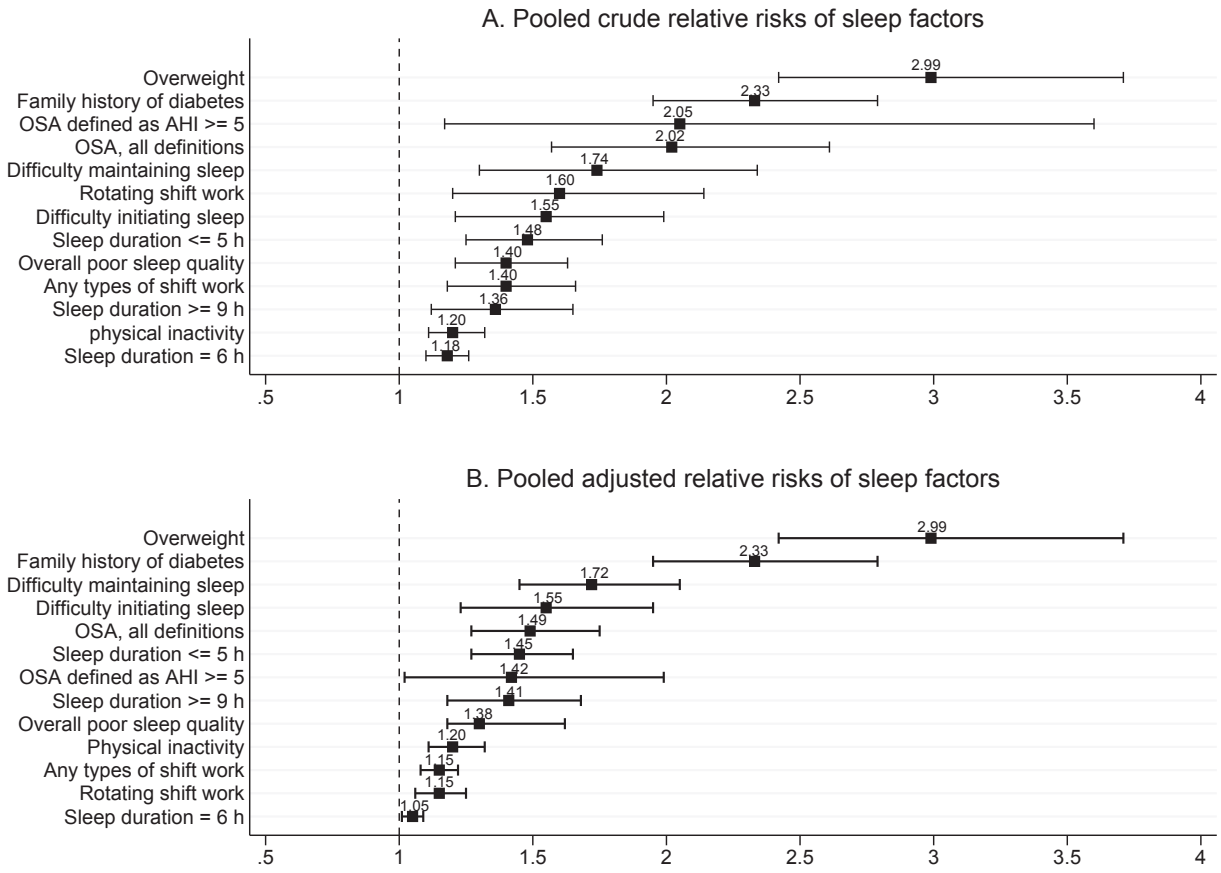

Fig. 4. Comparison of risk of diabetes associated with sleep disturbances as compared to traditional risk factors. A: pooled unadjusted RRs of sleep disturbances relative to traditional risk factors, B: pooled adjusted RRs of sleep disturbances relative to traditional risk factors. Note that none of the studies of traditional risk factors adjusted for sleep disturbances while a majority of sleep disturbances studies adjusted for traditional risk factors (see the result section for more details).

alterations in growth hormone secretion and elevations in systemic inflammatory responses [2]. While experimental sleep restriction has also been shown to promote hunger and appetite, and multiple prospective studies have found a significant association between short sleep and greater weight gain [2,78,79], it is important to note that the estimations of diabetes risk in the present study remained significant after adjusting for BMI as well as other confounders. Despite a strong evidence of a causal relationship between sleep insufficiency and glucose metabolism, the gap of knowledge remains since there has been no interventional study exploring the role of sleep extension in diabetes prevention or treatment. However, one recent study explored the benefits of short-term home sleep extension on glucose metabolism for six weeks in 16 non-obese healthy adults who were habitual short sleepers [80]. On average, nightly sleep duration increased by 44 min during the intervention period. There was a significant positive correlation between changes in total sleep time with indices of insulin sensitivity at the end of the experiment. Future research is needed in larger studies to confirm these preliminary findings.

The mechanisms linking long sleep and diabetes remains poorly understood. Using self-reported sleep duration is the main limitation pertinent to this result. Indeed, it has been proposed that long sleepers are actually poor sleepers who extend their time in bed to try to compensate for poor sleep quality [81]. In addition, depression, undiagnosed OSA or generally poor health status could be associated with long sleep and put individuals at a higher risk for diabetes [82]. In fact, lifestyle modifications with diet and exercise in individuals with impaired glucose tolerances has been shown to eliminate the relationship between long sleep and incident diabetes, supporting the hypothesis that lifestyle factors play an important role in the diabetes risk associated with long sleep [45].

Poor sleep quality as defined by the presence of one or more insomnia symptoms included in the DSM-V diagnostic criteria was associated with a 40% increase in the risk of developing diabetes. When focusing only on difficulty initiating and maintaining sleep, the RRs were higher, at 55% and 74%, respectively, and remained virtually unchanged in the fully adjusted model. These estimates are comparable to those of a previous meta-analysis, but the current study has approximately double the number of participants [13]. Poor self-reported sleep quality may also be a marker of other co-morbid conditions, such as depression, undiagnosed OSA and insufficient sleep, themselves risk factors for diabetes. Adjusting for these covariates still resulted in a significant association between poor sleep quality and incident diabetes in several studies [10,42].

In the unadjusted model, OSA was the strongest predictor of diabetes among sleep factors. The effect was attenuated, but remained significant after adjustment for covariates including BMI, with a 49% increase in diabetes risk. Besides the adverse effects on glucose metabolism as a result of insufficient sleep and sleep fragmentation commonly associated with OSA, intermittent hypoxia itself also has been shown to increase insulin resistance [15]. The independent effect of OSA on diabetes risk is consistent with the robust associations between OSA and insulin resistance documented in laboratory studies that adjusted for age, sex, race and percent body fat or included only young lean adults [83]. In patients with diabetes, the severity of untreated OSA has been found to be

associated with lower glucose tolerance in several studies, after adjusting for multiple confounders, with an effect size as large as that associated with the impact of anti-diabetes drugs [84,85]. Despite the strong suggestion of causality between OSA and impaired glucose metabolism, the results of intervention studies using continuous positive airway pressure (CPAP) have been mixed, with some improvement in insulin resistance but the effect on diabetes control is questionable [86,87]. Issues on CPAP compliance, sample size or the use of sham CPAP may partly explain these inconsistent results.

It is important to note that lifestyle intervention, especially weight loss, has been shown to be beneficial for diabetes prevention as well as for reducing the severity of OSA, and improve markers of cardiometabolic risk [31,88,89]. In patients with type 2 diabetes and OSA, intensive lifestyle intervention led to a 10.8 kg weight loss at one year, along with a significant improvement in AHI of 9.7 events/h which persisted at 4-y follow up despite an almost 50% weight gain [90,91]. These data highlight the potential of lifestyle modifications involving weight loss to reduce the risk and severity of both diabetes and OSA.

There are multiple reasons why shift work may increase diabetes risk. Irregular sleeping and eating schedules result in circadian misalignment as these behaviors are not synchronized with endogenous circadian rhythms. Experimental studies of circadian misalignment observed decreased insulin sensitivity, reduced glucose tolerance, dysregulation of cortisol rhythms, and increased inflammatory markers [19–21]. Further, insufficient sleep and poor sleep quality, themselves associated with increased diabetes risk, are very common among shift workers. Compared to day workers, shift workers have higher rates of obesity and more unfavorable lifestyle factors, including excessive total energy intake, physical inactivity, alcohol consumption and habitual smoking [56,57,92]. Adjusting for these factors attenuated the relationship between shift work and diabetes in some studies but significant residual effects remained [23,51,56,57]. In contrast to a recently published meta-analysis of shift work and diabetes risk, that included both cross-sectional and cohort studies [93], our meta-analysis focusing on cohort studies found a similar risk of diabetes for non-specified shift work and for rotating shift work, consistent with the observation that less than 3% of permanent night workers have complete adjustment of their endogenous melatonin rhythm, and less than 25% have substantial adjustment [94]. As we are evolving into a 24-h society while the number of diabetes patients as well as cost of care is increasing, attention should be paid to metabolic health of shift workers. While pharmacotherapy has been shown to improve alertness and sleep quality in those with shift work disorder, including melatonin (to improve daytime sleep) and modafinil or armodafinil (wake-promoting agents) [95], it is unknown if these agents will help improve glucose metabolism. A more promising approach may be to develop work schedules that minimize exposure to circadian misalignment and sleep loss, along with keeping healthy lifestyles, which should decrease the metabolic risk of shift work.

When comparing sleep disturbances with traditional diabetes risk factors, a few considerations should be made. A risk factor such as family history is not modifiable while sleep disturbances can potentially be corrected. While there are currently no large prospective study demonstrating that optimizing sleep duration and quality may reduce the risk of diabetes, there is emerging evidence in this direction. The effects of CPAP treatment on glucose metabolism have been mixed. These gaps of knowledge have to be contrasted with the beneficial effects of diet and exercise for individuals at risk of diabetes demonstrated in large randomized clinical trials [31]. In addition, there are interactions between sleep disturbances, obesity and physical inactivity. For example, short sleep is also a risk factor for weight gain and obesity [78], which can in turn increase diabetes risk. Increased physical activity can lead to better sleep quality [96], while sleep restriction can result in decreased physical activity [97].

The strength and novelty of the present study lie in the comprehensive meta-analysis of the risk of diabetes imparted by common sleep disturbances and their quantitative comparison with the risk associated with widely accepted traditional factors. Limitations of this study include the fact that almost all sleep factors, except OSA, were derived from self-report. However, self-reported sleep duration has been widely used in epidemiological studies and has been shown to be moderately correlated with objectively measured sleep duration [98]. In addition, insomnia is a clinical diagnosis based on symptoms without objective sleep measurements. Self-reported physician diagnosis of diabetes was used in some studies without further verifications by blood test or chart review, but this method has been shown to have a high accuracy [99] and has also been used in some well-accepted studies of traditional risk factors. Furthermore, in our analysis, diabetes was not systematically specified as type 2. Since all studies were conducted in adults, it was presumed that incident diabetes was mostly type 2. Although we cannot exclude the possibility that some participants may have had type 1 diabetes, a sensitivity analysis performed according to type of diabetes did not reveal a significant impact of diabetes sub-type (data not shown). The diagnostic criteria for diabetes have also changed overtime according to the standard criteria while the studies were being conducted. We also did not compare all traditional diabetes risk factors, for example dietary pattern and hypertension, to the risk imparted by sleep disturbances in the current analyses but instead focused on a triad that appears consistently in all guidelines for diabetes screening and prevention. Lastly, for some sleep factors, there was moderate to high heterogeneity across studies without identifiable causes, despite explorations of many covariates including sex, age, BMI, current smoking and family history of diabetes. Some subgroup analyses have lowered the heterogeneity. There yet may be additional factors contributing to the heterogeneity that could not be explored given that the analyses were based on summary, not individual, patient data. Of note, a similar heterogeneity of predictors is present in studies of traditional risk factors.

In summary, sleep disturbances are significant risk factors for diabetes with effect sizes similar to those imparted by traditional risk factors. Sleep disturbances should therefore be systematically considered in guidelines for the screening of diabetes.

Practice points

1). Sleep disturbances are linked to increased risk of incident diabetes.
2). After adjustment for confounders, the risk of developing diabetes due to obstructive sleep apnea, difficulty maintaining or initiating sleep is slightly less than the risk of having a family history of diabetes but greater than that of being physically inactive.
3). The risk of developing diabetes associated with insufficient or excessive sleep duration or performing shift work is comparable to that of being physically inactive.
4). Sleep disturbances should be considered as risk factors when screening for diabetes and developing prevention strategies.

Research agenda

The risk of developing diabetes associated with sleep disturbances is well documented. Future research should consider:

1). Developing well-designed randomized controlled trials to evaluate the impact of sleep interventions, such as sleep extension and effective CPAP treatment of OSA, on diabetes risk and severity.
2). Sleep disturbances should be assessed in participants of clinical trials of lifestyle or pharmacologic interventions for the treatment or prevention of diabetes and treated as confounding co-morbidities.
3). Strategies to optimize sleep in shift workers to reduce the impact of circadian misalignment and insufficient sleep on glucose metabolism should be developed and evaluated.

Conflicts of interest

T.A. and A.T. reported no conflict of interest. S.R. receives speaker fee from Sanofi Aventis and grant support from Merck. E.V.C. receives grant support from Merck and Amylin/Astra Zeneca, is a consultant for Shire/Viropharma and Philips/Respironics and is an Associate Editor for the journal SLEEP.

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T.A. researched and analyzed the data, wrote manuscript, contributed to discussion, and reviewed/edited manuscript. S.R. contributed to conceptual design, researched the data, wrote manuscript, contributed to discussion, and reviewed/edited manuscript. E.V.C contributed to conceptual design, discussion, and reviewed/edited manuscript. A.T. contributed to discussion, and reviewed/edited manuscript. S.R. had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2015.10.002.

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