Prevalence of insomnia (symptoms) in T2D and association with metabolic parameters and glycemic control: meta-analysis

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Disclosure: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
Abstract

Objective: We aimed to determine the prevalence of insomnia and insomnia symptoms and its association with metabolic parameters and glycemic control in people with T2D in a systematic review and meta-analysis. Datasources: A systematic literature search was conducted in Pubmed/Embase until March, 2018. Studyselection: Included studies described prevalence of insomnia or insomnia symptoms and/or its association with metabolic parameters or glycemic control in adults with T2D. Dataextraction: Data extraction was performed independently by two reviewers, on a standardized, pre-piloted form. An adaptation of Quality Assessment Tool for Quantitative Studies was used to assess the methodological quality of the included studies. Datasynthesis: When possible, results were meta-analyzed using random-effects analysis and rated using GRADE. Results: A total of 11,329 titles/abstracts were screened and 224 were read full text in duplicate, of which 78 studies were included. The pooled prevalence of insomnia (symptoms) in people with T2D was 39% (95%CI:34-44) with $I^2$ statistic of 100% ($P<0.00001$), with a very low GRADE of evidence. Sensitivity analyses identified no clear sources of heterogeneity. Meta-analyses showed that in people with T2D, insomnia (symptoms) were associated with higher HbA1c levels (mean difference (MD): 0.23% (0.1-0.4)) and higher fasting glucose levels (MD: 0.40 mmol/l (0.2-0.7)), with a low GRADE of evidence. The relative low methodological quality and high heterogeneity of the studies included in this meta-analysis however complicate the interpretation of our results. Conclusions: The prevalence of insomnia (symptoms) is 39% (95%CI:34-45) in the T2D population and may be associated with deleterious glycemic control.
Using a systematic review and meta-analysis, we showed that the prevalence of insomnia (symptoms) is 39% (95%CI:34-45) in the T2D population and may be associated with deleterious glycemic control.
Introduction

Insomnia is defined as chronic difficulty of falling asleep, staying asleep or waking up early, despite opportunity to sleep, for at least 3 times a week during 1 month, resulting in daytime impairment [1]. In the general population the prevalence of symptoms of insomnia ranges from 30-40% [1-3], while the prevalence of insomnia is about 6-20% [3-5]. Insomnia and insomnia symptoms are thought to affect a wide range of body functions, including metabolic (decreased glucose tolerance, insulin resistance) [6] and endocrine regulation (elevated cortisol levels) [7]. Cross-sectional studies have shown that in healthy people, insomnia (symptoms) are associated with an increased risk of obesity with odds ratios ranging between 1.07 (1.0-1.1) [8] and 1.66 (1.4-1.9) [9] as well as disturbances in glucose homeostasis, with insomnia being associated with HOMA-S 0.03% (0.0-0.1) [10]. In addition, in the general population insomnia (symptoms) are associated with an increased risk of T2D, with odds ranging between 1.52 (1.05-2.20) and 2.98 (1.36–6.53), as well as with an increased risk of cardiovascular disease with a Risk Ratio of 1.05 (1.01-1.08) for hypertension incidence [11-15].

While the association between insomnia (symptoms) and the increased risk of developing T2D is consistently shown [16], it is still unclear whether people with T2D also have an increased risk of having insomnia and insomnia symptoms. Despite plenty of studies examining this association, the prevalence rates of insomnia and insomnia symptoms in people with T2D are inconclusive, ranging from 6% [17] to 80% [18]. This range could be due to different study populations, measurement instruments and co-morbidities, however this was never studied. Also the non-consistent definition of insomnia, using insomnia, insomnia symptoms and low sleep quality interchangeably might explain the range. In this review, we will use therefore the terms insomnia and insomnia symptoms.
A recent meta-analysis [19] did show that low sleep quality, assessed with the Pittsburgh sleep quality index (PSQI) questionnaire, is associated with higher HbA$_{1c}$ levels in adults with T2D. However, there is a lack of meta-analytic evidence on the other parameters of glycemic control and metabolic parameters such as: fasting glucose levels, high-density lipoprotein (HDL) / low-density lipoprotein (LDL) / total cholesterol levels, triglyceride levels, BMI, waist circumference and blood pressure (systolic and diastolic). Also this meta-analysis did not include other measures of insomnia symptoms or insomnia, such as self-report and other questionnaires and did not study the prevalence of insomnia. Therefore, the aim of our current study is to determine the prevalence of insomnia and insomnia symptoms and its association with metabolic parameters and glycemic control in people with T2D in a systematic review and meta-analysis.

**Methods**

**Data sources and searches**

A systematic search of the literature was conducted in MEDLINE (Pubmed) and Embase until March, 2018 by the investigators AK and FR, assisted by a librarian. Reference lists of included studies were searched manually for additional studies. In short, the search strategy focused on a combination of these terms and their synonyms: (Type 2 diabetes OR NIIDM OR T2DM OR diabetes) AND (Insomnia OR sleep quality OR disturbed sleep). The full search strategy is provided in File 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for experimental studies [20] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for observational studies [21]. The protocol of this review was registered in the PROSPERO database under number CRD42018089917.
Selection of studies

Studies were included if: 1) the study population consisted of adults (≥18 years) with T2D; 2) article was available as full text, either via our library or upon request authors; 3) the article was written in English or Dutch; 4) prevalence of insomnia or insomnia symptoms was reported as a percentage or could be calculated from the results and/or 5) the association between insomnia (symptoms) and glycemic control, defined as HbA1c levels and fasting plasma glucose levels, or metabolic parameters were studied, defined as BMI, waist circumference, levels of triglycerides, LDL/ HDL/ (total) cholesterol levels and/or systolic/ diastolic blood pressure. Studies were excluded if they reported solely on patients with Obstructive Sleep Apnea (OSA) and/or sleep apnea. When results from a study were reported more than once, the most recent article was used.

All studies identified in the literature search were screened for eligibility on title and abstract by two reviewers (TD and FR or AK). The full text versions of potentially eligible studies were independently assessed for inclusion by two reviewers (TD and FR or AK). Discrepancies were resolved through discussion, consulting a third reviewer, FR or AK.

Data extraction

Data extraction was performed independently by two reviewers, TD and FR or AK. A standardized, pre-piloted form was used to extract data from the included studies. Data extraction included: setting, country, years when data was collected, number of participants (% men), age, diabetes duration, diabetes diagnosis (e.g. self-report or clinically diagnosed), diabetes treatment, insomnia or insomnia symptoms measure and metabolic and glycemic control parameters. If studies reported multiple outcomes, all were extracted and reported separately. Discrepancies identified during the duplicate data extraction were resolved through discussion, consulting a third reviewer, JB.
Methodological quality assessment

An adaptation of the Quality Assessment Tool for Quantitative Studies, as developed by the Effective Public Health Practice Project (EPHPP), was used to assess the methodological quality of the included studies [22]. This nineteen-item tool, adapted by Mackenbach et al. 2014, is suitable for assessing the methodological quality of studies of observational and experimental design [23]. It contains eight domains of methodological quality on which studies were assessed: 1) study design; 2) blinding; 3) representativeness with regard to selection bias; 4) representativeness with regard to withdrawals/dropouts; 5) confounders; 6) data-collection; 7) data-analysis; and 8) reporting. The quality assessment was based on the outcome of interest, independent of the primary aim of the particular study.

The methodological quality was assessed separately for insomnia and insomnia symptoms prevalence and the association with metabolic parameters or glycemic control resulting in two ratings for methodological quality when a study examined both outcomes. For the assessment of prevalence studies, we scored ‘no rate’ on the domains confounders and data-analysis, because these domains were not applicable. Consequently, the prevalence outcome could only have four to six component ratings, while studies containing metabolic or glycemic control parameters could have six to eight component ratings, resulting in one overall rating, ranging from low risk of bias (high methodological quality) to high risk of bias (low methodological quality). If four ratings were given, the overall rating was scored as follows: high methodological quality was attributed to those studies with no ‘weak’ rating and at least two ‘strong’ ratings; moderate methodological quality was attributed to those studies with one ‘weak’ rating or fewer than two ‘strong’ ratings; low methodological quality was attributed to those studies with two or more ‘weak’ ratings. If six ratings were given, the overall rating was the same, except that there should be at least three ‘strong’ ratings to be scored as a study with high methodological quality.
All included studies were independently assessed for methodological quality by two raters, AK and FR/JB. The ratings of each domain and the overall ratings were compared between the two raters to reach consensus.

The measurement of insomnia and insomnia symptoms
The primary aim was to determine the prevalence of insomnia and insomnia symptoms in adults with T2D. Insomnia or having insomnia symptoms is defined as having the following symptoms: chronic difficulty of falling asleep, staying asleep or waking up early, for at least 3 times a week during 1 month [1], although an unequivocal way to for measuring insomnia (symptoms) does not exist. The PSQI questionnaire was most frequently used, with the questionnaire aiming to assess overall sleep quality, with a score of >5 points on the PSQI indicating poorer sleep quality, often referred to as insomnia (symptoms). But as depicted in Table 1A and 1B also other methods are used, such as self-report on having insomnia, the Insomnia Severity Index (ISI) and the Medical Outcomes Study - Sleep Scale.

Quantitative data synthesis and analysis
Meta-analyses were performed, using Review Manager 5.3 [Nordic Cochrane Center]. Since the inclusion criteria allowed for a large range of studies (i.e. all countries and all types of adults with T2D), random-effects meta-analyses were performed [24]. Prevalence data were entered on a log scale to correct for studies with a low variance due to a high or low prevalence. The level of evidence was applied to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria and reported. As is customary with GRADE, randomized control trials start as high quality and observational studies as low quality. While no trials were included, all studies start off with a low GRADE quality.

Statistical heterogeneity was assessed with the I² statistic, with the I² reflecting the percentage of the variability in effect estimates that is due to heterogeneity rather than
sampling error (chance), with 0% reflecting no heterogeneity and 100% high heterogeneity [25]. A P-value <0.05 was considered statistically significant. Funnel plots were used to assess publication bias.

*Prevalence of insomnia and insomnia symptoms*

Sensitivity analyses were performed to gain insight into how certain subgroups influenced the prevalence of insomnia and insomnia symptoms and to identify sources of heterogeneity. The sensitivity analysis for methodological quality of the studies (low/moderate/high) was pre-specified. In addition, due to the high heterogeneity, sensitivity analyses were performed on age of participants (age ≥60y), presence of comorbidities (e.g. lower limb amputation, neuropathy), geographical location (Asia versus Europe/America), year of analysis (year ≥2010), sample size (N<100, N=100–199, N=200–299, N=300–999, N>1000) and insomnia or insomnia symptoms measurement method (PSQI or not). Several studies have used different cut-off points for the PSQI, however we could not assess the effect of these different cut-offs in a sensitivity analysis, as the studies in this meta-analysis using a higher cut-off are mostly Asian studies and in Asia the validated PSQI cut-off is >8 instead of >5. After these primary sensitivity analyses, variables that explained most of the heterogeneity were selected and stratified for some of the remaining variables that could still make a large enough subgroup, to assess if more heterogeneity could be explained.

*Association between insomnia, insomnia symptoms and metabolic parameters and glycemic control*

The quantitative association between insomnia, insomnia symptoms and metabolic parameters or glycemic control was examined in two ways. First, we included studies that examined the association by means of adjusted regression analyses, resulting in a beta-coefficient or risk
estimate with 95% confidence intervals (CI). Studies were pooled in case of three or more studies reported on the same metabolic or glycemic control parameter, with the same regression analyses (logistic or linear). Second, we included studies that compared insomnia (symptoms) versus no insomnia (symptoms) and estimated the mean difference or risk ratio and 95% CI. When median values instead of mean values were reported, the mean and standard deviation was estimated from the sample size, median and interquartile range according to the method of Wan et al. 2014 [26]. Studies were pooled in case of three or more studies reported on the same outcome.

Subgroup analyses were performed to examine possible sources of heterogeneity by excluding poor quality studies and outliers. In addition, for the analyses on the mean differences, a sensitivity analysis was performed on studies with a reported mean versus a calculated mean.

Results

Description of included studies

The systematic literature search identified 11,329 articles. After screening titles and abstracts, 224 potentially eligible articles were read full text. As three studies reported the prevalence of insomnia and insomnia symptoms in the same population [27-29], only the most recent [28] was included. In total, 78 studies met the inclusion criteria and were therefore included in this systematic review (see Figure 1). Of these 78 studies, 71 reported on the insomnia and insomnia symptoms prevalence in T2D and 35 on the associations with metabolic parameters or glycemic control. An overview of the 147 excluded studies and reason for exclusion is provided in File 2.

An overview of the characteristics of the included studies is shown in Table 1 and 2. Sample sizes ranged from 35 [30] to 18,888 [31] participants, with only six studies reporting
on >1000 participants. Both male and female participants were included except for two studies, which included only women [32] or men [33]. Most studies were conducted in Asia (35 studies). Thirty-two studies were conducted in outpatient and diabetes clinics and 11 studies were conducted in the general population.

As shown in Table 1 and 2, insomnia and insomnia (symptoms) were measured differently among the studies. Of the 78 studies, 50 used the PSQI questionnaire to determine insomnia symptoms. Among others, also self-reported diagnosis of insomnia by a physician, the Medical Outcomes Study-Sleep Scale (MOS-SS) and the Athens Insomnia Scale (AIS) were used and additionally only once a diagnostic interview was used to assess insomnia and insomnia symptoms.

**Methodological quality rating**

An overview of the methodological quality assessment of the studies is presented in Table 3. With regard to the prevalence outcome, the methodological quality of the studies was considered to be strong (low risk of bias) in 31 studies, moderate (moderate risk of bias) in 36 studies and weak (high risk of bias) in four studies. With regard to metabolic parameters or glycemic control, the quality assessment resulted in six strong methodological quality studies, nine moderate quality studies and 20 weak studies. Only two studies adjusted for age, sex and diabetes duration and were therefore rated as strong regarding the domain confounding in the methodological quality assessment. The other studies did not adjust for diabetes duration and were therefore rated as moderate, but these studies did adjust for other confounders such as BMI and insulin use.
Prevalence of insomnia and insomnia symptoms in T2D

A random-effects meta-analysis of 71 studies with 84 prevalence estimates, revealed an insomnia and insomnia symptoms prevalence of 39% with a 95% CI of 34% - 44%. Heterogeneity between the 71 studies was high with an I^2 statistic of 100% (p<0.00001%) (Table 4). Visual examination of the funnel plot showed there was no publication bias (Figure 2).

Sensitivity analyses showed that the prevalence of insomnia and insomnia symptoms was higher when age was ≥60 years (44%), when the study was conducted in 2010 or later (42%). When the PSQI questionnaire was used (46%), when the methodological quality of the studies was weak (44%) and when participants with comorbidities (lower limb amputation, neuropathy) were studied (60%) (Table 4). Stratifying for geographical location showed the prevalence was 49% versus 40% in Asia versus Europe/America. Stratifying for sample size showed that in studies with >1000 participants, the prevalence was the lowest (24%), however no clear pattern of larger studies reporting a lower prevalence of insomnia and insomnia symptoms was observed. Although in some subgroups (comorbidities and PSQI use) differences were observed, the I^2 statistic remained 100% in almost all subgroups. Due to limited reporting in the original papers, we could not investigate type of population (population-based or hospital), type of diabetes medication or glycemic control as possible sources of heterogeneity. Also due to the large unexplained heterogeneity, we did not test for statistical differences in prevalence between the subgroups.

Since the first set of sensitivity analyses showed that the presence of comorbidities was the largest source of heterogeneity, followed by using the PSQI or not, we performed an additional sensitivity analysis, including only the studies without comorbidities, that used the PSQI, were of strong methodological quality and had a sample size of more than 200 participants to examine the prevalence in the most reliable subset of studies (n=17). This
sensitivity analysis resulted in a prevalence of insomnia and insomnia symptoms of 39% (95%CI: 30–51). However, heterogeneity remained very high with an \( I^2 \) statistic of 100% (p<0.00001). The level of evidence for the prevalence of insomnia and insomnia symptoms by GRADE was very low quality due to the findings being downgraded due to heterogeneity.

**Insomnia and insomnia symptoms in T2D and metabolic parameters and glycemic control**

*Insomnia and insomnia symptoms and glycemic control unadjusted for confounders*

We investigated whether an elevated level of insomnia and insomnia symptoms were associated with glycemic control. For the meta-analysis of the HbA1c levels, the data are presented in two ways in Figure 3; as a dichotomized and as a continuous variable. Data from seven cross-sectional studies [34-40] showed that insomnia and insomnia symptoms were associated with an increased risk of an elevated HbA1c level (Figure 3A), defined as HbA1c levels \( >6.5\% \) (\( >48 \text{ mmol/mol} \)) or \( \geq 7\% \) (\( >53 \text{ mmol/mol} \)) (Risk ratio: 1.18; 95%CI: 1.0-1.4; \( I^2 = 73\% \) (p=0.001)). Similar results were observed when HbA1c levels from 14 studies were analyzed as a continuous variable [35, 37, 41-52]; compared to people with T2D without insomnia (symptoms), those with insomnia (symptoms) showed significantly higher HbA1c levels with a mean difference (MD) of: 0.23\% (95%CI: 0.1-0.4); \( I^2 = 76\% \), p<0.00001 (Figure 3B).

The pooled data of 10 studies [35, 41, 44-47, 49, 50, 52-54] on fasting glucose levels showed that fasting glucose levels were 0.40 mmol/l (95%CI: 0.2-0.7) higher in people with T2D and insomnia (symptoms), compared to people with T2D without insomnia (symptoms) (\( I^2 = 57\% \), p=0.01) (Figure 3C).
Insomnia, insomnia symptoms and BMI and waist circumference

The pooled data of 14 studies [35, 36, 41, 44-47, 49-52, 55-57] on BMI showed that people with T2D and insomnia (symptoms) had a significantly higher BMI, compared to those without insomnia (symptoms) (MD: 0.38 kg/m²; 95%CI: 0.1-0.7; I² =47%, p=0.03) (Figure 4A).

Studies on waist circumference could not be pooled in a meta-analysis as there were only two studies reporting on waist circumference [41, 57].

Insomnia, insomnia symptoms and lipid levels

The pooled data of eight studies [35, 41, 44, 46, 47, 49, 50, 52] on triglyceride levels showed that there were no differences in triglyceride levels between the groups (Figure 4B). Similarly, for levels of HDL [41, 44, 46, 47, 49, 50, 52] and LDL [41, 44, 46, 48-50, 52], the meta-analysis showed no differences for people with T2D with and without insomnia (symptoms) (Figure 4C and D).

The pooled data of five studies [41, 44, 47, 49, 56] on total cholesterol levels showed that people with T2D and insomnia (symptoms) had significantly higher total cholesterol levels, compared to people with T2D without insomnia (symptoms) (MD: 0.15 mmol/l; 95%CI: 0.03-0.3; I²=0%, p=0.43) (Figure 4E).

Insomnia, insomnia symptoms and blood pressure

The pooled data on blood pressure showed that the systolic [41, 44, 46-50, 52, 58] blood pressure was 2.69 mmHg higher (95%CI: 0.1-5.3) in people with T2D and insomnia (symptoms), compared to those without insomnia (symptoms) (Figure 4F). We observed a non-significant difference in diastolic blood pressure [41, 44, 46-50, 52] of 1.13 mmHg (95%CI: -0.1-2.3) (Figure 4G), higher in people with T2D and insomnia (symptoms),
compared to those without insomnia (symptoms). \(I^2\) statistic was 60% (\(p=0.01\)) and 25% (\(p=0.23\)) for respectively the systolic and diastolic blood pressure.

**Insomnia, insomnia symptoms and glycemic control corrected for possible confounders**

Of the 12 studies that performed regression analysis adjusted for confounders, eight studies could not be included in the meta-analysis, because less than three studies reported on the same parameter and/or with same type of regression analysis. Only for HbA1c levels the data of the adjusted association could be pooled. A random-effects meta-analysis of four studies [39, 40, 52, 59] showed that people with T2D and insomnia (symptoms), according to the PSQI, had a higher, albeit non-significant, odds (Odds Ratio (OR): 1.38, 95\% CI 0.9-2.0) for poor glycemic control, defined as HbA1c levels >7/8.5\% (>53/69 mmol/mol), compared to people with T2D and insomnia (symptoms). Heterogeneity between studies was high with \(I^2\) statistic of 89\% (\(p<0.00001\)) (Figure 3D). Excluding the study [59] that defined poor glycemic control as HbA1c >8.5\% (>69 mmol/mol) and included only people with T2D with poor glycemic control, did not affect the OR; 1.38 (95\% CI 0.9-2.1) with \(I^2\) statistic of 91\%.

Excluding the study [39] with a small sample size of only 46 people with T2D, decreased the OR to 1.29 (95\% CI: 0.9-1.9), with \(I^2=92\%\).

**Sensitivity analyses**

Table 5 shows that, when excluding studies with low methodological quality, the mean difference between people with diabetes and with or without insomnia (symptoms) remained significant and increased for HbA1c levels, fasting glucose levels and systolic blood pressure compared to those with T2D and no insomnia (symptoms). The differences in triglycerides, HDL levels and diastolic blood pressure were not significant and remained non-significant after removing the studies with low quality. The difference in BMI and total cholesterol attenuated to non-significant when excluding low methodological quality studies and for LDL.
levels the opposite association was observed. However, in general, excluding low quality studies resulted in a small number of studies left that could be pooled.

Sensitivity analyses performed on studies with a reported mean versus a calculated mean had small effects on the mean differences, for example the mean HbA1c level difference changed from 0.23% (0.1 – 0.4) to 0.12% (-0.1- 0.3). The overall level of evidence for the association of insomnia, insomnia symptoms, metabolic parameters and glycemic control by GRADE was low quality due to the studies being observational, with no reasons to upgrade.

Discussion
This systematic review with meta-analysis aimed to determine the prevalence of insomnia and insomnia symptoms and the association with metabolic parameters and glycemic control in people with T2D. First, we identified 78 studies and our meta-analysis revealed a prevalence of 39% (95%CI: 34-44) of insomnia and insomnia symptoms with a very high degree of heterogeneity, with an I² of 100%. Second, we showed that in unadjusted studies people with T2D and insomnia (symptoms) had a small, but significantly higher level of fasting glucose, HbA1c and total cholesterol and a higher BMI and systolic blood pressure, compared to people with T2D without insomnia (symptoms). Overall, these results show a high prevalence of insomnia and insomnia symptoms in the T2D population, which may be associated with deleterious glycemic control. Due to the cross-sectional nature of the papers included in the review (as is standard with GRADE) and the large heterogeneity for the prevalence estimates, the level of evidence by GRADE was downgraded to (very) low, so the findings should be interpreted as (very) uncertain and likely to change after future research.

The first point of discussion is the high degree of heterogeneity of the insomnia and insomnia symptoms prevalence estimate, which could not be accounted for by a range of sensitivity analyses. One of the main sources of the high heterogeneity seems to be the
presence of comorbidities, with people with comorbidities having a higher prevalence of insomnia (symptoms) as well as poorer metabolic parameters or poorer glycemic control (3).

Although we explored several potential sources of heterogeneity, not all possible sources of heterogeneity could be assessed in this meta-analysis, such as whether people were treated in primary, secondary or tertiary care, with the latter 2 groups representing those with many more comorbidities. Most of the studies included in the review did not provide information on the true source of people with T2D, which made it impossible to determine if they came from primary, secondary or tertiary care. Second, information regarding important possible confounding factors such as (diabetes) medication or other sleep problems were not reported on, and could be a source of heterogeneity. For example, obstructive sleep apnea, a highly prevalent comorbid condition in T2D, has been associated with increased HbA1c levels [60, 61] and is associated with insomnia and insomnia symptoms. Participants could be reporting insomnia (symptoms), which could be due to sleep apnea. Finally, information on certain mediating factors has not been reported in most studies, such as the comorbidities restless leg syndrome, depression, or hypoglycemia [51], which are prevalent comorbidities in people with T2D [62] and can affect sleep as well as glycemic control [63].

Second point of discussion is that the method of insomnia and insomnia symptoms measurement seems to play an important role in the high heterogeneity. Most methods define insomnia and insomnia symptoms in liberal terms, such as the PSQI [64, 65], which solely focus on the presence of nocturnal sleep disturbances e.g. sleep initiation or maintenance difficulties, whereas the more conservative definitions [4, 66] require additional functional impairment e.g. sleep dissatisfaction. In addition, as insomnia (symptoms) is a combination of symptoms, the heterogeneity might be due to differences in presence of certain symptoms, i.e. is a patient with high sleep latency but low daytime dysfunction the same as a patient with low sleep latency and high daytime dysfunction, while both are defined as having insomnia.
(symptoms). We chose not to define specific inclusion criteria for the insomnia and/or insomnia symptoms measure, resulting in included studies that used a wide range of measures to assess insomnia and insomnia symptoms. While in our meta-analysis most of the measures used liberal terms, this may suggest that our meta-analysis provided a pooled prevalence of 39% with a 95% CI of 34% - 44% for insomnia symptoms rather than insomnia. These estimates are slightly higher, compared to the prevalence estimates in the general population [3-5]. For future research insomnia and insomnia symptoms should be operationalized more clearly with less variation in measures of insomnia or a clear definition of insomnia symptoms and insomnia, for example by using 1 instrument to measure them, i.e. the Insomnia Severity Index [67].

Final point of discussion is, that the four studies that we could meta-analyze, that adjusted for confounders, showed no significant association between insomnia, insomnia symptoms and poor glycemic control, although a trend towards an increased risk was visible. However, in addition to real confounders, corrections also included mediators, such as neuropathy, depression and BMI. Data from strong methodological studies, correcting or stratifying for at least age, sex and diabetes duration are therefore necessary to draw firm conclusions regarding the association between insomnia, insomnia symptoms and metabolic parameters and glycemic control. Overall, this study adds to the previous meta-analysis of Lee et al. 2017[19], while we studied the prevalence of insomnia, insomnia symptoms as well as the association with metabolic parameters.

Possible mechanisms

The mechanisms underlying the association between insomnia, insomnia symptoms and glycemic control are complex and bidirectional. In other words, T2D can cause sleep disorders for example via nightly hypoglycemia, neuropathic pain and nocturia [68]. On the other hand, insomnia and insomnia symptoms can disturb glycemic control, via several
physiological pathways [69], including decreased brain glucose utilization, which leads to hyperglycemia. Second, via activation of the hypothalamic-pituitary-adrenal axis, which in turn promotes insulin resistance and hyperglycemia[69]. Third, via an alteration in appetite-regulating hormones, including ghrelin and leptin[69]. Fourth, via behavioral changes such as suboptimal self-care activities, with fatigue leading to impaired decision-making (e.g., unhealthy food choice and sedentary behaviors) [70] and less medication adherence [71], which in turn may lead to poorer glycemic control. Finally, concomitant sleep disorders to insomnia and insomnia symptoms, such as sleep fragmentation and intermittent hypoxia arising might trigger some of the changes in glycemic control. However, further research is required to explore whether improving insomnia and insomnia symptoms improves glycemic control as well as the underlying mechanisms.

**Implications**

Our results suggest that while insomnia and insomnia symptoms are common in T2D and associated with metabolic parameters and glycemic control, this may offer an opportunity for improvement of T2D treatment. Health care providers should be more aware of the magnitude and impact of insomnia and insomnia symptoms. Efforts towards educating people with T2D about the importance of sleep could be a first strategy to help patients to improve their glycemic control. Furthermore, an improvement of insomnia and insomnia symptoms by improvement of sleep hygiene, cognitive behavioral therapy or certain types of sleep medication will improve quality of life. In addition, improvement of insomnia symptoms could improve glycemic control, although not many studies have been conducted [72, 73]. To assess which treatment to improve insomnia symptoms is optimal and if glycemic control is improved, we need intervention studies in people with T2D.
Strengths and limitations

This is the first systematic review and meta-analysis to quantify and assess – when weighted for risk of bias – the prevalence of insomnia, insomnia symptoms and associated metabolic parameters and glycemic control (other than HbA1c levels) in adults with T2D. Strengths of this review include the methodological quality assessment of each individual study, the inclusion of 78 publications and inclusion of studies from all continents. However, some limitations must be taken into account. First, the grey literature was not captured, since unpublished reports and non-English or non-Dutch papers were not included. Second, most studies that investigated metabolic parameters and glycemic control were of low methodological quality, because they scored weak on the domains confounding and data-analysis. Third, there was little consensus regarding the choice of confounders and lack of adjustment may have overestimated the observed association between insomnia, insomnia symptoms and metabolic parameters and glycemic control. Fourth, there was a lack of a clear conceptualization of the term insomnia and insomnia symptoms and standardization of the measurement of these constructs, which results in a combined construct, possibly complicating the interpretation of our results. Finally, even after stratifying, the included prevalence studies were characterized by a high heterogeneity, with an $I^2$ of 100%.

In conclusion, the prevalence of symptoms of insomnia and insomnia is 39% (95%CI: 34-45) in the T2D population and may be associated with deleterious glycemic control. Future prospective studies should aim to explain the heterogeneity and account for confounding factors. Overall, these findings point towards insomnia and insomnia symptoms screening in care for adults with T2D, where treatment could help minimize its negative metabolic impact.
**Author contributions**

ADMK performed the literature search, study selection, data extraction, quality assessment and data synthesis, and drafted the manuscript, tables and figures. TD performed study selection, data extraction and data synthesis. JWB performed the quality assessment, provided support in design and execution of the review and meta-analyses and made major revisions to the manuscript. FP, MAB and AvS provided support in design and execution of the review and meta-analyses, and made major revisions to the manuscript. FR performed study selection and quality assessment, made major revisions to the manuscript, is the guarantor of this work and takes responsibility for the integrity of the work and analyses. This manuscript has not been submitted elsewhere and it is original.
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Table legends

Table 1. Characteristics of included studies in the systematic review (n=78), studies A t/m K.

Table 2. Characteristics of included studies in the systematic review (n=78), studies L t/m Z.

NR = not reported; PSQI = Pittsburgh Sleep Quality Index; DM = Diabetes Mellitus; OAD = Oral Antidiabetic Drugs; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders-IV; GLP = Glucagon-like peptide; AIS = Athens Insomnia Scale; NHANES = National Health and Nutrition Examination Survey; PHQ9 = Patient Health Questionnaire; CES-D = Center for Epidemiologic Studies Depression scale; MOS-SS = Medical Outcomes Study - Sleep Scale; UAE = United Arab Emirates; GDS = Geriatric Depression Scale; NA = not applicable.

Table 3. Methodological quality rating per domain per study.

Table 4. Prevalence, 95% confidence intervals (CI) and I² statistic overall and for several sensitivity analyses.

PSQI=Pittsburgh Sleep Quality Index

Table 5. Sensitivity analyses of the mean difference analyses in metabolic and glycemic parameters between type 2 diabetes patients with and without insomnia (symptoms).

MD=mean difference; CI=confidence interval. *For poor glycemic control it is not the mean difference but the Risk ratio. Bold=P<0.05
Figure legends

**Figure 1.** Flowchart of the search and selection process.

**Figure 2.** Funnel plot of the studies with prevalence estimates.

**Figure 3.** Forest plots of meta-analyses of mean differences and regression analysis of metabolic and glycemic parameters between people with T2D with and without insomnia symptoms. **A:** Poor glycemic control. **B:** HbA1c levels. **C:** Fasting plasma glucose levels. **D:** BMI. **E:** Odds Ratio for poor glycemic control. IV= inverse variance; Random= random effects model; CI= confidence interval.

**A:** Poor glycemic control: HbA1c levels >6.5 / 7.0% (>48 / 53 mmol/mol)

**D:** Odds Ratio for poor glycemic control: HbA1c levels >7 / 8.5% (>53 / 69 mmol/mol)

**Figure 4.** Forest plots of meta-analyses of mean differences and regression analysis of metabolic and glycemic parameters between people with T2D with and without insomnia symptoms. **A:** BMI. **B:** Triglyceride levels. **C:** HDL levels. **D:** LDL levels. **E:** Total cholesterol levels. **F:** Systolic blood pressure. **G:** Diastolic blood pressure. IV= inverse variance; Random= random effects model; CI= confidence interval.
| Author (year), reference | Setting - Country (period of analysis) | N (%men) - age±SD/IQR | Diabetes duration - Diabetes diagnosis - Diabetes treatment | Insomnia or insomnia symptoms measure - Distribution/cut-off | Metabolic parameters and glycemic control |
|-------------------------|-------------------------------------|-----------------------|---------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------|
| Abdelgadir (2009) [74]  | Outpatient clinic - Sudan (NR)      | 60 (67%) - 57y        | - 16±NR - Clinically diagnosed - NR                           | - MOS-SS - Insomnia yes/no                                | HbA1 FPG BMI Waist HDL LDL Chol SBP DBP |
| Al Tannir (2016) [75]   | General population - Saudi Arabia (2014-2015) | 161 DM (42% in general population) | - NR - Self-report - NR                                       | - Unknown questionnaire - Sleep disturbance yes or maybe/no | x |
| Aribas (2015) [41]      | Outpatient clinic - Turkey (NR)     | 78 (39%) - 50±9y      | - 6[2-12]y - Clinically diagnosed - NR                       | - PSQI - PSQI >5 = insomnia symptoms                       | x x x x x x x x |
| Bani-Issa (2017) [42]   | Community health care setting - UAE (NR) | 268 (38%) - 42±13y    | - 75% = 0-10 y - Clinically diagnosed - NR                   | - PSQI - PSQI ≥5 = insomnia symptoms                      | x |
| Bedi (2011) [76]        | Outpatient clinic - India (NR)      | 201 (50%) - 40-60y    | - NR - Clinically diagnosed - 100% oral medication           | - PSQI - PSQI >5 = insomnia symptoms                       | x |
| Bener (2010) [77]       | Health care center /primary care - Qatar (2009) | 847 (47%) - 59% = 40-59y | - NR - Clinically diagnosed - 100% oral medication           | - PSQI - PSQI >5 = insomnia symptoms                       | x |
| Bhaskar (2016) [78]     | Outpatient clinic - India (2015)    | 68 (NR) - 18-60y      | - NR - NR - NR                                                | - AIS - score >6 = insomnia                                | x |
| Bilge (2016) [18]       | Outpatient clinic - Turkey (2015)   | 40 (30%) - 48±10y     | - NR - NR - NR                                                | - PSQI - PSQI >5 = insomnia symptoms                       | x |
| Budhiraja (2011) [79]   | General population - USA (<2010)    | 207 (NR) - General population: 42±13y | - NR - Self-report - NR                                       | - DSM-IV insomnia criteria - yes/no                         | x |
| Celik (2012) [80]       | Tertiary care - Turkey (NR)         | 46 (52%) - 59±12y     | - NR - Clinically diagnosed - NR                              | - PSQI - PSQI >5 = insomnia symptoms                       | x |
| Study                  | Setting          | Country/Year       | Sample Size | Age | Sex | Follow-up  | BMI | Type of Sleep Disturbance | Insomnia Variable 1 | Self-report | Insomnia Variable 2 | PSQI                        |
|------------------------|------------------|--------------------|-------------|-----|-----|------------|-----|--------------------------|----------------------|-------------|---------------------|-----------------------------|
| Chang (2017) [32]      | Secondary care   | Taiwan (2013-2014) | 275 (0%)    | 58±8y | -   | ≥3 months  | -   | Clinically diagnosed     | PSQI >6 = insomnia symptoms | x           | x                   |                             |
| Cheng (2017) [55]      | Secondary care   | Taiwan (2014-2016) | 201 (52%)   | 70±6.9y | -   | -           | -   | Self-report + insulin    | PSQI >6 = insomnia symptoms | x           |                     |                             |
| Cho (2014) [81]        | Secondary care   | South-Korea (2011) | 614 (62%)   | 60±11y | -   | Clinically diagnosed | -   | Self-report              | PSQI >6 = insomnia symptoms | x           | x                   |                             |
| Colbay (2015) [58]     | Secondary care   | Turkey (2011)      | 53 (42%)    | 51±8y | -   | -           | -   | Clinically diagnosed     | PSQI >5 = insomnia symptoms | x           |                     |                             |
| Cuellar (2008) [30]    | Secondary care   | USA (2004-2005)    | 35 (44%)    | 61±11y | -   | -           | -   | Clinically diagnosed     | PSQI >6 = insomnia symptoms | x           |                     |                             |
| Cunha (2008) [34]      | Secondary care   | Brazil (2005)      | 50 (24%)    | -    | Median: 62 (range 44–79)y | -   | Clinically diagnosed     | PSQI >5 = insomnia symptoms | x           |                     |                             |
| El-Aghoury (2017) [82] | NR               | Egypt (NR)         | 46 (NR)     | 48±7y | -   | -           | -   | Clinically diagnosed     | NHANES sleep questionnaire | x           |                     |                             |

**Insomnia variable 1:**
- Self-report
- Insomnia = difficulty falling asleep, maintaining sleep, early morning waking and non-restorative sleep ≥3 times/week

**Insomnia variable 2:**
- PSQI
- PSQI ≥5 = insomnia symptoms
| Study                  | Setting                              | Country   | Year(s)          | Population Size | Age Range   | Methodology                                                                 |
|-----------------------|--------------------------------------|-----------|------------------|-----------------|-------------|-----------------------------------------------------------------------------|
| Ford (2015) [83]      | General population                    | USA       | 2002, 2007, 2012 | 2179 (43%)      | 45±7y       | Self-report, “During the past 12 months, have you regularly had insomnia or trouble sleeping?” |
| Fritschi 2017 [84]   | Veteran Hospital + flyers             | USA       | 2012-2013        | 80 (53%)        | 64±10y      | Actigraph: sleep efficiency, wake after sleep onset - not applicable       |
| Fukui (2012) [33]     | Outpatient clinic                     | Japan     | NR               | 296 (100%)      | 63±11y      | PSQI >5 = insomnia symptoms                                                |
| Gozashti (2016) [43]  | Outpatient clinic                     | Iran      | 2014             | 118 (76%)       | NR          | PSQI >5 = insomnia symptoms                                                |
| Grandner (2011) [31]  | General population                    | USA       | 2006             | 18888 DM (41%)  | ±53y        | Self-report, Sleep complaints: reporting difficulty falling asleep, staying asleep or sleeping too much ≥6 days over 2 weeks |
| Han (2002) [56]       | Hospital                              | Korea     | NR               | 82 (61%)        | 50±9y       | Self-report, Reporting difficulty falling asleep, awakening during the night, or/and early morning awakening for ≥2 months = insomnia |
| Hayashino (2013) [51] | Outpatient clinic                     | Japan     | 2009-2010        | 1513 (51%)      | 63±13y      | PSQI >5 = insomnia symptoms                                                |
| Hood (2014) [85]      | Endocrinology clinic                  | USA       | NR               | 194 (30%)       | 58±13y      | PSQI >5 = insomnia symptoms                                                |
| Authors (Year) | Setting | Diagnosis Criteria | Mean Age ± SD | History of Insomnia | Insomnia Variable 1: | Comment |
|---------------|---------|--------------------|---------------|---------------------|---------------------|---------|
| Huang (2017)  | Endocrinology department in hospital - China (2014-2015) | - Clinically diagnosed - Diet or OAD | 66±10y | - Clinical diagnosis | - PSQI >7 = insomnia symptoms | x x x x x x x |
| Hung (2013)   | Prevention Health Center - Taiwan (2002-2006) | - Clinically diagnosed - NA: newly diagnosed | 56±9y | - Clinical diagnosis | - PSQI >5 = insomnia symptoms | x |
| Hyyppa (1989) | Diabetics born and living in a particular district - Finland (NR) | - Clinically diagnosed - NR | 45-65y | - Clinical diagnosis | - Questionnaire on sleep habits 1. Sleep latency >50 min 2. Habitual insomnia 3. Difficulty maintaining sleep | x |
| Jain (2012)   | Diabetic clinic - USA (NR) | - Clinically diagnosed - 0% insulin | 6±50y | - Clinical diagnosis | - History of insomnia - yes/no | x x x |
| Johnson (2017)| Diabetic clinic - USA (NR) | - Clinically diagnosed - NR | 66±10y | - Clinical diagnosis | - Self-report - ‘Ever been told by a doctor or health professional that you have a sleep disorder?’ | x |
| Kara (2015)   | Outpatient clinic - Turkey (2013-2014) | - Clinically diagnosed - NR | 55±17y | - Clinical diagnosis | - PSQI >5 = insomnia symptoms | x |
| Kasenova (2017)| NR - Kazakhstan (NR) | - Clinically diagnosed - NR | 59±6y | - Clinical diagnosis | Insomnia variable 1: - PSQI - PSQI >5 = insomnia symptoms | x |
| Study (Year) | Study Type / Location | Participants | Follow-up | Insomnia Variable 1 | Insomnia Variable 2 |
|--------------|-----------------------|--------------|-----------|---------------------|---------------------|
| Katic (2015) [17] | Websurvey - USA (2013) | 405 DM (49%) - 56±10y | 11±9y - Self-report - NR | Self-report - At risk for insomnia: waking up unrefreshed, difficulty falling asleep, waking in the middle of the night or waking too early at least a few nights/week and affecting daily activities | |
| Keskin (2015) [35] | Family medicine clinics - Turkey (2014) | 575 (33%) - 57[50–64]y | 7[3–12]y - Clinically diagnosed - 66% OAD - 30% insulin | PSQI - PSQI ≥5 = insomnia symptoms | |
| Keskin (2016) [91] | Outpatient clinic - Turkey (2014) | 208 (29%) - Adult group: 53±9y; Geriatric group: 71±5y | NR - Clinically diagnosed - NR | PSQI - PSQI ≥5 = insomnia symptoms | |
| Khosravan (2015) [92] | Diabetes Clinic - Iran (2012) | 1600 (NR) - 35–70y | NR - Clinically diagnosed - NR | PSQI - PSQI >5 = insomnia symptoms | |
| Knutson (2011) [93] | General population - USA (2003–2006) | 40 DM (30%) - 46±4y | NR - Clinically diagnosed - NR | PSQI + actigraph - Insomnia: not falling asleep <30 min >3 times/week or waking up in the middle of the night >3times/week + sleep efficiency <80% | |
| Knutson (2006) [6] | Tertiary care - USA (NR) | 161 (26%) - 57±13y | 11±9y - Clinically diagnosed - 48% insulin or in combination with OAD | PSQI - PSQI >5 = insomnia symptoms | |
| Study | Setting | Country | Participants | Age | Sex | Diagnosis | Outcome measure | Comments |
|-------|---------|---------|--------------|-----|-----|-----------|----------------|----------|
| Koyanagi (2014) | General population | Finland, Poland, Spain (2011-2012), China, Ghana, India, Mexico, Russia, South Africa (2007-2010) | 3285 DM (NR) | Median: 60-65y | NR | Self-report | - Sleep problems: severe or extreme problems with falling asleep, waking up frequently during the night or waking up too early in the morning the last 30 days | x |
| Lecube (2016) | Outpatient clinic | Spain (2013-2014) | 135 (44%) | >5y | Clinically diagnosed | PSQI >5 = insomnia symptoms | x |
| Lopes (2005) | Outpatient clinic | Brazil (NR) | 100 (27%) | 10±8y | Clinically diagnosed | PSQI ≥6 = insomnia symptoms | x |
| Lou (2012) | General population | China (2008) | 954 DM (43%) | 49±13y | NR | Clinically diagnosed | Self-report | x |
| Lou (2015) | Health centers | China (NR) | 114 (43%) | 64±10y | NR | Clinically diagnosed | Self-report | x |
| Luyster (2011) | NR | USA (NR) | 300 (43%) | 64±10y | NR | Clinically diagnosed | Insomnia: 35% | X |
| Manodpitipong (2017) | Hospital | Thailand (2014) | 189 (40%) | Unemployed: 65±8 Day work: 53±9 | Unemployed: 14±10 Day work: 9±8 | Clinically diagnosed | PSQI ≥ 5 = insomnia symptoms | X |
| Mahmood (2013) | Diabetes clinic | Ireland (NR) | 114 (64%) | Healthy: 64±11 Insomnia: 66±10 | NR | Clinically diagnosed | PSQI ≥ 6 = insomnia symptoms | X |

**Table 2.** Characteristics of included studies in the systematic review (n=78), studies L t/m Z.
| Study                | Type of care          | Country (Years)                  | Sample Size | Mean Age | Follow-up | Diagnosis Method             | PSQI Category | Symptom Criteria | Results |
|----------------------|-----------------------|----------------------------------|-------------|----------|-----------|------------------------------|---------------|------------------|---------|
| Medeiros (2013) [98] | Outpatient clinic     | Brazil (NR)                      | 110 (35%)   | 58±11y   | NR        | Clinically diagnosed         | PSQI >6       | insomnia symptoms | x       |
| Meng (2015) [46]    | Hospital              | China (2014-2015)                | 332 (57%)   | 59±9y    | 7±7y      | Clinically diagnosed         | PSQI ≥7       | insomnia symptoms | x x x x x |
| Narisawa (2017) [99]| Outpatient clinic     | Japan (2014)                     | 622 (76%)   | 57±10y   | 10% OAD   | 27% insulin                  | PSQI >5.5     | insomnia symptoms | x       |
| Nefs (2015) [37]    | Websurvey             | Netherlands (2011)               | 361 (54%)   | 62±9     | 11±8y    | Self-report 44% OAD 49% insulin | PSQI >5       | insomnia symptoms | x       |
| Osonoi (2015) [47]  | Outpatient clinic     | Japan (2013-2014)                | 724 (63%)   | 58±9y    | 10±7y    | Clinically diagnosed 86% OAD/insulin/both | PSQI ≥9      | insomnia symptoms | x x x x x |
| Rajendran (2012) [100]| Tertiary care        | India (2010-2011)                | 120 (54%)   | 54±9y    | 7±6y     | Clinically diagnosed 100% OAD/insulin/both | PSQI ≥5      | insomnia symptoms | x       |
| Ramos (2015) [101]  | Registry black       | USA (NR)                         | 612 (NR)    | 62±14y   | NR        | Clinically diagnosed         | Unspecified   | insomnia symptoms | yes/no  |
| Ramtahal (2015) [102]| Outpatient clinics   | Trinidad and Tobago (2013)       | 291 (33%)   | 59±11y   | 10 [6–19]y | Clinically diagnosed 30% OAD 17% insulin 47% both | NHANES sleep questionaire | Insomnia = patients answered 'often' or 'almost always' to sleep related questions | x       |
| Study                          | Setting                  | Location/Year          | Sample Size | Mean Age (SD) | Sex Distribution | Sleep History Criteria                                                                                                                                                                                                 | Insomnia Symptoms |
|-------------------------------|--------------------------|------------------------|-------------|---------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Sakamoto (2018) [103]         | Hospital                 | Japan (2014-2016)      | 3294        | 65[55-72]y    | 61%              | - 11[5-17]y Clinically diagnosed 60% OAD 29% insulin/GLP - PSQI >5 = insomnia symptoms                                                                                                                                      | x                |
| Seligowski (2013) [104]       | Primary care             | USA (NR)               | 86          | 62±8y         | 97%              | - NR Clinically diagnosed 100% insulin or OAD - PSQI >5 = insomnia symptoms                                                                                                                                                | x                |
| Shamshirgaran (2017) [38]     | Diabetes clinic          | Iran (2013-2014)       | 256         | 54±9y         | 29%              | - NR Clinically diagnosed 58% OAD 29% OAD + insulin - PSQI >5 = insomnia symptoms                                                                                                                                             | x                |
| Shim (2011) [105]             | Outpatient clinic        | Korea (2008)           | 784         | 54±12y        | 50%              | - 9±7y Clinically diagnosed 0% insulin - PSQI >5 = insomnia symptoms                                                                                                                                                    | x                |
| Skomro (2001) [106]           | Outpatient clinic        | Canada (NR)            | 58          | 57±15y        | 50%              | - 10y Clinically diagnosed - NR - Interview Difficulty with sleep onset or maintenance ≥3 times/week                                                                                                                       | x                |
| Sokwalla (2017) [57]          | Outpatient clinic        | Kenya (2012)           | 228         | 57±12y        | 42%              | - 10±8y Clinically diagnosed 36% OAD 13% insulin 50% insulin + OAD - PSQI >5 = insomnia symptoms                                                                                                                            | x                |
| Song (2013) [107]             | Outpatient clinic        | China (2012)           | 140         | 57±14y        | 59%              | - 20% = >10y Clinically diagnosed 100% insulin - PSQI >5 = insomnia symptoms                                                                                                                                             | x                |
| Sridhar (1994) [108]          | Diabetes centre          | India (NR)             | 184         | 46±NR         | 82%              | - Normal sleep: 5±6y Abnormal sleep: 4±5y Clinically diagnosed - NR - Self-report - **Variable 1**: difficulty falling asleep ≥3 times/week for ≥2 weeks - **Variable 2**: difficulty in maintaining sleep: interrupted sleep ≥2/night and problems going back to sleep | x                |
| Study (Year) | Setting | Country | Sample Size | Age | Follow-up | Diagnosis | Sleep Assessment | Insomnia Criteria | Notes |
|-------------|---------|---------|-------------|-----|-----------|------------|------------------|------------------|-------|
| Sudore (2012) [109] | Diabetes registry | USA (2005–2006) | - 13171 (52%) | - 10±8y | - Clinically diagnosed | - PHQ9 | Sleep disturbance= almost every day difficulty initiating or maintaining sleep or excessive sleep | x | |
| Tang (2014) [40] | Hospital | China (2013-2014) | - 551 (55%) | - 9±8y | - Clinically diagnosed | - PSQI | PSQI >5 = insomnia symptoms | x | |
| Tanjani (2015) [110] | General population | Iran (2012) | - 297 DM (41%) | - NR | - Self-report | - GDS | Insomnia: yes/no | x | |
| Telford (2018) [48] | Primary care clinic | USA (NR) | - 281 (52%) | - NR | - Clinically diagnosed | - PSQI | PSQI >5 = insomnia symptoms | x | |
| Thongsai (2013) [111] | Outpatient clinic | Thailand (2013) | - 209 (40%) | - 62±9y | - Clinically diagnosed | - CES-D questionnaire | Difficulty sleeping (never, sometimes, quite often, always) | x | |
| Torella (2015) [59] | Diabetes clinic | Spain (2011-2013) | - 145 (51%) | - 14±10y | - Clinically diagnosed | - PSQI | PSQI >5 = insomnia symptoms | x | |
| Trento (2008) [112] | NR | Italy (NR) | - 47 (68%) | - 61±5y | - Clinically diagnosed | - Actigraphy: sleep efficiency + sleep latency | NA | x | |
| Tsai (2012) [39] | Outpatient clinic | Taiwan (2009) | - 46 (61%) | - >1y | - Clinically diagnosed | - PSQI | PSQI >8 = insomnia symptoms | x | |
| Tsujimura (2009) [113] | NR | Japan (NR) | - 19 (58%) | - 7 (1-20)y | - Clinically diagnosed | - Actigraphy: sleep efficiency + wake after sleep onset | NA | x | |
| Vernon (2008) [114] | Clinical centers | North America, Australia, Germany, Hungary, Poland, | - 388 (±58) | - ±11y | - Clinically diagnosed | - MOS-SS questionnaire | MOS score >52.5 = sleep disturbance | x | |
| Study                  | Setting                      | Country/Region          | Sample Size | Age | Duration | Diagnosed Year | Insulin Use | PSQI/Clinical Diagnosed | Sleep Disturbance |
|-----------------------|------------------------------|-------------------------|-------------|-----|----------|----------------|-------------|------------------------|-------------------|
| Wei (2017) [50]       | Outpatient clinic            | South Africa, United Kingdom | 206 (50%)   | 60±63y | 2015     | Newly diagnosed | WHO 1999    | 0% OAD                | PSQI >5 = insomnia |
| Yagi (2011) [115]     | Outpatient clinic            | Japan (baseline 1996-1998) | 270 (55%)   | 67±10y | 1996-1998 | Clinically diagnosed | 41% insulin | PSQI >5.5 = insomnia symptoms |                |
| Zelman (2006) [116]   | Tertiary care                | USA (2003)               | 255 (45%)   | 61±13y | 2003     | Clinically diagnosed | NR          | MOS-SS                | No, some or sleep problems |
| Zhang (2016) [28]     | T2D registry                 | China (2012)             | 944 (39%)   | 64±10y | 2012     | Clinically diagnosed | 12% insulin | PSQI ≥7 = insomnia symptoms |                |
| Zhu (2014) [52]       | Hospital                     | China (2013-2014)        | 206 (66%)   | 57±11y | 2013-2014 | Clinically diagnosed | 60% insulin | PSQI ≥8 = insomnia symptoms |                |
| Zhu (2018) [117]      | Convenience sample           | USA (2013-2014)          | 90 (48%)    | 57±8y  | 2013-2014 | Self-report    | NR          | PROMIS                | Sleep disturbance = perceived difficulties in getting or staying asleep |

*PSQI: Pittsburgh Sleep Quality Index, OAD: Oral Antidiabetic Drugs, NR: Not reported, T2D: Type 2 Diabetes, MOS-SS: MOS Sleep Scale, PROMIS: PatientReported Outcomes Measurement Information System.*
| Author, year (ref) | Prevalence outcome (P) | Metabolic/glycemic (M) | SD | BL | RSB | RWD | CF | DC | DA | RP | OVERALL |
|-------------------|------------------------|------------------------|----|----|-----|-----|----|----|----|----|--------|
| Abdelgadir 2009 [74] | P                      | M                      | NR | W  | NR  | NR  | S  | NR | M  |     | moderate          |
| Al Tannir 2016 [75] | P                      | M                      | NR | M  | NR  | W  | NR | S  |     |     | moderate          |
| Aribas 2015 [41]   | P                      | M                      | NR | W  | NR  | S  | NR | S  |     |     | moderate          |
| Aribas 2015        | M                      | M                      | NR | W  | NR  | W  | M  | S  |     | weak             |
| Bani-Issa 2017 [42] | P                      | M                      | NR | S  | NR  | S  | NR | S  |     |     | strong           |
| Bani-Issa 2017     | M                      | M                      | NR | S  | NR  | W  | W  | M  |     | weak             |
| Bedi 2011 [76]     | P                      | M                      | NR | W  | NR  | S  | NR | S  |     |     | moderate          |
| Bener 2010 [77]    | P                      | M                      | NR | M  | NR  | S  | NR | S  |     |     | strong           |
| Bhaskar 2016 [78]  | P                      | M                      | NR | S  | NR  | M  | S  |     |     | strong           |
| Bilge 2016 [18]    | P                      | M                      | NR | W  | NR  | S  | NR | S  |     |     | moderate          |
| Budhiraja 2011 [79] | P                      | M                      | NR | S  | NR  | S  | NR | S  |     |     | strong           |
| Celik 2012 [80]    | P                      | M                      | NR | W  | NR  | S  | NR | S  |     |     | moderate          |
| Chang 2017 [32]    | P                      | M                      | NR | W  | NR  | S  | NR | S  |     |     | moderate          |
| Cheng 2017 [55]    | P                      | M                      | NR | W  | NR  | W  | NR | S  |     | weak            |
| Cheng 2017         | M                      | M                      | NR | W  | W  | M  | S  |     |     | weak             |
| Cho 2014 [81]      | P                      | M                      | NR | M  | NR  | S  | NR | S  |     |     | strong           |
| Colbay 2015 [58]   | P                      | M                      | NR | M  | NR  | M  | NR | S  |     | moderate         |
| Colbay 2015        | M                      | M                      | NR | M  | NR  | W  | S  | M  |     | moderate         |
| Cuellar 2008 [30]  | P                      | M                      | NR | W  | NR  | S  | NR | S  |     |     | moderate          |
| Cunha 2008 [34]    | P                      | M                      | NR | W  | NR  | S  | NR | S  |     |     | moderate          |
| Cunha 2008         | M                      | M                      | NR | W  | NR  | W  | W  | W  |     | weak            |
| El Aghoury 2017 [82]| P                      | M                      | NR | W  | NR  | S  | NR | S  |     |     | moderate          |
| Ford 2015 [83]     | P                      | M                      | NR | S  | NR  | W  | NR | S  |     |     | moderate          |
| Fritschi 2017 [84] | M                      | M                      | NR | M  | NR  | W  | M  | M  |     | weak            |
| Fukui [33]         | P                      | M                      | NR | W  | NR  | S  | NR | M  |     |     | moderate          |
| Gozashti 2016 [43] | P                      | M                      | NR | W  | NR  | S  | NR | S  |     |     | moderate          |
| Gozashti 2016      | M                      | M                      | NR | W  | NR  | W  | S  | S  |     | weak            |
| Study                          | Direction | M | NR | S | NR | W | NR | S | Effect Size |
|-------------------------------|-----------|---|----|---|----|----|----|---|-------------|
| Grandner 2011 [31]           | P         | M | NR | S | NR | W | NR | S | moderate    |
| Han 2002 [56]                | P         | M | NR | W | NR | W | NR | S | weak        |
| Han 2002                     | M         | M | NR | W | NR | W | M  | M | weak        |
| Hayashino 2013 [51]          | P         | M | NR | M | NR | S | NR | S | strong      |
| Hayashino 2013               | M         | M | NR | M | NR | W | W | M | weak        |
| Hood 2014 [85]               | P         | M | NR | M | NR | S | NR | S | strong      |
| Huang 2017 [44]              | P         | M | NR | W | NR | S | NR | S | moderate    |
| Huang 2017                   | M         | M | NR | W | NR | W | M  | S | weak        |
| Hayashino 1989 [87]          | P         | M | NR | M | NR | S | NR | S | strong      |
| Jain 2012 [45]               | P         | M | NR | M | NR | W | NR | M | moderate    |
| Jain 2012                    | M         | M | NR | M | NR | W | W | M | weak        |
| Johnson 2017                 | P         | M | NR | S | NR | W | NR | M | moderate    |
| Kara 2015 [89]               | P         | M | NR | M | NR | S | NR | S | strong      |
| Kasenova 2017 [90]           | P         | M | NR | W | NR | M | NR | S | moderate    |
| Katic 2015 [17]              | P         | M | NR | M | NR | M | NR | S | moderate    |
| Keskin 2016 [91]             | P         | M | NR | S | NR | S | NR | S | strong      |
| Keskin 2016                  | M         | M | NR | S | NR | M | M  | S | strong      |
| Keskin 2015 [35]             | P         | M | NR | S | NR | S | NR | S | strong      |
| Keskin 2015                  | M         | M | NR | S | NR | W | S  | M | moderate    |
| Khosravan 2015 [92]          | P         | M | NR | M | NR | S | NR | S | moderate    |
| Knutson 2006 [6]             | P         | M | NR | S | NR | S | NR | S | strong      |
| Knutson 2006                 | M         | M | NR | S | NR | M | S  | S | strong      |
| Knutson 2011 [93]            | P         | M | NR | M | NR | S | NR | S | strong      |
| Knutson 2011                 | M         | M | NR | M | NR | M | S  | S | strong      |
| Koyagani 2014 [94]           | P         | M | NR | S | NR | W | NR | S | moderate    |
| Lecube 2016 [53]             | P         | M | NR | W | NR | S | NR | S | moderate    |
| Lecube 2016                  | M         | M | NR | W | NR | W | W  | W | weak        |
| Lopes 2005 [54]              | P         | M | NR | M | NR | S | NR | S | strong      |
| Lopes 2005                   | M         | M | NR | M | NR | W | W  | W | weak        |
| Lou 2012 [95]                | P         | M | NR | M | NR | M | NR | S | moderate    |
| Study Reference | Type | M | NR | S | NR | S | NR | S | Strength |
|-----------------|------|---|----|---|----|---|----|---|----------|
| Lou 2015 [36]   | P    | M | NR | S | NR | S | NR | S | strong   |
| Lou 2015        | M    | M | NR | S | NR | W | S | M | moderate |
| Luyster 2011 [96] | P   | M | NR | W | NR | S | NR | S | moderate |
| Mahmood 2013 [49] | P   | M | NR | S | NR | S | NR | S | strong   |
| Mahmood 2013    | M    | M | NR | S | NR | M | W | S | moderate |
| Manodpitipong 2017 [97] | M | M | NR | M | NR | S | S | S | strong   |
| Medeiros 2013 [98] | P   | M | NR | S | NR | S | NR | S | strong   |
| Meng 2015 [46]  | P    | M | NR | W | NR | S | NR | S | moderate |
| Meng 2015       | M    | M | NR | W | NR | W | M | M | weak     |
| Narisawa 2017 [99] | P  | M | NR | S | NR | S | NR | S | strong   |
| Nefs 2015 [37]  | P    | M | NR | M | NR | S | NR | S | strong   |
| Nefs 2015       | M    | M | NR | M | NR | W | W | M | weak     |
| Osonoi 2015 [47] | P   | M | NR | M | NR | S | NR | S | strong   |
| Osonoi 2015     | M    | M | NR | M | NR | M | M | S | weak     |
| Rajendran 2012 [100] | P | M | NR | W | NR | S | NR | S | moderate |
| Ramos 2015 [101] | P    | M | NR | W | NR | S | NR | S | moderate |
| Ramtahal 2015 [102] | P  | M | NR | S | NR | S | NR | S | strong   |
| Sakamoto 2018 [103] | P  | M | NR | S | NR | S | NR | S | strong   |
| Seligowski 2013 [104] | M | M | NR | M | NR | W | W | M | weak     |
| Shamshirgaran 2017 [38] | P | M | NR | W | NR | S | NR | S | moderate |
| Shamshirgaran 2017 | M   | M | NR | W | NR | W | W | M | weak     |
| Shim 2011 [105]  | P    | M | NR | M | NR | S | NR | S | strong   |
| Skomro 2001 [106] | P    | M | NR | W | NR | S | NR | M | moderate |
| Sokwalla 2017 [57] | P   | M | NR | M | NR | S | NR | S | strong   |
| Sokwalla 2017    | M    | M | NR | M | NR | W | S | M | moderate |
| Song 2013 [107]  | P    | M | NR | W | NR | S | NR | S | moderate |
| Sridhar 1994 [108] | P   | M | NR | W | NR | S | NR | M | moderate |
| Sudore 2012 [109] | P    | M | NR | S | NR | M | NR | S | strong   |
| Tang 2014 [40]   | P    | M | NR | M | NR | S | NR | S | strong   |
| Tang 2014        | M    | M | NR | M | NR | S | M | S | strong   |
| Tanjani 2015 [110] | P  | M | NR | W | NR | W | NR | M | weak     |
| Study                  | Type | M | NR | W | NR | S | NR | S | Mod  |
|-----------------------|------|---|----|---|----|---|----|---|------|
| Telford 2018 [48]     | P    | M | NR | W | NR | S | NR | S | moderate |
| Telford 2018          | M    | M | NR | W | NR | M | M | S | S | moderate |
| Thongsai 2013 [111]   | P    | M | NR | W | NR | W | NR | S | weak |
| Torrella 2015 [59]    | P    | M | NR | W | NR | S | NR | S | moderate |
| Torrella 2015         | M    | M | NR | W | NR | M | M | S | S | moderate |
| Trento 2015 [112]     | M    | M | NR | W | NR | W | W | M | S | weak |
| Tsai 2012 [39]        | P    | M | NR | M | NR | S | NR | S | strong |
| Tsai 2012             | M    | M | NR | M | NR | M | M | S | S | moderate |
| Tsujimura 2009 [113]  | M    | M | NR | W | NR | W | M | M | weak |
| Vernon 2008 [114]     | P    | M | NR | W | NR | S | NR | S | moderate |
| Wei 2017              | M    | M | NR | W | NR | W | S | M | S | weak |
| Yagi 2011 [115]       | P    | M | NR | M | NR | S | NR | S | strong |
| Zelman 2006 [116]     | P    | M | NR | W | NR | S | NR | M | moderate |
| Zhang 2016 [28]       | P    | M | NR | M | NR | S | NR | S | strong |
| Zhu 2014 [52]         | P    | M | NR | M | NR | S | NR | S | strong |
| Zhu 2014              | M    | M | NR | M | NR | S | S | S | strong |
| Zhu 2018 [117]        | M    | M | NR | W | NR | W | W | M | M | weak |
Table 4

|                          | Number of prevalence estimates | Prevalence (%) | 95% CI   | I² (p-value) |
|--------------------------|---------------------------------|----------------|----------|--------------|
| Overall                  | 84                              | 39             | 34 - 44  | 100% (p<0.00001) |
| Sensitivity analyses     |                                 |                |          |              |
| Age <60 years            | 56                              | 37             | 31 – 44  | 100% (p<0.00001) |
| Age ≥60 years            | 28                              | 44             | 36 – 55  |              |
| Year of analysis <2010   | 31                              | 35             | 31 – 40  | 100% (p<0.00001) |
| Year of analysis ≥2010   | 53                              | 42             | 32 – 54  |              |
| PSQI                     | 48                              | 46             | 35 – 62  | 100% (p<0.00001) |
| Other than PSQI          | 36                              | 31             | 27 – 36  |              |
| Strong quality           | 34                              | 39             | 33 – 47  | 100% (p<0.00001) |
| Moderate quality         | 46                              | 39             | 32 – 48  | 100% (p<0.00001) |
| Weak quality             | 4                               | 44             | 29 – 68  | 99% (p<0.00001)  |
| With comorbidities       | 9                               | 60             | 46 – 79  | 99% (p<0.00001)  |
| No comorbidities         | 74                              | 37             | 33 – 43  | 100% (p<0.00001)  |
| N < 100                  | 22                              | 40             | 25 – 64  | 100% (p<0.00001)  |
| N = 100 – 199            | 21                              | 55             | 46 – 67  | 99% (p<0.00001)  |
| N = 200 – 299            | 14                              | 46             | 38 – 55  | 99% (p<0.00001)  |
| N = 300 – 999            | 18                              | 32             | 22 – 47  | 100% (p<0.00001)  |
| N > 1000                 | 9                               | 24             | 17 – 34  | 100% (p<0.00001)  |
| Studies with no comorbidities, with PSQI, of strong quality and with sample size >200 | 17                              | 39             | 30 - 51   | 100% (p<0.00001)  |
Table 5

| Metabolic parameter          | Type of analysis                        | Number of studies (left) | MD*   | 95% CI     | I² (p-value) |
|------------------------------|-----------------------------------------|--------------------------|-------|------------|--------------|
| HbA1c levels (%)             | Overall                                  | 14                       | 0.23  | 0.1 – 0.4  | 76% (p<0.00001) |
|                              | Excluding studies with calculated mean  | 12                       | 0.12  | -0.1 – 0.3 | 68% (p=0.0006) |
|                              | Excluding studies with weak quality      | 5                        | 0.49  | 0.2 – 0.8  | 77% (p=0.002)  |
| Poor glycemic control (risk ratio) | Overall                              | 7                        | 1.18  | 1.0 – 1.4  | 73% (p=0.001)  |
|                              | Excluding studies with weak quality      | 4                        | 1.22  | 1.1 – 1.3  | 30% (p=0.23)  |
|                              | Excluding outlier                       | 6                        | 1.22  | 1.1 – 1.3  | 0% (p=0.44)  |
| Fasting glucose levels (mmol/l) | Overall                             | 11                       | 0.40  | 0.2 – 0.7  | 57% (p=0.01)  |
|                              | Excluding studies with calculated mean  | 8                        | 0.33  | 0 – 0.7    | 50% (p=0.05)  |
|                              | Excluding studies with weak quality      | 4                        | 0.64  | 0.3 – 1.0  | 50% (p=0.11)  |
| BMI (kg/m²)                  | Overall                                  | 14                       | 0.38  | 0.1 – 0.7  | 47% (p=0.03)  |
|                              | Excluding studies with calculated mean  | 12                       | 0.34  | 0.1 – 0.6  | 5% (p=0.40)   |
|                              | Excluding studies with weak quality      | 4                        | 0.63  | -0.01 – 1.3 | 67% (p=0.01) |
| Triglycerides (mmol/l)       | Overall                                  | 8                        | 0.16  | -0.1 – 0.5 | 91% (p<0.00001) |
|                              | Excluding studies with calculated mean  | 4                        | 0.02  | -0.4 – 0.5 | 68% (p=0.02)  |
|                              | Excluding studies with weak quality      | 4                        | 0.33  | -0.04 – 0.7 | 91% (p<0.00001) |
|                              | Excluding outlier                       | 7                        | 0.26  | -0.02 – 0.5 | 90% (p<0.00001) |
| HDL levels (mmol/l)          | Overall                                  | 7                        | 0.02  | -0.01 – 0.1 | 0% (p=0.43)  |
|                              | Excluding studies with calculated mean  | 6                        | 0.02  | -0.01 – 0.1 | 10% (p=0.35)  |
|                              | Excluding studies with weak quality      | 3                        | 0.05  | 0 – 0.1    | 0% (p=0.96)  |
| LDL levels (mmol/l)          | Overall                                  | 7                        | 0.05  | -0.1 – 0.2 | 48% (p=0.08)  |
|                              | Excluding studies with calculated mean  | 6                        | 0.09  | -0.03 – 0.2 | 28% (p=0.23)  |
|                              | Excluding studies with weak quality      | 3                        | 0.18  | 0.04 – 0.3 | 0% (p=0.64)  |
| Total cholesterol levels (mmol/l) | Overall                             | 5                        | 0.15  | 0.03 – 0.3 | 0% (p=0.43)  |
|                              | Excluding studies with weak quality      | 2                        | 0.21  | -0.01 – 0.4 | 42% (p=0.19)  |
| Systolic blood pressure (mmHg) | Overall                             | 9                        | 2.69  | 0.1 – 5.3  | 60% (p=0.01)  |
|                              | Excluding studies with calculated mean  | 8                        | 3.14  | 0.3 – 6.0  | 62% (p=0.01)  |
|                              | Excluding studies with weak quality      | 5                        | 4.42  | 0.1 – 8.7  | 72% (p=0.006)  |
|                              | Overall                                  | 8                        | 1.13  | -0.1 – 2.3 | 25% (p=0.23)  |
| Diastolic blood pressure (mmHg) | Excluding studies with calculated mean | 7 | 1.00 | -0.5 – 2.5 | 34% (p=0.27) |
|---------------------------------|---------------------------------------|---|------|----------|--------------|
| Excluding studies with weak quality | 4 | 1.28 | -1.1 – 3.6 | 54% (p=0.09) |
Figure 1

LITERATURE SEARCH N=16311
05-03-2018
Pubmed (N=5241)
Embase (N=11070)

Exclusion duplicates
N=4902

Screening title/abstract
N=11329

Exclusion based on
title/abstract
N=11105

Full text read
N=224

Exclusion after full text reading
N=147

Inclusion bibliography check
N=1

Final inclusion
N=78

Studies with metabolic outcomes
N=35

Studies with prevalence estimates
N=71 with 84 data estimates

Mean difference meta-analysis
N=25

Regression meta-analysis
N=4
Figure 2

Funnel plot (18-12-2018)
Figure 3

A:

| Study or Subgroup | Risk Ratio | Risk Ratio |
|-------------------|------------|------------|
|                   | IV, Random, 95% CI | IV, Random, 95% CI |
| Curns 2005        | 0.64 [0.24, 1.21]  | 1.18 (1.02, 1.36) |
| Keskin 2015       | 1.16 (1.02, 1.37)  | 1.09 (0.93, 1.15) |
| Liu 2015          | 1.33 (1.04, 1.71)  | 1.20 (0.98, 1.45) |
| Neelin 2015       | 1.27 (1.05, 1.54)  | 1.87 (1.41, 2.41) |
| Shamshiripan 2017 | 1.20 (0.98, 1.45)  | 1.27 (1.05, 1.54) |
| Tang 2014         | 1.27 (1.05, 1.54)  | 1.87 (1.41, 2.41) |
| Tsai 2012         | 1.87 (1.41, 2.41)  | 1.27 (1.05, 1.54) |
| **Total (95% CI)**| **1.18 [1.02, 1.36]** |

Total events

Heterogeneity: Tau² = 0.02; Chisq = 22.48, df = 6 (P = 0.001), I² = 73%.
Test for overall effect: Z = 2.19 (P = 0.03)

Favours [poor sleep]  Favours [good sleep]

B:

| Study or Subgroup | Mean Difference | Mean Difference |
|-------------------|-----------------|-----------------|
|                   | IV, Random, 95% CI | IV, Random, 95% CI |
| Arbab 2015        | -0.40 [-0.55, 0.25] | -0.40 [-0.55, 0.25] |
| Besharat 2017     | 0.04 [0.33, 0.41]  | 0.04 [0.33, 0.41]  |
| Goebel 2016       | 0.20 [0.29, 0.09]  | 0.20 [0.29, 0.09]  |
| Hayashino 2013    | 0.00 [0.13, 0.13]  | 0.00 [0.13, 0.13]  |
| Huang 2017        | 0.30 [0.06, 0.54]  | 0.30 [0.06, 0.54]  |
| Jain 2012         | -0.40 [-0.66, 0.06] | -0.40 [-0.66, 0.06] |
| Kesten 2015       | 0.56 [0.33, 0.79]  | 0.56 [0.33, 0.79]  |
| Meng 2015         | -0.15 [-0.52, 0.23] | -0.15 [-0.52, 0.23] |
| Nefed 2015        | 0.20 [0.07, 0.43]  | 0.20 [0.07, 0.43]  |
| Osmon 2015        | 0.20 [0.00, 0.40]  | 0.20 [0.00, 0.40]  |
| Tisba 2010        | 0.10 [0.32, 0.52]  | 0.10 [0.32, 0.52]  |
| Watan 2011        | 0.60 [0.17, 1.03]  | 0.60 [0.17, 1.03]  |
| Wei 2017          | 0.54 [0.26, 0.81]  | 0.54 [0.26, 0.81]  |
| Zhu 2014          | 1.23 [0.60, 1.76]  | 1.23 [0.60, 1.76]  |
| **Total (95% CI)**| **0.23 [0.06, 0.40]** |

Heterogeneity: Tau² = 0.07; Chisq = 54.26, df = 13 (P < 0.00001), I² = 76%.
Test for overall effect: Z = 2.64 (P = 0.008)

Favours [poor]  Favours [good]

C:

| Study or Subgroup | Mean Difference | Mean Difference |
|-------------------|-----------------|-----------------|
|                   | IV, Random, 95% CI | IV, Random, 95% CI |
| Arbab 2015        | 0.44 [-1.22, 2.09] | -0.44 [-1.22, 2.09] |
| Huang 2017        | 0.70 [0.15, 1.24]  | 0.70 [0.15, 1.24]  |
| Jain 2012         | 0.15 [-0.66, 0.96] | 0.15 [-0.66, 0.96] |
| Keskin 2015       | 0.80 [0.47, 1.33]  | 0.80 [0.47, 1.33]  |
| Laccab 2010       | 0.89 [0.14, 1.53]  | 0.89 [0.14, 1.53]  |
| Lopes 2005        | -0.04 [-1.00, 0.70] | -0.04 [-1.00, 0.70] |
| Meng 2015         | -0.13 [-0.52, 0.26] | -0.13 [-0.52, 0.26] |
| Osmon 2015        | 0.22 [0.00, 0.44]  | 0.22 [0.00, 0.44]  |
| Watan Mahmood 2013| 0.80 [0.14, 1.34]  | 0.80 [0.14, 1.34]  |
| Wei 2017          | 0.20 [-0.01, 0.41] | 0.20 [-0.01, 0.41] |
| Zhu 2014          | 0.20 [0.32, 1.30]  | 0.20 [0.32, 1.30]  |
| **Total (95% CI)**| **0.40 [0.15, 0.65]** |

Heterogeneity: Tau² = 0.06; Chisq = 23.05, df = 10 (P = 0.01), I² = 57%.
Test for overall effect: Z = 3.10 (P = 0.002)

Favours [poor]  Favours [good]
| Study or Subgroup | log(Odds Ratio) | SE | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|------------------|----------------|----|--------|-------------------|-------------------|
| Tang 2014        | 0.0469         | 0.0204 | 42.2%  | 1.05 [1.01, 1.09] | 1.47 [1.43, 1.51] |
| Torelli 2015     | 0.3148         | 0.3664 | 15.1%  | 1.37 [1.23, 1.52] | 0.80 [0.68, 0.94] |
| Total 2012       | 1.3573         | 0.8783 | 3.5%   | 6.04 [1.92, 7.22] | 1.59 [1.35, 1.88] |
| Zhu 2014         | 0.4862         | 0.0844 | 39.2%  | 1.86 [1.46, 2.35] | 0.75 [0.63, 0.89] |
| Total (95% CI)   | 100.0%         | 1.38 [0.94, 2.00] |

Heterogeneity: Tau² = 0.09, Chi² = 27.34, df = 5 (P = 0.000001); I² = 89%
Test for overall effect: Z = 1.66 (P = 0.10)
Figure 4

A: BMI

| Study or Subgroup | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-----------------------------------|-----------------------------------|
| Arbas 2015        | 1.40 [-1.48, 3.20]                |                                   |
| Cheng 2017        | -0.60 [-1.71, 0.51]               |                                   |
| Han 2002          | -0.10 [-1.36, 1.16]               |                                   |
| Hayashi 2013      | 0.80 [-0.09, 1.19]                |                                   |
| Huang 2017        | 0.80 [-1.19, 2.28]                |                                   |
| Jain 2012         | -0.25 [-2.96, 2.90]               |                                   |
| Keskin 2015       | 1.05 [-0.86, 2.94]                |                                   |
| Lou 2015          | 0.50 [-0.17, 0.51]                |                                   |
| Meng 2015         | 0.15 [-0.04, 0.19]                |                                   |
| Oesnol 2015       | 1.40 [-0.36, 3.42]                |                                   |
| Sokwalska 2017    | 0.50 [-0.15, 0.25]                |                                   |
| Wam Mahmood 2013  | 0.25 [-1.82, 2.42]                |                                   |
| Wei 2017          | -0.03 [-0.49, 0.43]               |                                   |
| Zhu 2014          | -0.04 [-1.03, 0.95]               |                                   |
| Total (95% CI)    | 0.38 [0.06, 0.71]                 |                                   |

Heterogeneity: $\tau^2 = 0.14$, $\chi^2 = 24.86$, df = 13 ($P = 0.03$); $P = 4.7\%$

Test for overall effect $Z = 2.32$ ($P = 0.02$)

B: Triglyceride levels

| Study or Subgroup | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-----------------------------------|-----------------------------------|
| Arbas 2015        | 0.27 [0.11, 0.70]                 |                                   |
| Huang 2017        | 0.30 [0.22, 0.28]                 |                                   |
| Keskin 2015       | 0.37 [0.25, 0.79]                 |                                   |
| Meng 2015         | 0.43 [0.10, 0.83]                 |                                   |
| Oesnol 2015       | 0.09 [0.03, 0.25]                 |                                   |
| Wam Mahmood 2013  | 0.33 [0.01, 0.65]                 |                                   |
| Wei 2017          | -0.01 [-0.15, 0.13]               |                                   |
| Zhu 2014          | -0.18 [-0.35, 0.71]               |                                   |
| Total (95% CI)    | 0.16 [-0.13, 0.45]                |                                   |

Heterogeneity: $\tau^2 = 0.14$, $\chi^2 = 7.32$, df = 6 ($P < 0.00001$), $P = 91\%$

Test for overall effect $Z = 1.10$ ($P = 0.27$)

C: HDL

| Study or Subgroup | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-----------------------------------|-----------------------------------|
| Arbas 2015        | -0.03 [-0.15, 0.09]               |                                   |
| Huang 2017        | -0.10 [-0.23, 0.03]               |                                   |
| Meng 2015         | 0.03 [-0.02, 0.10]                |                                   |
| Oesnol 2015       | 0.05 [-0.04, 0.14]                |                                   |
| Wam Mahmood 2013  | 0.07 [-0.05, 0.19]                |                                   |
| Wei 2017          | 0.00 [-0.07, 0.07]                |                                   |
| Zhu 2014          | 0.05 [0.04, 0.14]                 |                                   |
| Total (95% CI)    | 0.02 [-0.01, 0.05]                |                                   |

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.80$, df = 6 ($P = 0.43$), $P = 0\%$

Test for overall effect $Z = 1.23$ ($P = 0.22$)
D: LDL

| Study or Subgroup | Mean Difference | Mean Difference |
|-------------------|----------------|----------------|
|                  | IV, Random, 95% CI | IV, Random, 95% CI |
| Artesas 2015      | 0.18 [0.16, 0.21] | - |
| Huang 2017        | 0.03 [0.20, 0.30] | - |
| Meng 2015         | -0.11 [-0.31, 0.09] | - |
| Telford 2018      | 0.23 [0.01, 0.47] | - |
| Wan Mahmood 2013  | 0.22 [0.03, 0.47] | - |
| Wei 2017          | -0.10 [-0.23, 0.03] | - |
| Zhu 2014          | 0.08 [0.17, 0.33] | - |
| **Total (95% CI)** | **0.05 [-0.07, 0.17]** | **-** |

Heterogeneity: Tau² = 0.01; Chi² = 11.46, df = 6 (P = 0.08); I² = 48%
Test for overall effect: Z = 0.80 (P = 0.43)

E: Total cholesterol levels

| Study or Subgroup | Mean Difference | Mean Difference |
|-------------------|----------------|----------------|
|                  | IV, Random, 95% CI | IV, Random, 95% CI |
| Artesas 2015      | 0.28 [0.13, 0.89] | - |
| Hani 2002         | -0.03 [-0.48, 0.42] | - |
| Huang 2017        | -0.10 [-0.60, 0.40] | - |
| Oosanai 2015      | 0.13 [-0.03, 0.29] | - |
| Wan Mahmood 2013  | 0.37 [0.06, 0.68] | - |
| **Total (95% CI)** | **0.15 [0.03, 0.28]** | **-** |

Heterogeneity: Tau² = 0.00; Chi² = 3.82, df = 4 (P = 0.43); I² = 0%
Test for overall effect: Z = 2.42 (P = 0.02)

F: Systolic blood pressure

| Study or Subgroup | Mean Difference | Mean Difference |
|-------------------|----------------|----------------|
|                  | IV, Random, 95% CI | IV, Random, 95% CI |
| Artesas 2015      | -2.00 [-7.57, 3.57] | - |
| Colbay 2015       | 12.10 [9.94, 20.26] | - |
| Huang 2017        | 2.10 [-3.21, 7.41] | - |
| Meng 2015         | 3.69 [-0.86, 9.04] | - |
| Oosanai 2015      | 5.00 [1.03, 8.07] | - |
| Telford 2018      | -0.70 [-5.23, 3.83] | - |
| Wan Mahmood 2013  | 8.88 [3.16, 16.66] | - |
| Wei 2017          | -0.67 [-5.63, 4.29] | - |
| Zhu 2014          | -0.49 [-3.31, 1.43] | - |
| **Total (95% CI)** | **2.60 [-5.50, 5.34]** | **-** |

Heterogeneity: Tau² = 9.43; Chi² = 23.11, df = 6 (P = 0.010); I² = 62%
Test for overall effect: Z = 2.00 (P = 0.05)

G: Diastolic blood pressure

| Study or Subgroup | Mean Difference | Mean Difference |
|-------------------|----------------|----------------|
|                  | IV, Random, 95% CI | IV, Random, 95% CI |
| Artesas 2015      | -2.03 [-5.08, 0.20] | - |
| Huang 2017        | 1.10 [2.15, 4.35] | - |
| Meng 2015         | 1.82 [0.85, 3.19] | - |
| Oosanai 2015      | 2.00 [0.30, 3.00] | - |
| Telford 2018      | 2.20 [0.80, 3.69] | - |
| Wan Mahmood 2013  | 3.61 [-0.54, 7.75] | - |
| Wei 2017          | 1.65 [-0.30, 3.72] | - |
| Zhu 2014          | -1.92 [-4.79, 0.95] | - |
| **Total (95% CI)** | **1.13 [-0.95, 2.34]** | **-** |

Heterogeneity: Tau² = 0.78; Chi² = 9.32, df = 7 (P = 0.23); I² = 25%
Test for overall effect: Z = 1.82 (P = 0.07)
K Odds Ratio for poor glycemic control: HbA1c levels >7 / 8.5% (>