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CLINICAL REVIEW

The impact of sleep amount and sleep quality on glycemic control in type 2 diabetes: A systematic review and meta-analysis

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SUMMARY

Recent epidemiological studies have suggested that there is an association between glycemic control and sleep disturbances in patients with type 2 diabetes, but the extent is unclear. A systematic literature search was performed in nine electronic databases from inception until August 2015 without any language restriction. The search identified 20 studies (eight studies reporting duration of sleep and 15 studies evaluating sleep quality), and 15 were included in the meta-analysis. Short and long sleep durations were associated with an increased hemoglobin A_{1c} (HbA1c) (weighted mean difference (WMD): 0.23% [0.10–0.36], short sleep; WMD: 0.13% [0.02–0.25], long sleep) compared to normal sleep, suggesting a U-shaped dose–response relationship. Similarly, poor sleep quality was associated with an increased HbA1c (WMD: 0.35% [0.12–0.58]). Results of this study suggest that amount of sleep as well as quality of sleep is important in the metabolic function of type 2 diabetes patients. Further studies are needed to identify for the potential causal role between sleep and altered glucose metabolism.

Introduction

The prevalence of sleep disturbances and deprivation has been increasing dramatically over the past decade, together with the growing epidemic of type 2 diabetes mellitus (T2DM) and obesity worldwide. Recent epidemiological studies suggest that nearly two-fifth of American adults sleep less than 7 h of sleep per day [1], resulting in feelings of fatigue as well as reduced physical activities. Sleep deprivation is thought to affect a variety of body functions including metabolic health [2], endocrine system [3] as well as immune pathway [4]. Specifically, sleep disturbance, insufficient or excessive sleep, and irregular sleep wake patterns have been associated with adverse outcomes such as obesity and impaired glucose metabolism [5].

Recent observational evidence suggests that both sleep duration and sleep quality are linked to metabolic health in adults. For example, a cross-sectional analysis of the Fukuoka diabetes registry, including 4870 T2DM patients showed a clear association between short or long duration of sleep with higher hemoglobin A_{1c} (HbA1c) levels. This association was significant even after adjusting for obesity, total energy intake and depressive symptoms, suggesting that these patients should be considered high risk for poor glycemic control. Similarly, analysis of data from the Nurses' health study, involving 935 female nurses showed that short ($\leq$5 h per night) sleep duration is associated with higher HbA1c levels [6]. While several meta-analyses have confirmed the independent association between sleep duration and sleep quality with the risk of developing T2DM [7,8], there is currently no review which examines the global evidence for the causal link between how deranged sleep can affect glycemic control in patients with T2DM. This study aims to assess the epidemiological evidence and systematically examines the relationship between glucose control in patients with T2DM and the amount of sleep as well as quality of sleep.

Materials and methods

Data sources and searches

We performed a systematic search on PubMed, CENTRAL, Embase, PsycInfo, CINAHL Plus, OpenGrey, DART-Europe,

Abbreviations: AHI, apnea-hypopnea index; CI, confidence interval; HbA1c, hemoglobin A_{1c}; MOOSE, meta-analyses and systematic reviews of observational studies; OSA, obstructive sleep apnea; PSQI, Pittsburg sleep quality index; T2DM, type 2 diabetes mellitus; UKPDS, UK prospective diabetes study; WMD, weighted mean difference.

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Dissertation & Theses Collections (DTC) and EThOS to identify for published studies examining the link between sleep quality and duration with glycemic control in type 2 diabetes patients since inception to 31 August 2015. The search terms included "diabetes" [Mesh] and "sleep", without any language restriction. This was supplemented with a manual search of references, relevant reviews as well as conference abstracts to identify for additional eligible studies.

Study selection

Only studies which fulfilled the following criteria were eligible for inclusion: 1) studies that reported on adults aged 18 and above who were diagnosed with T2DM (either self-reported or doctor diagnosis); 2) studies that examined sleep quality, where sleep quality was assessed by either objective measurements (e.g., actigraphy) or an explicit questionnaire asking about sleep quality; or 3) studies that assessed sleep quantity, and reported the amount of sleep duration in hours; 4) those where study design was prospective, and 5) available as full text. Studies were excluded if they had reported patients with pre-existing breathing or sleeping disorders. In the event that a particular study was reported more than once, we used the latest results. Based upon the above criteria, articles were screened independently based on the relevance of titles and abstracts by two authors (SWHL and WKC) and potentially relevant articles were retrieved. Any disagreement was resolved through a discussion among the authors or an adjudicator if consensus could not be reached.

Data extraction & quality assessment

Data from eligible studies were extracted independently by two authors (SWHL and KYN) using a standardized extraction template developed for the study including the eligibility criteria, methods, participants, interventions, outcomes, results and other relevant notes from the authors. We subsequently assessed the study quality using the Newcastle–Ottawa quality criteria for observational studies [9]. Any disagreement was resolved through discussion and an adjudicator if necessary.

Contact with study authors

We contacted another eight corresponding authors and requested that they complete a standardized result table to provide us with additional relevant data. This resulted in the inclusion of an additional two studies (Fig. 1). Two authors declined our request for additional data, while four other authors did not respond to our request despite multiple attempts to contact them.

Outcome measures

The primary outcome of interest was HbA1c levels, as it is the most reliable test for glycemic control in T2DM which is reported by most studies. The other outcome examined was fasting plasma glucose levels.

Data synthesis and analysis

To estimate the quantitative relationship between sleep duration and diabetes, we generated three sleep categories (short, long and reference) for each study. These categories corresponded to the shortest, longest and reference group as reported by each study respectively. We subsequently estimated the mean difference and 95% confidence intervals (CIs). To account for clinical heterogeneity, we used an inverse variance-weighted random effects analysis based upon the DerSimonian and Laird method [10].

Similarly, we compared the reference category for good versus poor sleep quality and estimated the pooled risk ratio or mean difference using the method described above. To test for study heterogeneity, we used the I^2 statistics and Cochran's Q test. Potential publication bias was evaluated by visual inspection of the funnel plots as well as Egger regression asymmetry test for meta-analyses which contained more than five studies. Sub-group analyses were carried out to examine for possible sources of heterogeneity and check for potential impact of differences in definition of sleep duration or sleep quality, reference category used, geographic location (Asia/others) and population source (community/hospital). For sensitivity analysis, we used the fixed-effect model as well as omitting one study at a time to determine the effects of a single study omission on the pooled estimates. All statistical analyses were performed using the Cochrane's collaboration RevMan (Version 5.3) and Stata version 13.0 (StataCorp, College Station, TX, USA).

Results

Literature search and quality assessment

Of 3889 articles identified, 61 were selected for full text review and 22 articles describing 20 studies were deemed suitable to be included in this review (Fig. 1). These studies involved 69,329 participants, who were primarily located in China (seven studies) [11–17], United States (three studies) [2,6,18], Japan (two studies) [19,20] and Korea (two studies) [21,22]. The other study population were located in India [23], Turkey [24], Netherlands [25], Ireland [26], Taiwan [27], and Brazil [28]. The cohort sizes varied from 46 [27] to 56,032 [15] participants, and participant's age ranged between 20 and 89 years. Most studies included both male and female participants except one study which recruited only females as it was a nurse health study [6]. The mean Newcastle–Ottawa quality score was 7.3 out of 9, suggesting the high quality of studies included in the current review. A summary of the baseline characteristics of the studies is presented in Table 1.

Sleep quantity

Eight studies assessed the relationship between sleep amount and glycemic control in T2DM patients [6,12,15,16,18,19,22,26]. The duration of sleep was assessed by using either a single survey item or extracted from the Pittsburg sleep quality index (PSQI) questionnaire. There was substantial convergence in the definition of normal sleep, but the most common reference category was 6–8 h of sleep per night [12,16,26], while others used 6–7 h [6], 6.5–7.4 h [19], 6–7.9 h [15] or 7 h of sleep [22] per night as the reference category. Short sleep was most commonly defined as <6 h per night (n = 5) [12,15,16,22,26], while two other studies each defined it as either <4.5 h [19] or <5 h [6]. Long sleep was defined as >8 h per night in two studies [12,16,26], ≥9 h in two studies [6,22], >8.5 h in one study [19] and >9 h in one study [15]. The study by Reutrakul and colleagues [18] reported patients preference to be a "morning" or "evening" person and examined its potential association with HbA1c levels.

HbA1c levels were reported in all eight studies. In addition, five studies also reported the fasting plasma glucose levels. Five out of the eight studies reported significant associations between sleep quantity and glycemic control. Three studies reported that short and long sleep was associated with higher levels of HbA1c [15,19,22], while another two studies reported that only short sleep duration was associated with higher levels of HbA1c [12,26].

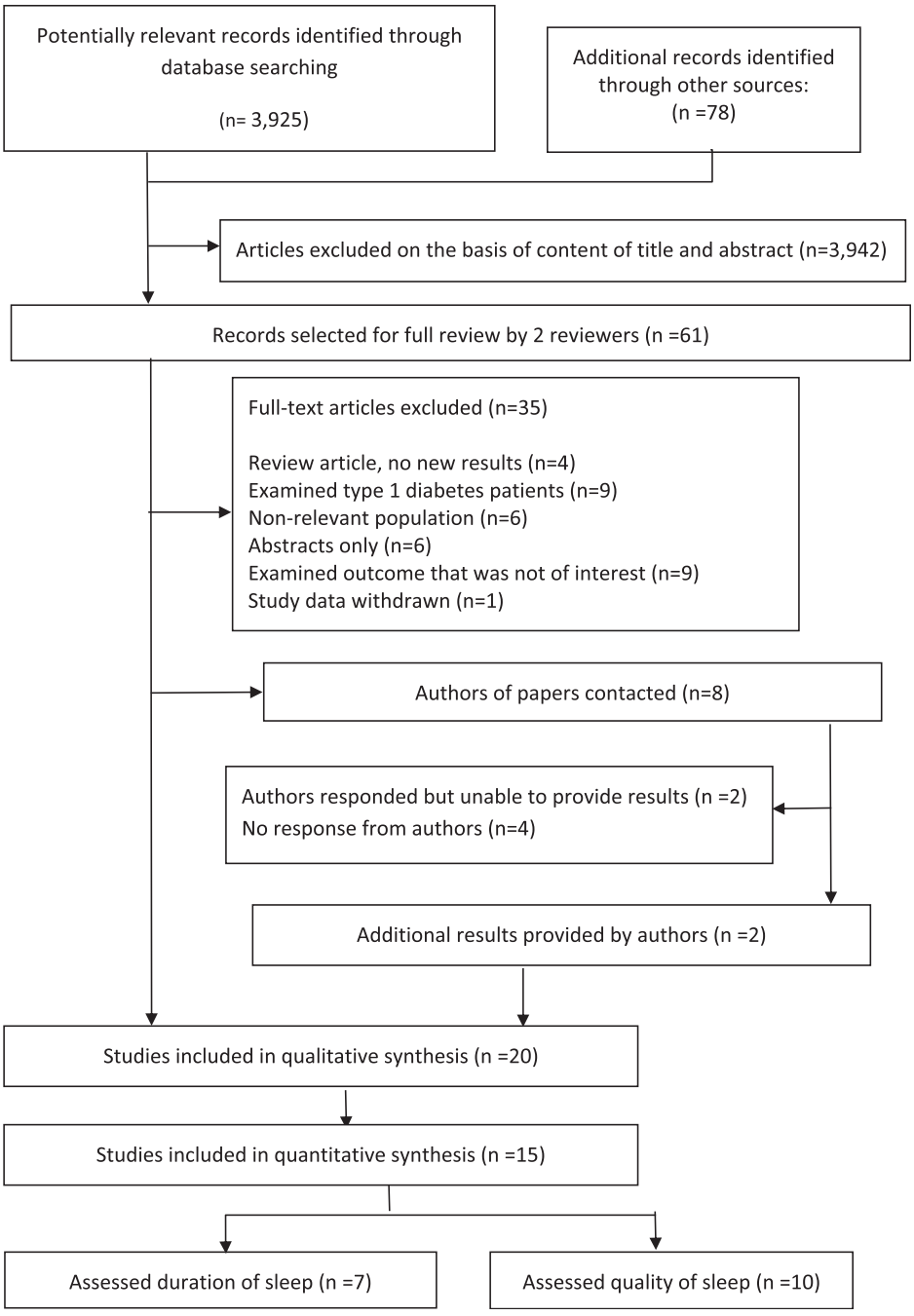

Fig. 1. Flow chart of the study selection process.

Short duration of sleep

Seven studies involving 29,649 participants examining the effects of sleep duration on HbA1c was included in the meta-analysis. Compared to normal sleep, short sleep was associated with significantly higher HbA1c levels [weighted mean difference (WMD): 0.23; 95% CI: 0.10–0.36, Fig. 2]. There was evidence of moderate statistical heterogeneity ($Q = 18.18$, $I^2 = 67\%$, $p < 0.01$), Short sleep duration was also associated with higher levels of fasting plasma glucose (WMD: 0.22; 95% CI: 0.08–0.36, Fig. 3) compared to normal sleep. Analyses of funnel plots for all studies suggest that there was some evidence of publication bias (Egger's test, $p = 0.06$).

Long duration of sleep

Long duration of sleep was similarly associated with higher HbA1c levels and fasting plasma glucose levels among patients with T2DM (Figs. 2 and 3). The pooled mean difference in HbA1c levels comparing long sleep duration with reference category was 0.13% (0.02–0.25), but there was presence of moderate heterogeneity ($Q = 13.45$, $I^2 = 55\%$, $p = 0.04$). Similarly, long sleep was

Table 1
Cross-sectional studies of sleep duration and glycemic control included in the current study.

Author, country, year [reference]	Cohort size	Age, range or mean (y)	% males	Sleep measure assessment	Population source	Relevant finding	Quality score
Aribas et al., Turkey, 2015 [24]	78	48.9	38.4	PSQI questionnaire	Endocrinology outpatient clinic	Patients with poor sleep quality had higher BMI as well as asymmetric dimethylarginine (ADMA) levels, an independent predictor of cardiovascular mortality and morbidity. ADMA levels may provide an insight into the mechanism(s) by which poor sleep quality can adversely affect patients with type 2 diabetes.	8
Cho et al., Korea, 2014 [21]	614	59.7	62.1	PSQI questionnaire	Hospital outpatient clinic	Sleep disturbances such as snoring, short sleep duration and insomnia were common among patients with type 2 diabetes. However, no significant association between HbA1c levels and sleep disturbances.	6
Cunha et al., Brazil, 2008 [28]	50	44–79	24.0	PSQI questionnaire	University research center	Nearly half (48%) of patients with type 2 diabetes reported poor sleep quality, which was associated with a longer history of type 2 diabetes and hypertension.	5
Jin et al., China, 2012 [14]	130	65–88	59.2	PSQI questionnaire	Hospitalized patients	Elderly patients with type 2 diabetes usually reported poor sleep quality. Factors affecting sleep quality were higher levels of FPG and HbA1c, longer duration of diabetes, presence of diabetes complications, depression, poor quality of life and insulin use.	8
Kim et al., Korea, 2013 [22]	2134	61.7	49.9	One sleep question	National health and nutrition examination survey of Korea	Type 2 diabetes patients with 7 h sleep duration a day had the lowest HbA1c and FPG levels compared to a sleep duration of $\leq$6 h/d or $\geq$8 h/d, suggesting a U-shaped relationship.	8
Knutson et al., USA, 2006 [2]	122	58.3	–	PSQI questionnaire & difference between referred and actual sleep duration	Hospital	Sleep duration and sleep quality are significant predictors of glycemic control. The predicted increase in HbA1c was 1.1% above the median with every 3 h of perceived sleep debt per day	8
Lou, China, 2012 [16]	954	48.6	43.4	Self-reported questionnaire	Population-based cohort of Xuzhou City	Subjects with poor sleep quality and sleep duration of $\leq$6 h were more likely to have diabetes compared to those with good sleep quality who sleep for 6–8 h.	7
Lou, China, 2015 [17]	944	64.1	38.7	PSQI questionnaire	Population-based cohort of Xuzhou City	One third (33.6%) of patients with type 2 diabetes reported poor sleep quality. In patients with poor quality sleep, it was associated with lower health-related quality of life.	7
Nefs et al., Netherlands, 2015 [25]	361	62	54.0	PSQI questionnaire	Dutch Diabetes registry and general public	Poor sleep quality was reported by 42% of patients with type 2 diabetes. In patients with poor sleep quality, there was a higher self-care burden, and higher levels of daytime sleepiness, fatigue, depressive and anxiety symptoms and diabetes-specific distress.	8
Ohkuma et al., Japan, 2013 [19]	4870	66	57.0	One sleep question	Fukuoka diabetes registry	Short or longer sleep duration was associated with a higher level of HbA1c and higher BMI compared with a sleep duration of 6.5–7.4 h.	8
Osonoi et al., Japan, 2015 [20]	734	57.8	62.9	PSQI questionnaire	Hospital outpatient clinic	Patients with type 2 diabetes who reported poor quality sleep tend to be obese, depressed, and have higher fasting blood glucose and HbA1c. Poor sleep quality was also correlated with arterial stiffness, a cardiovascular risk factor for atherosclerosis.	6
Rajendran, India, 2012 [23]	120	53.9	54.2	PSQI questionnaire	Hospital outpatient clinic	A large proportion (69%) of patients with type 2 diabetes have sleep dysfunction (disturbed and reduced sleep quality). Duration of diabetes was the greatest predictor of sleep disturbance among the study population	7
Reutrakul et al., USA, 2013 [18]	194	18–85	30.4	PSQI questionnaire	Hospital outpatient clinic	Each hour delay in mid-sleep time on free days was associated with an increase in patients HbA1c value independent of sleep disturbance.	8
Song et al., China, 2013 [11]	140	56.8	59.3	PSQI questionnaire	Hospital outpatient clinic	Female patients with type 2 diabetes are 2.55 times more likely to develop subjective sleep disorders with insulin therapy than males	7

Tang et al., China, 2014 [12]	551	20–89	55.0	PSQI questionnaire	Hospital outpatient clinic	More patients who have insufficient sleep and poor sleep quality have worse glycemic levels, even after adjusting for gender, age, BMI, and disease duration. control	8
Tsai et al., Taiwan, 2012 [27]	46	43–83	60.9	PSQI questionnaire	Hospital outpatient clinic	Both poor sleep quality and less-efficient sleep are significantly correlated with worse glycemic control	8
Wan Mahmood et al., Ireland, 2013 [26]	114	64.9	54.4	PSQI questionnaire	Hospital outpatient clinic	Poor quality sleep (PSQI $\geq$ 6) is associated with worse glycemic, blood pressure and lipid control. Sleep quantity has an independent negative impact on lipids.	8
Wang et al., China, 2015 [15]	56,032	60.7	38.7	Self-reported questionnaire	Risk evaluation of cancers in Chinese diabetic individuals: a longitudinal study	Long night sleep duration of >9 h was associated with higher HbA1c, FPG, PPG as well as triglyceride	8
Williams et al., USA, 2007 [6]	935	43–69	0	Sleep diary	Nurses' health study	Sleep duration and snoring is associated with higher HbA1c levels in patients with type 2 diabetes	6
Zhu, China, 2014 [13]	206	57.2	66.0	PSQI questionnaire	Hospital outpatient clinic	HbA1c levels in patients with sleep disorders (PSQI $\geq$ 8) were significantly higher compared to patients without sleep disorders (PSQI < 8). Compared with subjects with good glycemic control (HbA1c < 7%), subjects with poor glycemic control (HbA1c $\geq$ 7%) had significantly lower PSQI score and factor scores except for the factor score of the use of sleeping medication. Sleep latency, sleep disturbance, daytime dysfunction were found to be the risk factors for poor glycemic control among the patients.	6

AMDA – asymmetric dimethylarginine; BMI – body mass index; FPG – fasting plasma glucose; HbA1c – hemoglobin A_{1c}; PPG – post prandial glucose; PSQI – Pittsburg sleep quality index.

associated with higher levels of fasting plasma glucose (WMD: 0.44; 95% CI: 0.07–0.82) compared to normal sleep. No publication bias was noted (Egger's test, p = 0.62).

Sleep quality

Fifteen studies reported the effects of sleep quality on glycemic control. The PSQI questionnaire was used to determine the sleep quality in all studies. The definition of poor sleep varied between studies, ranging from a cut off PSQI global score of 5–8. Global score of >5 [2,11,18,24,25,28] was used in six studies, ≥5 in two studies [21,23], >8 in two studies [12,27], ≥8 in two studies [13,17], ≥6 in one study [26], ≥7 in one study [14] and ≥9 in one study [20]. Seven studies performed an unadjusted analysis [13,14,17,21,24,27,28], and two of these found a significant association between sleep quality and HbA1c levels [13,27]. Univariate and multivariate analyses were carried out in six studies, and two of these studies demonstrated a significant association between sleep quality and HbA1c levels [13,20]. In the study by Osonoi et al. [20], the authors noted that both HbA1c and fasting glucose levels were significantly associated with poor sleep quality, after adjusting for age and sex. This association was similarly reported by Tang and colleagues [12] after adjusting for age, gender, body mass index as well as disease duration.

Poor sleep quality

For meta-analysis of sleep quality, the data are presented in two ways: as a dichotomized and as continuous variable for HbA1c levels. Only 10 [11–14,17,20,24–27] out of the 11 studies were included in the meta-analysis, as there was data ambiguity in one study [28]. Attempts to contact the author to clarify the data were futile and hence the study was excluded from further analysis. In patients with a difficulty in initiating or maintaining sleep, data pooled from five studies showed that there was no difference in the chance of attaining the goal of HbA1c less than 6.5% or 7% (risk ratio: 1.10; 95% CI: 0.85–1.42, I^2 = 77%; Fig. 4). There was some evidence suggestive of publication bias (Egger's test: p = 0.07), but this may be due to the small number of studies included in the current analysis. When HbA1c levels were analyzed as a continuous variable, poorer sleep quality was associated with higher HbA1c levels, indicating poor glycemic control (WMD: 0.35%; 95% CI: 0.12–0.58, Fig. 5). No publication bias was noted (Egger's test, p = 0.19), but there was moderate amount of statistical heterogeneity (Q = 22.84, I^2 = 65%, p < 0.001).

Sensitivity and subgroup analyses

To explore for potential sources of heterogeneity and to confirm the robustness of our analyses, we conducted several sensitivity analyses. Omission of the study by Lou and colleagues [16] from short sleep analysis reduced heterogeneity to 17% and the overall effect to 0.15% (0.07–0.24). For the analysis of long sleep, exclusion of the study by Kim et al. [22] reduced heterogeneity as well as overall effects estimate (WMD: 0.09; 95% CI: 0.01–0.18, I^2 = 33%). In the sensitivity analyses for studies examining quality of sleep, exclusion of study by Zhu et al. [13] reduced pooled mean difference in HbA1c levels to 0.25%. Repeating the analysis using a fixed effect model did not significantly alter the results (Table 2).

Subgroup analysis showed that the results were relatively similar when examining studies comparing short duration of sleep. However, cohorts recruited from the community reported higher levels of HbA1c compared to cohorts recruited from hospital. In the analysis of long sleep, studies carried out in Asia reported larger differences in HbA1c levels compared to studies conducted in

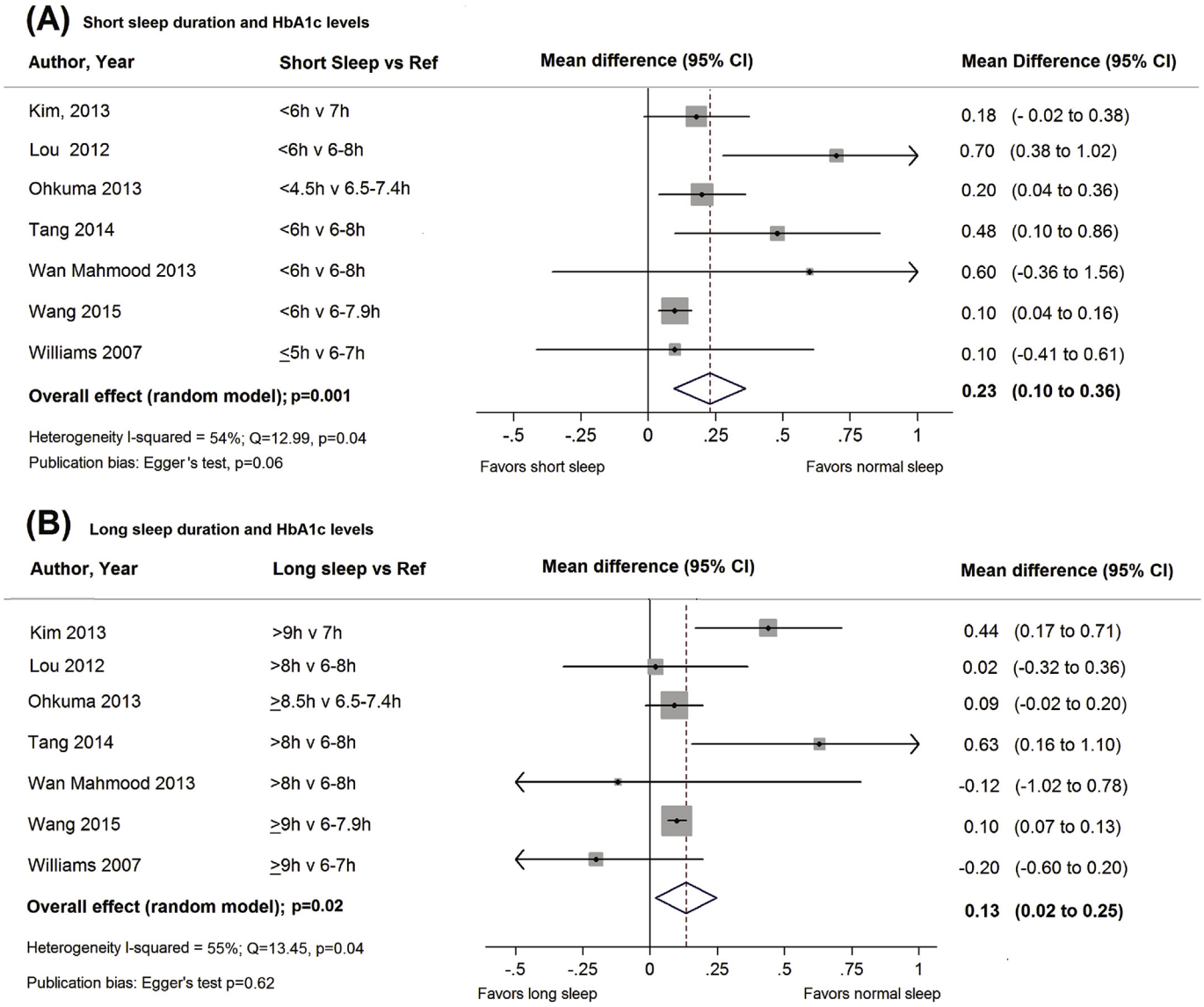

Fig. 2. Quantity of sleep and the weighted mean difference in HbA1c levels among patients with type 2 diabetes.

Europe or USA. Studies which used a higher PSQI cut off score for good sleep reported significantly better HbA1c control in their cohort compared to studies which used a cut off score of 5 and below.

Discussion

To our knowledge, our study is the first systematic review and meta-analysis to examine the evidence for an association between sleep quantity and/or quality with glycemic control in T2DM patients. Overall, we identified 20 studies and found that sleep disturbance as well as altered sleep duration is associated with higher HbA1c levels. There was a 0.23% increase in HbA1c levels in patients who reported insufficient sleep durations of <4.5–6 h/night and 0.13% increase in those with long sleep duration of 8 h or more. The accumulated evidence suggests that short and long sleep duration is significantly associated with higher HbA1c levels, indicating poorer glycemic control compared to normal sleep duration, with the relationship being U-shaped. The associations are consistent, as shown in our sensitivity analysis, particularly for short and long sleep duration. Insufficient evidence exists to draw a firm conclusion regarding the association between sleep quality and HbA1c levels. We found that sleep disturbance resulted in higher HbA1c levels. However, disturbed sleep did not seem to affect HbA1c levels.

Results of this study are in part consistent with many other similar epidemiological studies which show that perceived insufficient and poor sleep were detrimental to various health aspects such as glycemic control [2,29], increased risk of coronary artery calcification [30] and hypertension [31]. Several meta-analyses conducted on published epidemiological studies examining the effects of sleep duration on the risk of T2DM confirm the results of our study. Indeed, two recent studies by Cappuccio et al. [8] and Shan et al. [7], consistently found that sleep duration was significantly associated with a risk for T2DM, with a relative risk between 1.28 for short sleep duration or a 1.09 risk for every hour of short sleep duration compared to those who sleep between 7 and 8 h (normal sleep).

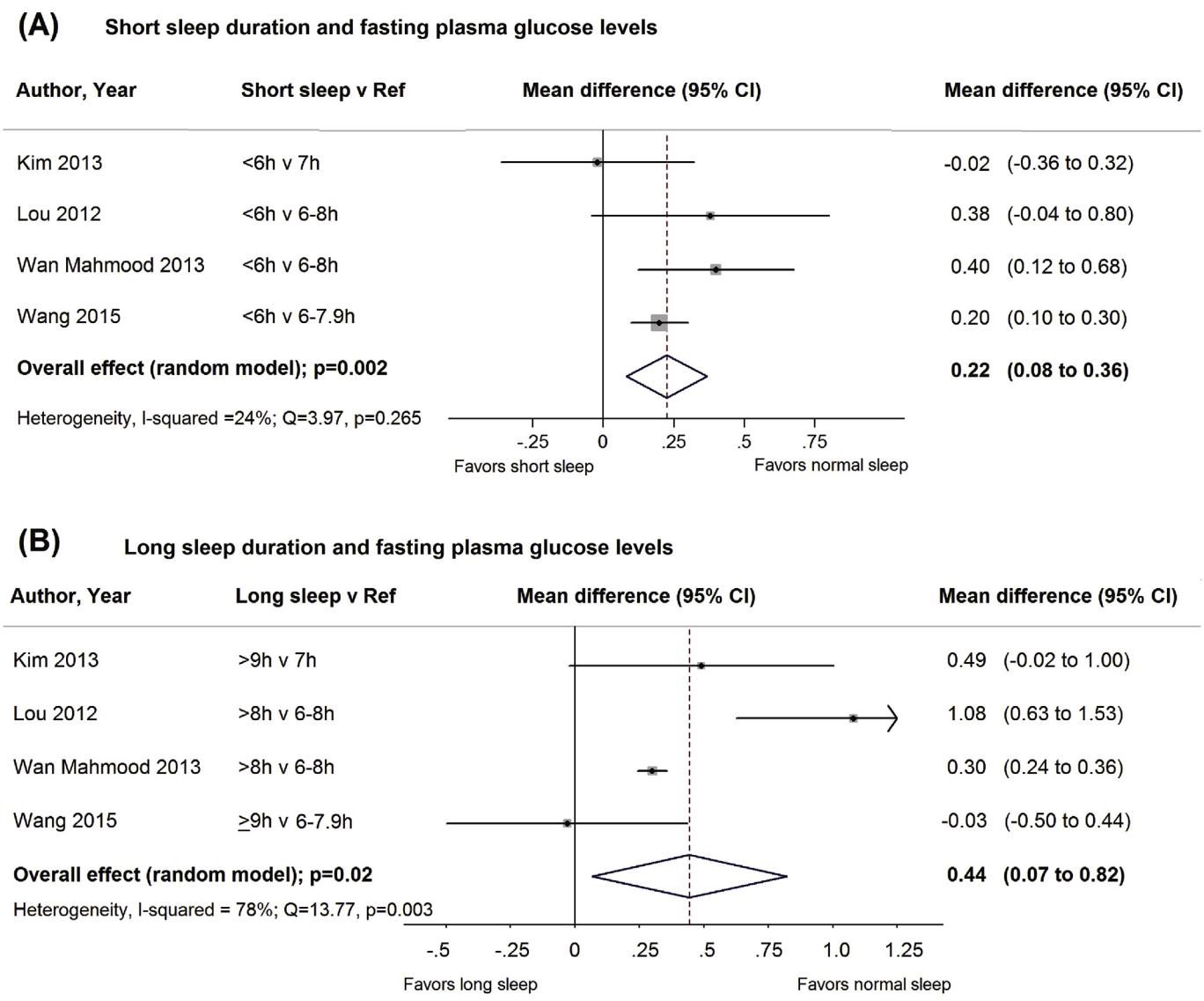

Fig. 3. Sleep quantity and the weighted mean difference in fasting plasma glucose levels among patients with type 2 diabetes.

Possible explanations and implications

While the mechanisms that underlie these associations are not well understood, sleep curtailment is associated with insulin resistance, increased appetite and impaired glucose tolerance in healthy subjects in both laboratory as well as epidemiological studies [32,33]. Sleep restriction is thought to affect energy balance via upregulation of appetite, increased time for eating as well as reduced energy expenditure. Indeed, nocturnal awakening and arousal has been associated with altered leptin levels and leptin resistance leading to dysregulation of the hypothalamic–pituitary–adrenal axis, resulting in glucose impairment [34,35]. Evidence from several studies has shown that recurrent partial sleep deprivation as well as chronic short sleep is associated with decreased levels of leptin and increased ghrelin levels. In the Wisconsin sleep cohort study [34], a significant reduction in leptin levels and elevation of ghrelin was noted among subjects with partial sleep deprivation. As both hormones play a regulatory role in controlling appetite, elevated appetite could lead to an increase in body mass index and in turn increases insulin resistance.

Apart from direct effects on glucose metabolism, sleep disturbance may also indirectly affect glycemic control through suboptimal diabetes self-care [36]. In a study examining 107 T2DM patients, Chasens and colleagues demonstrated that poor sleep quality was associated with suboptimal self-care activities such as medication adherence, exercise as well as diet, which in turn may lead to poorer glycemic control. Data from other studies also suggest that sleep disturbances can affect other aspects of daily functioning and well-being, including mood, fatigue [37] as well as daytime sleepiness [38]. In the study by Sundaram et al. [39], the authors reported that T2DM patients with emotional distress had higher HbA1c levels. In another study, T2DM patients with restless legs syndrome reported worse sleep quality, which affected their daytime functioning and feeling of fatigue. This is thought to affect their personal self-care, including diet and exercise activities [38], resulting in poor glycemic control. Taken together, these cascades of negative events are likely to contribute to part of our observations.

There is less research on the potential association between sleep quality and its metabolic consequences [2,40,41]. Most of the work stems from epidemiological studies of patients with obstructive

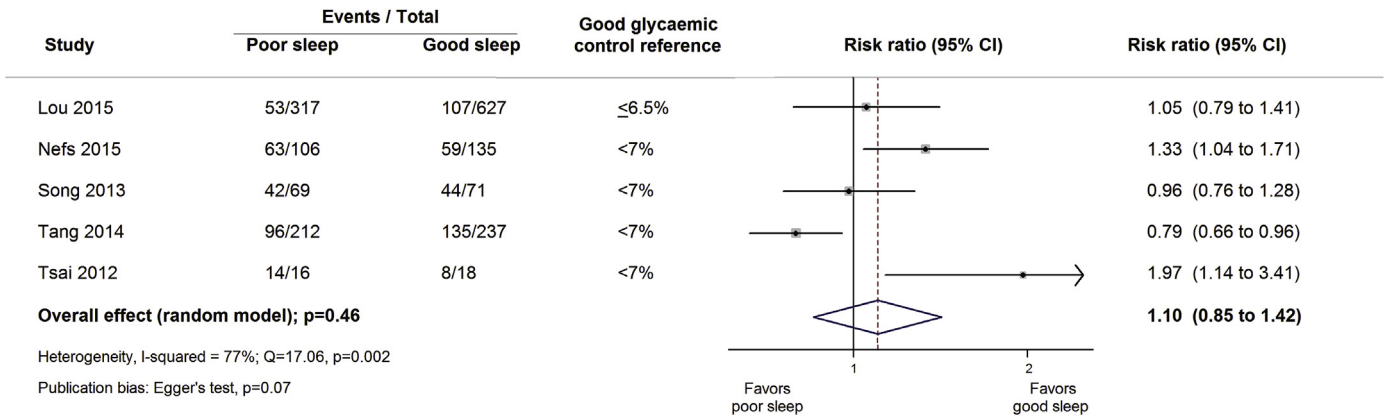

Fig. 4. Risk ratio for achieving good glycemic control between good sleep and poor sleep quality.

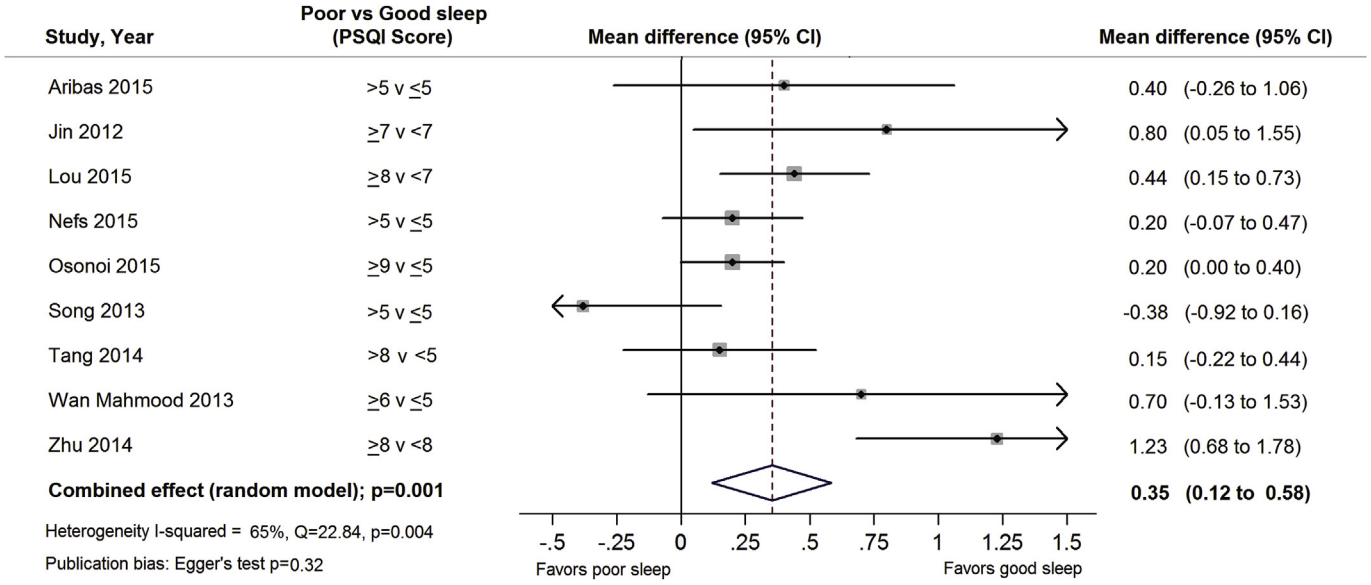

Fig. 5. Weighted mean difference of change in HbA1c levels between type 2 diabetes patients with poor sleep versus good sleep quality.

sleep apnea (OSA), which is a highly prevalent comorbid condition particularly in obese T2DM patients [42,43]. Evidence suggests that OSA can alter glucose metabolism, particularly insulin resistance and glucose tolerance, in individuals without T2DM [44–48]. In particular, OSA severity was associated with a poorer glucose control, independent of obesity and other confounding factors. Aronsohn et al. [49] examined the impact of untreated OSA on glucose control in T2DM patients. They reported that the adjusted mean HbA1c levels increased by 1.49% in patients with mild OSA (apnea-hypopnea index [AHI] $\geq$ 5 but <15), 1.93% in moderate OSA (AHI $\geq$ 15 but <30), and 3.69% in severe OSA (AHI > 30) compared with patients without OSA. A large multinational study European sleep apnea cohort (n = 6616) has confirmed this finding by showing that the adjusted mean HbA1c levels were 0.72% higher in severe OSA patients (oxyhemoglobin desaturation index $\geq$ 30) when compared with patients without OSA [50]. Both studies have concluded that OSA increases HbA1c levels.

Because these comorbid conditions may represent important confounders in this association, one of the a priori of this study was to include all studies that had adjusted for comorbid conditions as a subgroup analysis. Unfortunately, due to the small number of studies reporting this association, this subgroup analysis was not performed. As such, it remains possible that these confounders may result in an under or overestimation of the association, and should be read with caution, until further studies have been done to confirm this association.

Overall, our results suggest that sleep health is an important modifiable risk factor for improving glycemic control in T2DM patients in addition to smoking [51] and obesity [52]. We recognize that while the complete prevention of sleep loss in a globalized world is unfeasible, with increased understanding of the physiological consequence of such condition, an optimized sleep schedule or even working schedule for shift workers could be developed. In addition, an improvement to the sleep environment or even systematic manipulation through enhancement of slow sleep wave could also be used as an adjunct to improve sleep quality and thus enhance the body's restorative function to maintain glucose homeostasis. Furthermore, efforts towards educating patients about the importance of sleep health to improve glucose metabolism could represent a viable strategy to help T2DM patients to improve their glycemic control [53].

If widely implemented, this could have important public health implications. For example, data from the United Kingdom prospective diabetes study (UKPDS) suggested that for every 1%

Table 2
Subgroup analyses to explore sources of heterogeneity in studies.

Subgroup	No. of studies	Fixed effect (95% CI)	Random effect (95% CI)
Short duration of sleep	**7**	**0.14 (0.08–0.19)**	**0.23 (0.10–0.36)**
Study population			
Community cohort	4	0.58 (0.31–0.85)	0.58 (0.31–0.85)
Hospital cohort	3	0.12 (0.06–0.17)	0.12 (0.06–0.17)
Location			
Asia	5	0.14 (0.08–0.19)	0.24 (0.09–0.39)
Europe/US	2	0.21 (−0.24 to 0.67)	0.21 (−0.24 to 0.67)
Definition of short sleep			
≤5 h	2	0.19 (0.04–0.34)	0.19 (0.04–0.34)
Long duration of sleep	**7**	**0.10 (0.07–0.13)**	**0.13 (0.02–0.25)**
Study population			
Community cohort	4	0.10 (0.07–0.14)	0.12 (−0.08 to 0.32)
Hospital cohort	3	0.11 (0.01–0.22)	0.23 (−0.17 to 0.63)
Location			
Asia	5	0.11 (0.07–0.14)	0.16 (0.04–0.28)
Europe/US	2	−0.19 (−0.55 to 0.18)	−0.19 (−0.55 to 0.18)
Definition of long sleep			
≥9 h	3	0.10 (0.07–0.14)	0.14 (−0.13 to 0.41)
Sleep quality	**9**	**0.29 (0.17–0.41)**	**0.35 (0.12–0.58)**
Poor quality PSQI ≥ 7	5	0.34 (0.20–0.49)	0.48 (0.16–0.80)
Good quality, PSQI ≤ 5	6	0.18 (0.04–0.32)	0.17 (0.00–0.34)
Good quality, PSQI ≤ 8	3	0.63 (0.39–0.87)	0.78 (0.25–1.31)

CI – confidence interval; PSQI – Pittsburg sleep quality index.

reduction in mean HbA1c, this would translate to a 21% reduction in death, 14% reduction in myocardial infarction and 37% decrease in microvascular complications at population level [54]. We noted that having sufficient sleep as well as good sleep quality would reduce HbA1c between 0.13% and 0.35%, which may translate to a 3% reduction in death, 2% reduction in myocardial infarction and 5% reduction in microvascular complications. Of note, a clinical trial that is planned to assess the effects of sleep hygiene in improving glycemic control (NCT01881724), will be of particular interest and if proven effective may have important public health implications.

Strengths and limitations of this study

This study offers several strengths. We conducted an exhaustive literature search, without any language limitations and included nearly 70,000 patients with T2DM, pooled from twenty studies. Our studies are consistent with prior hypotheses in literature, suggesting that sleep quality and quantity is a novel risk factor for glycemic control in type 2 diabetes patients. In line with international guidelines, we adhered to the meta-analysis of observational studies in epidemiology (MOOSE) [55] and PRISMA statement [56]. We assessed the quality of study using the Newcastle–Ottawa scale criteria, of which most were of high quality. We note that there was substantial statistical heterogeneity as evidenced by the high I^2 statistics, hence these findings should be interpreted with caution. Nevertheless, we believe that in all comparisons, the estimates showed the same directions of effect, which is suggestive that these associations are real [57].

This study has several limitations. Firstly, it is possible some studies that were either published or unpublished may not be identified. Secondly, a meta-analysis based upon observational studies is open to bias as it cannot directly control for the various confounding factors that maybe inherent in the original study. As the pooled studies in this study are cross-sectional in nature, they cannot therefore determine the temporal sequence and hence causality of poorer glycemic control in our population. Nevertheless, we believe that the results of the current meta-analysis support the notion that sleep amount and quality adversely affects glycemic control. Additional support for this can be seen in some experimental studies on healthy human volunteers exposed to severe sleep deprivation lasting one to five days, and developing insulin resistance and β-cell dysfunction [58]. The metabolic profile shares similarities with T2DM, including decreased muscle glucose uptake and increased hepatic glucose production [32].

Another limitation of this study is that the results can only represent the studies that have been included and cannot be extrapolated to other settings. The wide variety of classifications of short, normal as well as long sleep also reflect the current poor understanding of what is the most common reference category for normal sleep. Given that all studies used a single question to measure sleep duration rather than objective measurements, it is possible that these maybe under or over reported by each participant. As sleep diaries have become a standard assessment in insomnia outcome research, this could be considered in future studies to better collect data pertaining to sleep duration and amount. Finally, as quantity and quality of sleep were only assessed in a single time point in all studies, this may not sufficiently capture the sustained effect of sleep disruption in patients with T2DM. Instead, a change in sleep patterns and glycemic control over time maybe a better reflection of the actual impact of the exposure.

Conclusions

In summary, findings from the current review suggest that sleep duration as well as sleep quality may be a novel and independent risk for poorer glycemic control in T2DM patients. However, further research is needed to establish the potential causal link between sleep and altered glucose metabolism. These studies ideally should stem from large prospective cohorts, with objective measurements of sleep and glycemic control, repeated over a period of time. If proven true, these findings may open up new strategies for targeted intervention to improve quality and quantity of sleep. On the basis of current evidence, health care professionals should encourage and motivate their patients to enjoy sufficient sleep.

Practice points

1. Adequate sleep may play an important role in regards to metabolic control in patients with type 2 diabetes. Physicians should consider inquiring about patients' sleep health in their regular care.
2. Too much or too little sleep disrupts glycemic control in patients with type 2 diabetes. Insufficient evidence exists on the association between sleep quality and HbA1c levels.
3. Results of this study suggest that sleep health is a new and important modifiable risk factor for better glycemic control in type 2 diabetes patients.

Research agenda

1. Increased awareness of the magnitude and impact of sleep among patients and clinicians can provide an opportunity to test different lifestyles or pharmacological interventions to promote healthy sleep. This should ideally be conducted as a randomized controlled study, with objective measurements of sleep and glycemic control, repeated over a period of time.
2. The mechanistic pathways linking sleep health and glycemic control are likely to be complex, and bidirectional.

The underlying mechanism remains poorly understood, and further research is warranted.

3. A standard protocol should be established and subsequently used to determine the sleep quantity and quality in individuals. This will allow for more accurate determination of any associations, and facilitate a cross studies comparison in the future. In addition, self-care status, well-being as well as other potential confounding factors need to be taken into account and examined in future prospective studies.

Author contribution

SLWH: study conception; SLWH, CWK, NKY: conduct of systematic review and drafting of manuscript; SLWH: data analysis; SLWH, NKY, CWK: review and editing of the manuscript.

Dr Shaun Lee is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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