

REVIEW ARTICLE



The association between social jetlag and parameters of metabolic syndrome and type 2 diabetes: a systematic review and meta-analysis

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Summary

This study aims to determine the association between social jetlag and parameters of metabolic syndrome and type 2 diabetes (T2D) in a systematic review and meta-analysis. A systematic literature search was conducted in PubMed/Embase/Scopus until May 2022. Included studies described an association between social jetlag and parameters of the metabolic syndrome and/or T2D, were available full text and written in English or Dutch. Data extraction and quality assessment were performed on pre-piloted forms independently by two reviewers. Results were meta-analysed using random-effects analysis. A total of 6,290 titles/abstracts were screened, 176 papers were read full-text, 68 studies were included. Three studies were rated as low quality, 27 were moderate, and 38 were high quality. High quality studies showed that having social jetlag compared to no social jetlag was significantly associated with higher body mass index in 20 studies (0.49 kg/m², 95% confidence interval [CI] 0.21–0.77; $I^2 = 100\%$), higher waist circumference in seven studies (1.11 cm, 95% CI 0.42–1.80; $I^2 = 25\%$), higher systolic blood pressure in 10 studies (0.37 mmHg, 95% CI 0.00–0.74; $I^2 = 94\%$) and higher glycosylated haemoglobin in 12 studies (0.42%, 95% CI 0.12–0.72; $I^2 = 100\%$). No statistically significant associations were found for obesity, abdominal obesity, high- and low-density lipoprotein levels, cholesterol, triglycerides, diastolic blood pressure, hypertension, fasting glucose, homeostatic model assessment for insulin resistance, metabolic syndrome or T2D. Sensitivity analyses did not reduce heterogeneity. Despite substantial heterogeneity, social jetlag is associated with certain parameters of the metabolic syndrome and T2D, but not with prevalent metabolic syndrome or T2D. These findings should be interpreted with caution as the level of evidence is low and mostly based on cross-sectional data. Longitudinal studies are needed to further assess the direction of causality.

KEYWORDS

meta-analysis, metabolic syndrome, social jetlag, type 2 diabetes

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INTRODUCTION

Sleep is an important risk factor in the development of type 2 diabetes (T2D) and the metabolic syndrome (Cappuccio, D'Elia, Strazzullo, & Miller, 2010). For example, people who curtail sleep (<5 h/night) have a 30% higher risk of developing T2D (Cappuccio et al., 2010) and a 80% higher risk of the metabolic syndrome (Choi et al., 2011), as compared to people who sleep 7–8 h/night. However, not only the amount of sleep is important, also the timing of sleep. With the rapid evolution into a 24-h society, individuals often have difficulties to reconcile work schedules, social obligations, and biological needs. Well-known and extreme examples of disturbed sleep timing are shift work and jetlag due to travel, these disruptions of the body's 24-h (circadian) rhythm have been associated with a 1.09 higher odds of T2D and a 1.14 higher odds of the metabolic syndrome (Gan et al., 2015; Khosravipour, Khanlari, Khazaie, Khosravipour, & Khazaie, 2021).

A more chronic and prevalent cause of circadian misalignment is social jetlag. Social jetlag is defined as the discrepancy between work schedules, social obligations, and biological need for sleep (Roenneberg, Allebrandt, Merrow, & Vetter, 2012; Roenneberg, Pilz, Zerbini, & Winnebeck, 2019; Wittmann, Dinich, Merrow, & Roenneberg, 2006). Especially evening types (people with a late chronotype) have social jetlag (Adan et al., 2012; Wittmann et al., 2006). People with a late chronotype have a longer internal rhythm (>24 h), which results in preferring to go to bed late and wake up late. This late internal rhythm can be in conflict with social obligations, in other words social jetlag (Adan et al., 2012). During weekends or days off work, these individuals switch to their natural rhythm of going to bed late and getting up late. This behaviour causes recurrent variation in sleep timing, every week there is a difference in sleep timing between weekdays and weekend/free days. To date, social jetlag is the less well-known form of sleep variability, but highly prevalent, affecting at least 50% of the general population (Koopman et al., 2017; Wittmann et al., 2006).

Recent systematic reviews by Beauvalet et al. (2017) and Sun et al. (Sun, Ling, Zhu, Lee, & Li, 2019) showed that social jetlag has negative consequences for health in both adults and juveniles. Both reviews observed several negative psychological effects of social jetlag, and negative effects on health, it being associated with poorer cardiometabolic risk profiles and adverse endocrine profiles, (e.g. higher prevalence of the metabolic syndrome or T2D) (Beauvalet et al., 2017; Sun et al., 2019). However, this literature search was limited to 'social jetlag' as search term, thereby omitting studies that measured the discrepancy in sleep timing between weekdays and weekends and did not label this as a measure of social jetlag. Additionally, as the reviews were based on only a limited number of publications, a meta-analysis could not be conducted. Many additional articles on social jetlag have been published in the past 5 years. We therefore aimed to determine the association between social jetlag

and parameters of the metabolic syndrome and T2D in a systematic review and meta-analysis.

METHODS

Data sources and searches

A systematic search of the literature was conducted in PubMed, Embase.com and Scopus until May 16, 2022 by the investigators LG, RK, EB and FR, assisted by a medical librarian (LS). Search terms included controlled terms (MeSH in PubMed, Emtree in Embase) as well as free-text terms. 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: social jetlag, sleep pattern, sleep timing, sleep disorders, circadian rhythm, week/school days, weekend days AND Metabolic Syndrome, Metabolic Syndrome parameters, T2D and glycaemic control parameters. A search filter was applied to limit the results to humans. The search was performed without date or language restrictions. Duplicate articles were excluded. The full search strategy for all databases is provided in Supplementary File 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for experimental studies (Page et al., 2021) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for observational studies (Stroup et al., 2000). The protocol of this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under number: CRD42020152956.

Selection of studies

Studies were included if: (i) the association between social jetlag and parameters of T2D and the metabolic syndrome were assessed (according to existing definitions Alberti & Zimmet, 1998; Alberti, Zimmet, & Shaw, 2005; Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults, 2001; Grundy et al., 2005; Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004); (ii) the article was available as full text, either via our library or upon request from authors; (iii) the article was written in English or Dutch; (iv) social jetlag was measured, with social jetlag defined as the difference in timing of sleep between weekdays and free days or weekend days. Studies in animals were excluded. When results from a study were reported more than once, the most recent article was chosen.

All studies identified in the literature search were screened for eligibility on title and abstract by two reviewers (combination of either RK/FR/LG or EB) in Covidence (Covidence, n.d.). The full-text versions of potentially eligible studies were independently assessed for inclusion by two reviewers (combination of either FR/LG or EB). Discrepancies were resolved through discussion, consulting a third reviewer (RK). The mean proportion of agreement between the different reviewers was

97.2% for title and abstract screening and 88.6% for the full-text screening.

Data extraction

Data extraction was performed independently by two reviewers (combination of either FR/LG or EB). A standardised, pre-piloted form was used to extract data from the included studies. Data extraction included: population and number included, observation period (cross-sectional or prospective), participants' characteristics such as age and sex, type of measure of social jetlag, whether possible conflicts of interest were reported, and an overview of parameters of metabolic syndrome or parameters of T2D studied. If studies reported multiple outcomes, all were extracted and reported separately. According to established definitions of the metabolic syndrome including the World Health Organization (WHO), International Diabetes Federation (IDF) and American Heart Association (AHA), we have included results for the association between social jetlag and measures of body composition, blood lipids, blood pressure, glycaemic parameters and metabolic syndrome and T2D (Alberti et al., 2005; Alberti & Zimmet, 1998; Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults, 2001; Grundy et al., 2004; Grundy et al., 2005). Effects of 1 h increase in social jetlag or differences between categories of social jetlag (e.g. >2 h versus <2 h) were used. To ensure comparability between studies, effect sizes adjusted only for confounding by sex and age were extracted when possible. Effect sizes were recalculated into comparable units (beta for continuous outcomes and odds ratio for dichotomous outcomes) as much as possible and log-transformed data was transformed back to comparable units, if necessary. Discrepancies identified during the duplicate data extraction were resolved through discussion.

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 (Thomas, Ciliska, Dobbins, & Micucci, 2004). This 19-item tool, adapted by Mackenbach et al. (2014), is suitable for assessing the methodological quality of studies of observational and experimental design (Mackenbach et al., 2014). It contains eight domains of methodological quality on which studies were assessed: (i) study design; (ii) blinding; (iii) representativeness with regard to selection bias; (iv) representativeness with regard to withdrawals/dropouts; (v) confounders; (vi) data-collection; (vii) data-analysis; and (viii) reporting. The quality assessment was based on the outcome of interest, independent of the primary aim of the particular study.

The rating of some sections was less straightforward and is therefore explained below. Confounding was scored as 'weak' when data were not corrected for any confounders; a 'moderate' score was attributed to studies that corrected for at least age or sex; a 'strong'

score was given when studies appropriately adjusted for age and sex, or if studies stratified for sex in advance. Data collection was scored as 'weak' when no measurement techniques of social jetlag or parameters of the metabolic syndrome or T2D were discussed; a 'moderate' score was attributed to studies that discussed the measurement technique, but no resources were provided, or when a national dataset was used, and authors provided adequate information to find explanation on validity and reliability. Data-collection of studies was rated as 'strong' when studies provided a comprehensive method of assessment with appropriate explanation and resources to provide more information. Data analysis was scored as 'weak' when data were not or inappropriately tested; a 'moderate' score was given when statistical methods were described but were less appropriate when for example only univariate analyses were conducted; a 'strong' rating was given for appropriate and well described statistical methods, such as multivariable analysis.

Depending on these criteria, studies could have between six to eight component ratings resulting in one overall rating, ranging from high methodological quality (low risk of bias) to low methodological quality (high risk of bias). High methodological quality was granted to those studies with no 'weak' ratings and at least three 'strong' ratings; moderate methodological quality was attributed to those studies with one 'weak' rating or fewer than three 'strong' ratings; low methodological quality was attributed to those studies with two or more 'weak' ratings. All included studies were independently assessed for methodological quality by two raters (combination of FR/EB or LG). The ratings of each domain and the overall ratings were compared between the two raters to reach consensus. The percentage of consensus between raters was 88%.

Data synthesis

Studies were meta-analysed using a random-effects model (due to differences in the methodology of studies) when three or more studies investigated the same determinant and outcome and reported similar effect measures. In addition, the studies had to provide standard errors for the effect measures to be included in the meta-analysis. Three papers (Bowman et al., 2020; Brouwer et al., 2020; Chontong, Saetung, & Reutrakul, 2016) were excluded from the meta-analysis, as they did not measure social jetlag as the difference in midpoint of sleep between week and weekend days and therefore could not be meta-analysed amongst each other. Secondly, three studies with a low methodological quality were excluded from meta-analyses (Karadag & Yilmaz, 2021; Kelly, Healy, Sreenan, McDermott, & Coogan, 2022; Larcher et al., 2016). Thirdly, we had to (partly) exclude some papers from the meta-analysis as they reported medians, and authors were unable to provide necessary additional data, or if less than three papers measured the same outcome. These outcomes were reported qualitatively.

Forest plots of random-effects meta-analysis were fitted to betas, odds ratios, and correlations. In the main analysis, we stratified for methodological quality, i.e., high-quality rating or moderate quality. Additionally, we performed stratified sensitivity analyses. Firstly, we

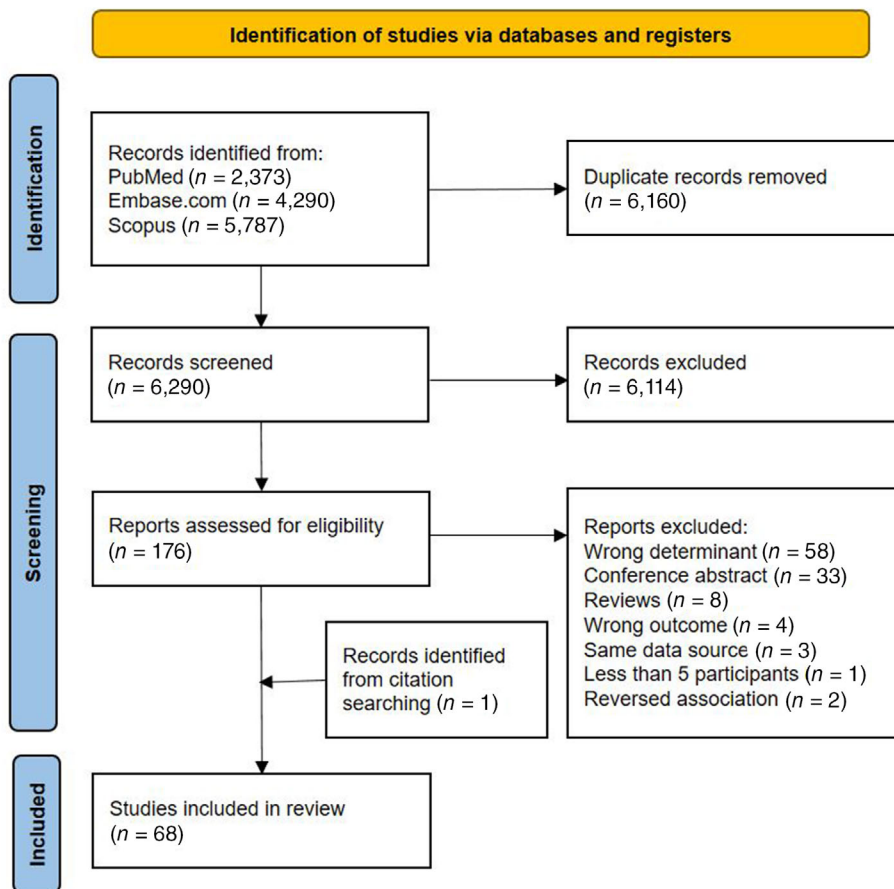


FIGURE 1 Flowchart of study selection in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 template

stratified based on health status of study populations, comparing the general population versus patient populations (participants with T2D, metabolic syndrome or bariatric surgery patients). Secondly, we compared quality of statistical analysis, with good correction for possible confounding factors performed and suitable analysis technique used and those that had not. We could not execute sensitivity analysis for age, because studies often did not stratify for age, and we had too few studies in a certain age group (i.e., adolescent).

Heterogeneity was tested using the Q test and I^2 statistic, reflecting the percentage of total variance that can be explained by heterogeneity, ranging from 0% (no heterogeneity) to 100% (Cuijpers, 2016), with an $I^2 > 75\%$ as cut off for substantial heterogeneity. The null hypothesis states there is no heterogeneity between the samples and will be rejected when the p value is below 0.05. Publication bias was evaluated by visual inspection of the funnel plots for all analyses and assessed using Egger's regression. The level of evidence was assessed with Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria. All analyses and plots were performed in RStudio (version 4.0.3) using the 'Metafor' package.

RESULTS

The systematic literature search identified 6,290 unique articles. After screening titles and abstracts, 176 potentially eligible

articles were identified and read full text. Reasons for exclusion after full-text screening are listed in Table S1. In total, 67 studies met the inclusion criteria (Figure 1) and one additional article was identified from citation searching (Brouwer et al., 2020). Of these 68 studies, 65 measured social jetlag as the difference in the midpoint of sleep between work days and weekend/free days and, three studies reported the standard deviation (SD) of the midpoint of sleep (Bowman et al., 2020; Brouwer et al., 2020; Chontong et al., 2016).

An overview of the characteristics of the included studies is shown in Table 1. Of the 68 studies, 43 were conducted in a general population, 23 in patient populations and two in a population of shift workers. A total of 12 studies were conducted in children, 17 studies in adolescents, and 39 in adult populations. The sample sizes ranged from 33 to 58,370 participants and studies were mostly cross-sectional ($n = 63$). Three studies did not report whether there was a conflict of interest (Randler, Haun, & Schaal, 2013; Roenneberg et al., 2012; von Schnurbein et al., 2018).

Methodological quality rating

An overview of the methodological quality assessment of the studies is presented in Table S2. The methodological quality of the studies was considered to be high (low risk of bias) in 38 studies, moderate

(moderate risk of bias) in 27 studies and weak (high risk of bias) in three studies. Most of the moderate ratings were due to a high risk of selection bias.

Association between social jetlag and measures of body composition

For the meta-analysis of BMI, the data are depicted in Figure 2a. Data from the 20 high-quality studies showed that social jetlag was associated with a higher BMI 0.49 kg/m² (95% confidence interval [CI] 0.21–0.77), $I^2 = 100\%$ (Figure 2a). Data from the total of 26 moderate- and high-quality studies combined, supported this finding (0.46 kg/m², 95% CI 0.21–0.70), $I^2 = 100\%$ (Figure 2a). Heterogeneity was very high in both analyses. Results from the meta-analysis of correlations using eight studies showed a similar direction, but the correlation coefficient did not meet statistical significance 0.04 (95% CI –0.03 to 0.11), $I^2 = 78\%$ (Figure 3a). Qualitative analysis of the studies that could not be included in the meta-analysis showed a statistically significant positive association between social jetlag and BMI (Cetiner, Yildirim, & Kalyoncu, 2021; Johnsen, Wynn, & Bratlid, 2013; Liang et al., 2022), as well as a positive correlation between social jetlag and BMI (Karadag & Yilmaz, 2021). Other studies (Berry et al., 2021; Constantino et al., 2021; Kelly et al., 2022; Larcher et al., 2016; Rusu, Ciobanu, Bala, Cerghizan, & Roman, 2019) showed no statistically significant difference in BMI between those with and without social jetlag.

For obesity, the meta-analysis of 11 high-quality studies showed no statistically significant association between social jetlag and higher odds of obesity 1.10 (95% CI 0.95–1.27), $I^2 = 94\%$ (Figure 2b), while analysis of all studies combined was borderline significant (1.19, 95% CI 1.00–1.41; $I^2 = 97\%$). Qualitative analysis showed a significantly increased odds of morbid obesity with increased social jetlag and significantly higher social jetlag in obese versus control participants (Dashti et al., 2020; Karadag & Yilmaz, 2021).

For waist circumference, the meta-analysis of seven high-quality studies showed a statistically significant association between social jetlag and larger waist circumference (1.11 cm, 95% CI 0.42–1.80; $I^2 = 25\%$), which was confirmed in an analysis of all studies together (1.08 cm, 95% CI 0.37–1.78; $I^2 = 94\%$) (Figure 2c). Analysis of correlations from two studies showed no significant correlation coefficient –0.00 (95% CI –0.20 to 0.20), $I^2 = 63\%$ (Figure 3b). Qualitative analysis of one study did show a significant correlation between social jetlag and waist circumference (Karadag & Yilmaz, 2021). Waist circumference was also analysed dichotomously as abdominal obesity (waist circumference >102 cm for men and >80 cm for women). Data from six studies showed no statistically significant association between social jetlag and abdominal obesity 1.20 (95% CI 0.89–1.62), $I^2 = 79\%$ (Figure 2d). One article in the qualitative analysis supported this finding (Johnsen et al., 2013).

No meta-analysis could be conducted for waist-to-hip ratio (less than three comparable studies). Qualitative analysis showed a significant positive association between social jetlag and waist-to-hip ratio (Bowman et al., 2020; Johnsen et al., 2013; Parsons et al., 2015; Stoner et al., 2018),

while one study found a non-significant correlation (Ali et al., 2020). Additionally, a significant positive association between social jetlag and waist-to-height ratio was observed (Malone et al., 2016), together with one non-significant positive association (Higgins et al., 2021).

Association between social jetlag and lipid measures

Meta-analysis of three high-quality studies showed no association between social jetlag and total cholesterol levels –1.06 mg/dl (95% CI –3.06 to 0.93), $I^2 = 100\%$ (Figure 2e). High-density lipoprotein (HDL) levels were also not significantly associated with social jetlag from an analysis using four high-quality studies –0.31 mg/dl (95% CI –0.79 to 0.17), $I^2 = 96\%$ (Figure 2f). Qualitative analysis supported this finding on HDL (Larcher et al., 2016). Additionally, three studies showed no significant association between social jetlag and low-density lipoprotein (LDL) levels –0.77 mg/dl (95% CI –2.37 to 0.83), $I^2 = 98\%$ (Figure 2g). Meta-analysis of correlations from three studies showed a significant correlation with total cholesterol 0.05 mg/dl (95% CI 0.01–0.09), $I^2 = 0\%$ (Figure 3c), but no significant correlations for HDL and LDL levels –0.01 (95% CI –0.17 to 0.15), $I^2 = 67\%$ (Figure 3d) and 0.04 (95% CI –0.01 to 0.09), $I^2 = 0\%$ (Figure 3e), respectively. Additionally, qualitative assessment found no significant correlation with cholesterol ratio 1 (Kwon & Lee, 2019).

Meta-analysis of five high-quality studies showed no significant association between social jetlag and log-transformed triglyceride levels 0.64 mmol/l (95% CI –0.58 to 1.85), $I^2 = 100\%$ (Figure 2h). Additionally, the analysis of correlations from three studies showed no statistically significant correlation with triglycerides 0.11 (95% CI –0.20 to 0.25), $I^2 = 71\%$ (Figure 3f). Qualitative analysis showed conflicting results: with a strong positive correlation in one study (Larcher et al., 2016) and no correlation in the other (Kantermann et al., 2014). Analysis using dichotomous triglyceride data showed increased risks of hypertriglyceridaemia in social jetlag groups, although not statistically significant (Carvalho et al., 2020; Islam et al., 2018).

Finally, qualitative assessment of dichotomous cholesterol measures showed a non-significantly higher odds of hypercholesterolemia in the social jetlag group (Carvalho et al., 2020), but also a significantly decreased odds of hypercholesterolaemia per 1 h increase in social jetlag (Dashti et al., 2020) and a non-significant decrease of hypercholesterolaemia with social jetlag categories (Gamboa Madeira et al., 2021).

Association between social jetlag and measures of blood pressure

Meta-analysis of 10 high-quality studies showed that social jetlag was statistically significantly associated with systolic blood pressure 0.37 mmHg (95% CI 0.00–0.74), $I^2 = 94\%$, although the total estimate of all studies was not significant (0.31 mmHg, 95% CI –0.02 to 0.63; $I^2 = 96\%$) (Figure 2i), and heterogeneity was very high. Meta-analysis of four high-quality studies showed a non-significant association with

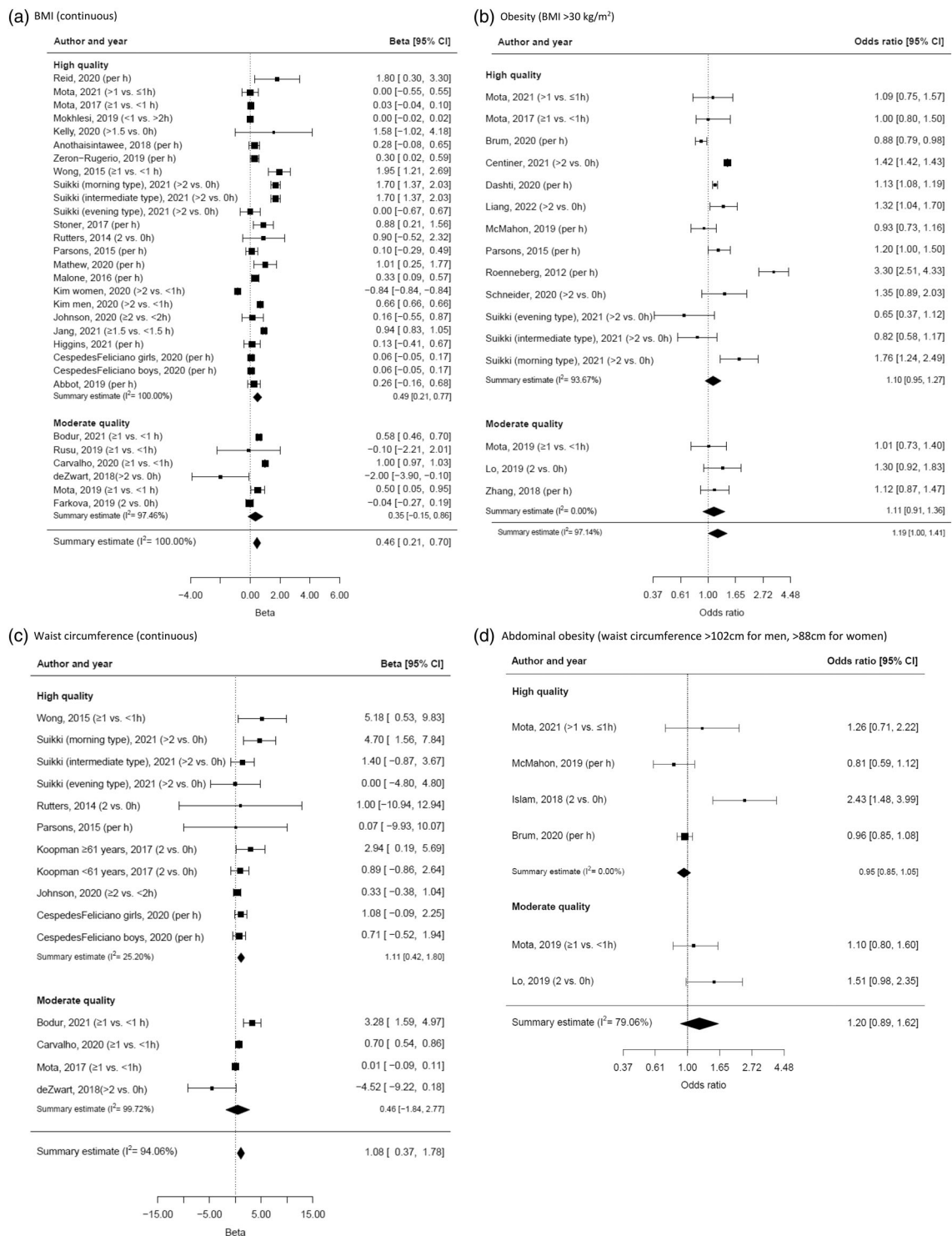
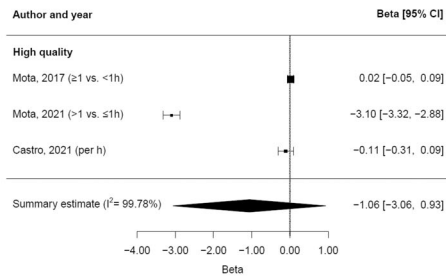


FIGURE 2 Forest plots of meta-analysis of mean differences and regression analysis of social jetlag with (parameters of) the metabolic syndrome and type 2 diabetes (T2D) stratified for methodological quality. (a) Body mass index (BMI); (b) Obesity; (c) Waist circumference; (d) Abdominal obesity; (e) Total cholesterol levels; (f) High-density lipoprotein (HDL) levels; (g) Low-density lipoprotein (LDL) levels; (h) Triglycerides; (i) Systolic blood pressure; (j) Diastolic blood pressure; (k) Hypertension; (l) Glycated haemoglobin (HbA1c) levels; (m) Fasting plasma glucose levels; (n) Homeostatic Model Assessment for Insulin Resistance (HOMA-IR); (o) T2D; (p) Metabolic syndrome. CI, confidence interval

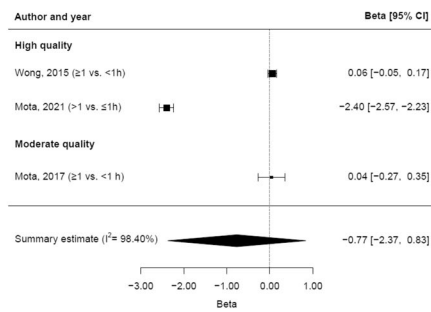
diastolic blood pressure 1.55 mmHg (95% CI -0.28 to 3.38), $I^2 = 100\%$, results were confirmed by the complete analysis (1.11 mmHg, 95% CI -0.35 to 2.57; $I^2 = 100\%$) (Figure 2j). Five

studies showed that social jetlag was not significantly associated with lower odds of hypertension 0.75 (95% CI 0.37-1.50), $I^2 = 100\%$ (Figure 2k). Qualitative analysis showed different results, with no

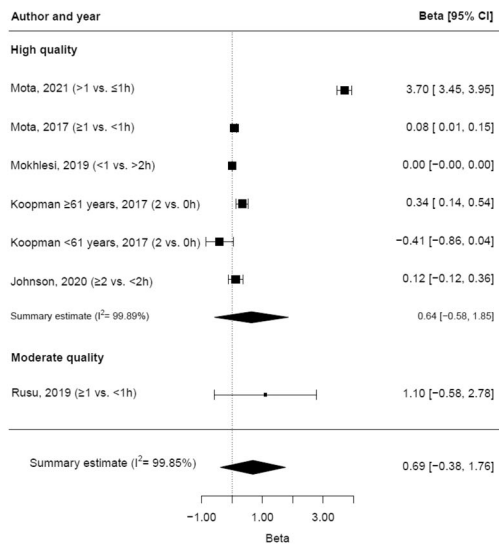
(e) Total cholesterol (continuous)



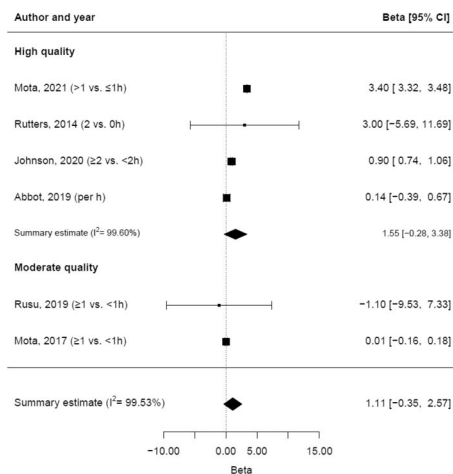
(g) LDL levels (continuous)



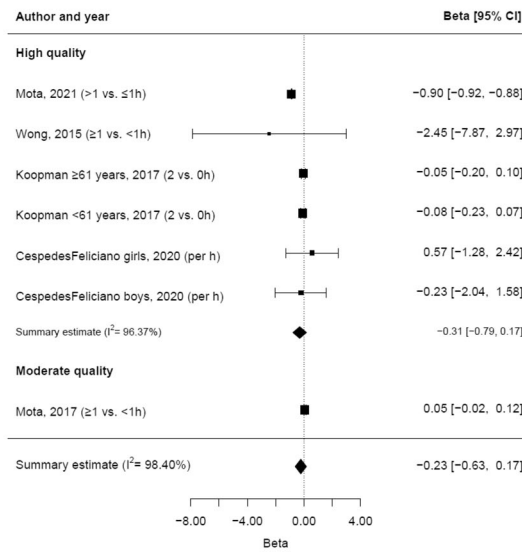
(h) Log of triglycerides (continuous)



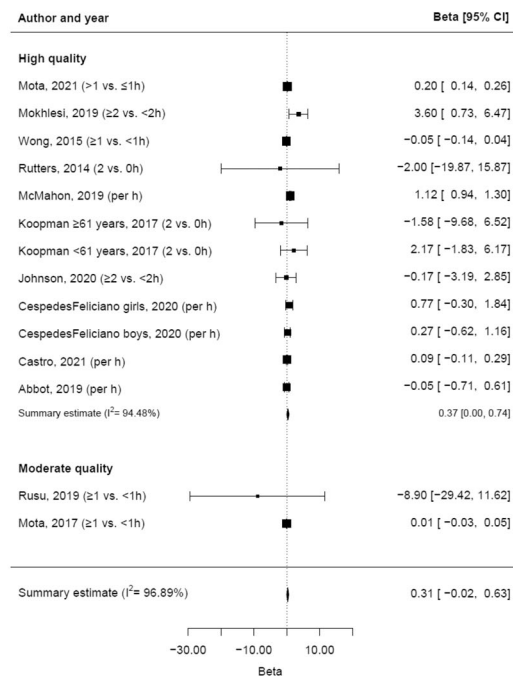
(j) Diastolic blood pressure (continuous)



(f) HDL levels (continuous)



(i) Systolic blood pressure (continuous)



(k) Hypertension

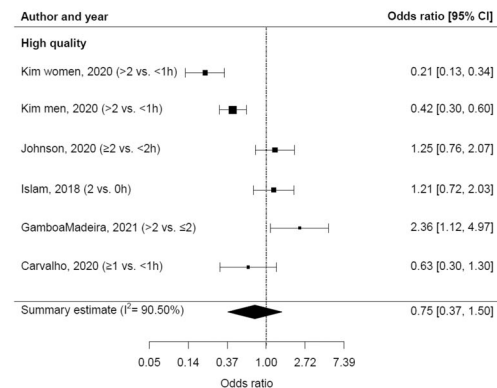
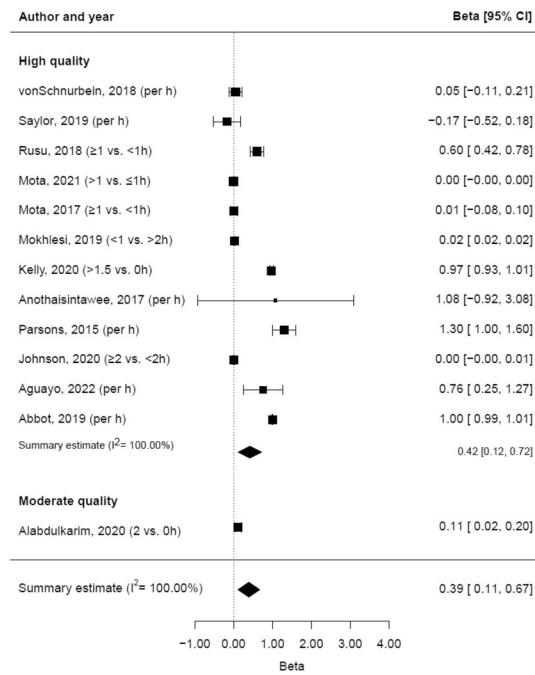
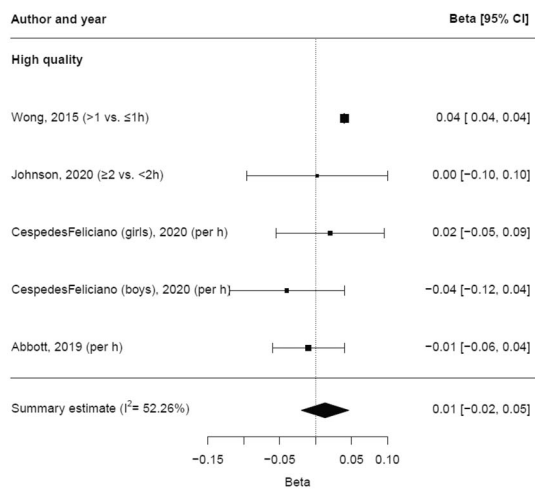


FIGURE 2 (Continued)

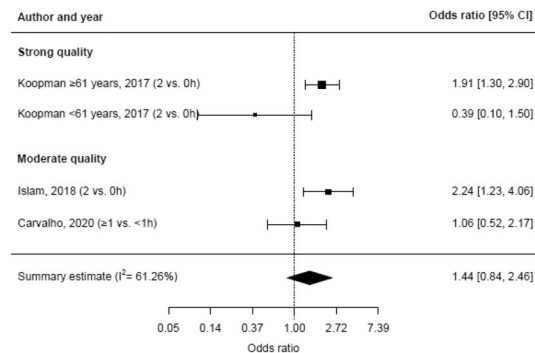
(l) HbA1c levels (continuous)



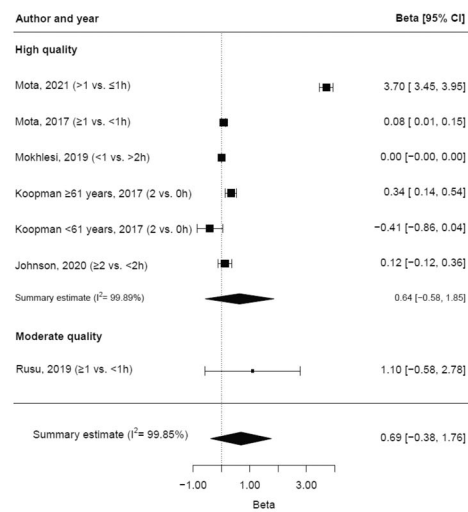
(n) Log of HOMA-IR (continuous)



(p) Metabolic syndrome



(m) Fasting plasma glucose levels (continuous)



(o) Type 2 diabetes

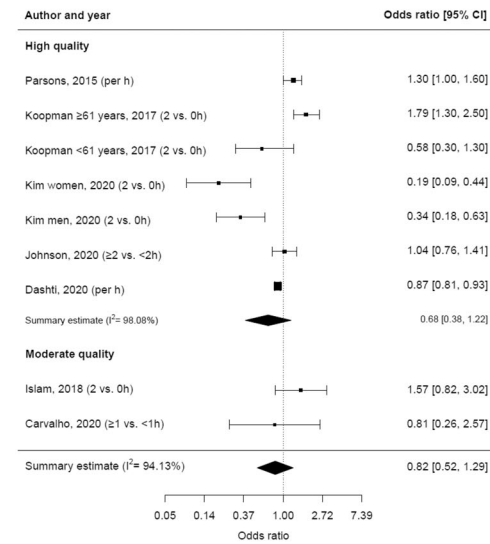


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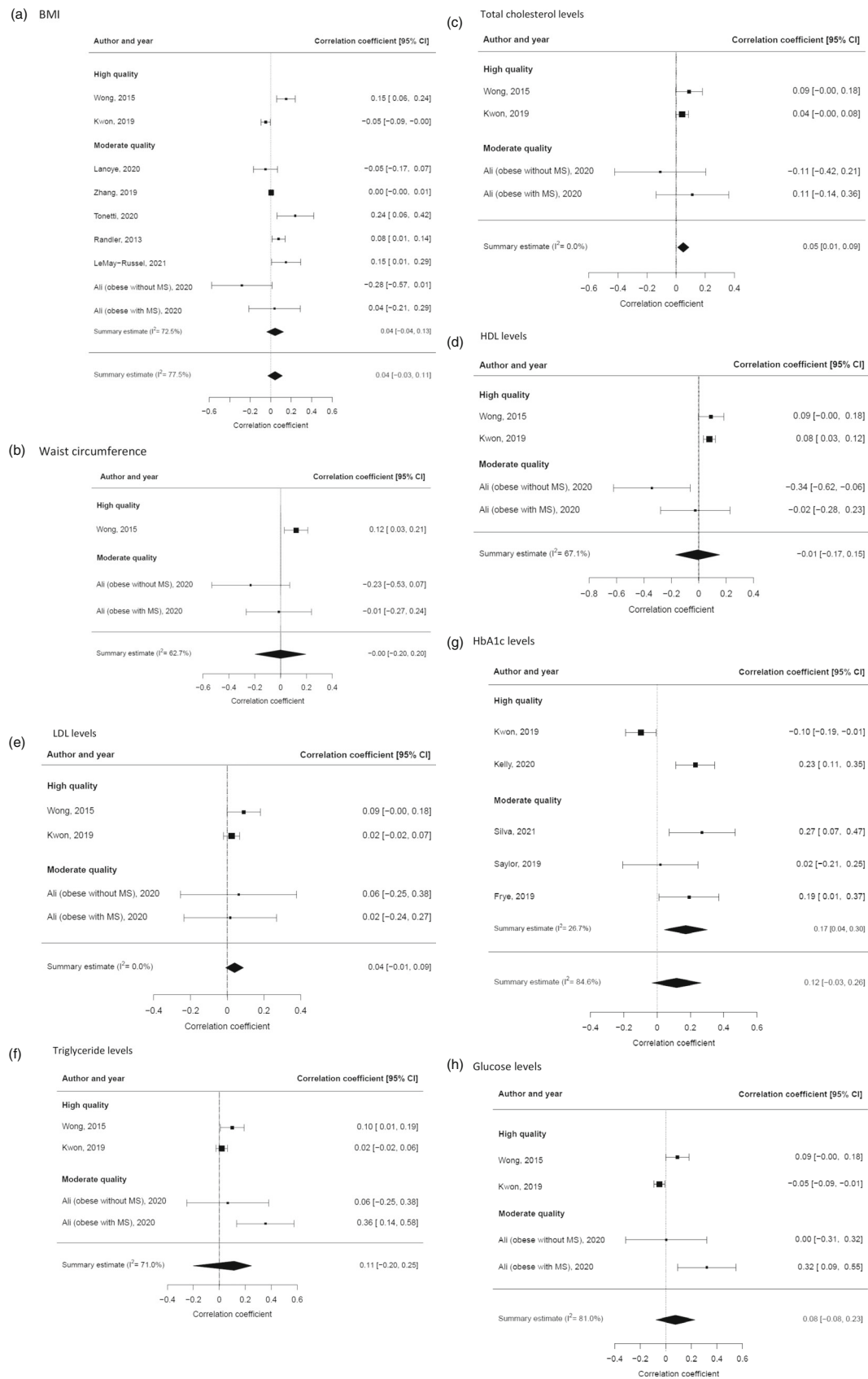


FIGURE 3 Forest plots of meta-analysis of correlations of social jetlag with (parameters of) the metabolic syndrome and type 2 diabetes (T2D) stratified for methodological quality. (a) BMI; (b) Waist circumference; (c) Total cholesterol levels; (d) High-density lipoprotein (HDL) levels; (e) Low-density lipoprotein (LDL) levels; (f) Triglycerides; (g) Glycated haemoglobin (HbA1c) levels; (h) Fasting plasma glucose levels. CI, confidence interval

differences in systolic blood pressure (Larcher et al., 2016), but a significant correlation between social jetlag and systolic blood pressure (Kelly et al., 2022). No difference was found for hypertension risk (Abbott et al., 2019). Qualitative assessment of two studies on diastolic blood pressure showed no significant association with social jetlag (Kelly et al., 2022; McMahon et al., 2019). Additionally, no significant correlations were found between social jetlag and mean arterial pressure (Ali et al., 2020; Kwon & Lee, 2019).

Association between social jetlag and measures of glycaemic control

Meta-analysis of 12 high-quality studies showed a statistically significant increase in glycated haemoglobin (HbA1c) levels 0.42% (95% CI 0.12–0.72), $I^2 = 100%$ (Figure 2i) in people with social jetlag, and heterogeneity was very high. Findings were confirmed by a complete analysis of all studies 0.39% (95% CI 0.11–0.67), $I^2 = 100%$ (Figure 2i). Results from a meta-analysis of correlations from five studies showed a similar direction, but no statistically significant correlation coefficient 0.12 (95% CI –0.03 to 0.26), $I^2 = 85%$ (Figure 3g). These findings were supported by qualitative findings (Frye, Perfect, & Silva, 2019; Kelly et al., 2022).

Meta-analysis of five high-quality studies showed no statistically significant association with plasma glucose levels 0.64 mg/dl (95% CI –0.58 to 1.85), $I^2 = 100%$, findings were confirmed by a complete analysis (0.69 mg/dl, 95% CI –0.38 to 1.76; $I^2 = 100%$) (Figure 2i) and heterogeneity was very high. Analysis of correlations of three studies showed non-significant results in the same direction 0.08 (95% CI –0.08 to 0.23), $I^2 = 81%$ (Figure 3h). These findings were supported by qualitative findings (Kantermann et al., 2014; Wong, Hasler, Kamarck, Muldoon, & Manuck, 2015).

Meta-analysis of four studies showed no association between social jetlag and log transformed Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) scores 0.01 (95% CI –0.02 to 0.05), $I^2 = 52%$ (Figure 2n). These findings were, supported by qualitative findings (Aguayo et al., 2022; Chen et al., 2021; Kelly et al., 2022).

Meta-analysis of five high-quality studies showed no association between social jetlag and T2D 0.68 (95% CI 0.38–1.22), $I^2 = 98%$ (Figure 2o), and heterogeneity was very high. Results from the complete analysis were similar 0.82 (95% CI 0.52–1.29), $I^2 = 94%$ (Figure 2o). Quantitative assessment found different results. Abbott et al. (2019) found no significant association, while Kelly et al. (2022) found significantly higher social jetlag in people with T2D versus healthy controls.

For the other glycaemic measures, no meta-analysis could be conducted (less than three comparable studies). Qualitative analysis showed mixed results, some showed an association with insulin (Wong et al., 2015) and diabetes medication requirement (von Schnurbein et al., 2018), while others showed no association with insulin (Kantermann et al., 2014), medication (Frye et al., 2019), or 2-h oral glucose tolerance test (Mokhlesi et al., 2019).

Association between social jetlag and prevalent metabolic syndrome

From meta-analysis of three studies, social jetlag was not associated with odds of the metabolic syndrome 1.44 (95% CI 0.84–2.46), $I^2 = 61%$ (Figure 2p), which was supported by the qualitative analysis (Cespedes Feliciano et al., 2019; Maghsoudipour et al., 2022).

Publication bias

Visual examination of the funnel plots and assessment using Egger's regression (Figure S1a–x) showed there was no publication bias, except for triglycerides, HOMA-IR and metabolic syndrome (Figure S1h,n,p), as these plots were asymmetric ($p = 0.001$, $p = 0.009$ and $p = 0.026$, respectively).

Level of evidence

The level of evidence for the association between social jetlag and parameters of metabolic syndrome and T2D as measured by GRADE is low quality, due to the observational nature of the included studies, cross-sectional study designs, and high heterogeneity for most analyses.

Sensitivity analyses

To assess sources of heterogeneity, we performed sensitivity analyses, which are summarised in Table S3.

First, analyses stratified for patient populations versus general study populations did not lead to large differences in pooled estimates and levels of heterogeneity for most outcomes (Figure S2a–o). However, we found a slightly smaller association of social jetlag with HbA1c levels for patient populations (0.22%, 95% CI –0.04 to 0.48), compared to general populations (0.76%, 95% CI 0.19–1.32), although this did not decrease the level of heterogeneity ($I^2 = 100%$ for both estimates) (Figure S2j). For sub-analyses for obesity, abdominal obesity and HDL levels (Figure S2b,d,e respectively), heterogeneity was lowered to 0%. No differences in effect estimates or different heterogeneity was observed for population sensitivity analyses for the other outcomes (Figure S2c,f,i,k–o).

Second, analyses stratified for statistical analysis quality did not result in differences in summary estimates or levels of heterogeneity (Figure S3a–f). However, for waist circumference, the analysis without Bodur et al. (weak statistical quality) led to a lower summary estimate of 0.66 cm (95% CI 0.20–1.12), $I^2 = 81%$, compared to the analysis with all studies 1.08 cm (95% CI 0.37–1.78), $I^2 = 94%$ (Figure S3c). Similar to the sensitivity analysis for populations, sub-analysis for high statistical quality studies for abdominal obesity resulted in an I^2 of 0% (Figure S3d).

DISCUSSION

We aimed to determine the association between social jetlag and parameters of the metabolic syndrome and T2D in a systematic review and meta-analysis. Based on data from 38 high-quality studies, we showed that people with social jetlag had significantly higher waist circumference as compared to people without social jetlag. We also found higher levels of BMI and HbA1c, and higher systolic blood pressure in people with social jetlag, although these results were limited due to high heterogeneity. No association was found for other parameters of the metabolic syndrome or prevalent metabolic syndrome or T2D. Findings from the meta-analysis were supported by the qualitative research. Sensitivity analyses did not show large differences in summary estimates and were not able to substantially decrease heterogeneity for all parameters of the metabolic syndrome and T2D. Because of the observational and cross-sectional design of the included studies and high levels of heterogeneity, the level of GRADE evidence was low. Our findings should therefore be interpreted with caution (Balshem et al., 2011; Schünemann, Brozek, Guyatt, & Oxman, 2013).

The findings of our meta-analysis are comparable to the previous systematic reviews by Beauvalet et al. (2017) and Sun et al. (2019). Both showed that social jetlag was associated with poorer cardiometabolic risk profiles, e.g., a higher prevalence of obesity (Beauvalet et al., 2017; Sun et al., 2019). However, our systematic review adds to previous systematic reviews that were limited regarding the description of the construct social jetlag (Chontong et al., 2016), only stating social jetlag and not looking at other definitions of the discrepancy between sleep timing in week and weekend/free days. Additionally, previous reviews were not able to include enough studies to meta-analyse (Beauvalet et al., 2017; Sun et al., 2019), most parameters of the metabolic syndrome and T2D, which we were able to with 68 studies included, compared to 26 (Beauvalet et al., 2017) and 24 (Sun et al., 2019) in previous studies.

A few points that warrant discussion. In the analyses for BMI, obesity, blood pressure, cholesterol, fasting glucose levels, HbA1c levels and T2D, heterogeneity remained very high (>75%), which markedly complicates the interpretation of our results. Our sensitivity analyses aimed at differentiating large differences in both study populations, as well as quality of statistical analysis. Because of this, we were able to explain (part of) the heterogeneity for some analyses (Figures S2b,d,e and S3d).

Sources of heterogeneity are diverse. First, outcome measurement techniques are not always similar. For instance, different assays are used for HbA1c measurement or BMI is self-reported versus measured in a clinical research setting, which might result in over- or underestimated effects.

A second and most important source of heterogeneity that we were not able to rule out is the effect of age. Some age groups may be more affected by social jetlag. Koopman et al. (2017) showed that working age groups are more affected, with the population aged <61 years having stronger associations with T2D, as compared to those aged >61 years. This might be explained by adherence to work

schedules causing more social jetlag in those working, as compared to older (retired) people. On the other hand, in young people with social jetlag, the exposure is not long enough to suffer long-term effects. In the present studies, age was not corrected for properly, with an extreme example by Kim et al. (Kim, Lyu, & Kim, 2020), who showed that in the general population people with social jetlag are on average 16 years younger than those without. Even though they correct for age (and not stratifying for age), age still affects the results and might explain the puzzling results, which are in contradiction with other studies, namely a trend towards less hypertension in those with social jetlag. Future studies should account for effect modification by age and conduct prospective studies.

However, literature also discusses issues and difficulty with the interpretation of I^2 as a measure of heterogeneity in meta-analyses. It is suggested that I^2 is highly driven upwards by the sample sizes (Rücker, Schwarzer, Carpenter, & Schumacher, 2008), as also demonstrated in our sensitivity analyses, and that it cannot be interpreted as an absolute measure of heterogeneity (Borenstein, Higgins, Hedges, & Rothstein, 2017). It is therefore suggested, when using I^2 in meta-analyses, to additionally focus on examination of the Forest plots of observed effects to assess outliers and clusters of effects (Hoaglin, 2017). Using this approach, our findings appear to correspond to the summary estimates that we found, suggesting robustness of our findings.

Possible mechanisms

There are several mechanisms hypothesised to underlie the association between social jetlag and obesity and HbA1c. First, social jetlag causes circadian misalignment, this is known to be associated with disruption of the hypothalamic-pituitary-adrenal (HPA) axis (Nader, Chrousos, & Kino, 2010). This enhances metabolic and glycaemic changes (Nieuwenhuizen & Rutters, 2007). Second, behavioural changes, such as unhealthy food choices and sedentary behaviour can cause an increase in waist circumference and BMI (Almoosawi, Palla, Walshe, Vingeliene, & Ellis, 2018; Alves et al., 2017; Silva et al., 2016). In turn, this can also lead to poorer glycaemic control and increased HbA1c (Espitia-Bautista et al., 2017). Finally, concomitant disorders such as depression or other sleep disorders (Beauvalet et al., 2017) (Sun et al., 2019) could also promote increases in BMI and HbA1c via changes in metabolic and glycaemic control. However, further research is required to further explore the underlying mechanisms of the negative effects of social jetlag.

Implications

Our results in the general population and the work by Roenneberg suggest that social jetlag is common (>50% of the population suffers from it) (de Zwart, Beulens, Elders, & Rutters, 2018; Koopman et al., 2017; Roenneberg et al., 2012). Although, limited by high heterogeneity between studies, this systematic review and meta-

analysis shows that social jetlag is associated with larger waist circumference, and possibly with higher BMI and HbA1c levels and systolic blood pressure. This may offer an opportunity for the prevention of metabolic syndrome and T2D. Healthcare providers should be more aware of the magnitude and impact of social jetlag. Efforts towards educating people about the importance of sleep and regular sleep timing could be a first strategy to help improve metabolic and glycaemic control. Future studies into the association between social jetlag and metabolic outcomes should use prospective study designs to further assess cause and effect of the observed associations and take into account the effect of age. Furthermore, to improve glycaemic and metabolic control in the future, we need to further elucidate the pathways and mechanisms that underlie this association. Subsequently, we would then need to assess which intervention is optimal to improve social jetlag and whether metabolic and glycaemic control can be improved through modifying social jetlag.

Strengths and limitations

This is the first systematic review and meta-analysis to quantify and assess, when weighted for risk of bias, the association between social jetlag and risk on the metabolic syndrome and T2D. Strengths of this review include the methodological quality assessment of each individual study and the inclusion of 46 publications, which were of high quality (only one study was low quality). Additionally, there was a clear conceptualisation of the term social jetlag and standardisation of the measurement of this construct in the articles included in the meta-analysis (except for some studies Bowman et al., 2020; Brouwer et al., 2020; Chontong et al., 2016).

However, some limitations must be taken into account. First, the complete grey literature was not captured, as unpublished reports and non-English or non-Dutch papers were not included. Second, funnel plots and Egger's regression test showed no symmetry for the analysis on some outcomes (Figure S1h,n). This may be a sign of publication bias in the literature or could also be related to the high heterogeneity.

Third, there was little consensus between studies regarding the choice of confounders. Although we have extracted comparable effect sizes adjusted only for confounding by sex and age, when possible, we may have over- or underestimated the observed associations due to differences in confounders between studies. Additionally, we were not able to assess confounding effects by other sleep-related factors that are related to social jetlag, such as short sleep timing and sleep apnea as almost none of the studies corrected for these. Finally, almost all included studies were cross-sectional, making it impossible to assess the cause and effect of the observed associations. However, of the few prospective studies that were included, two showed that social jetlag was associated with more weight gain (Jankovic et al., 2022; Kim et al., 2020) and one showed larger fasting glucose and triglycerides levels over a 1-year follow up in people with T2D and social jetlag (Mota et al., 2021). One study showed no significant

associations between social jetlag and change in BMI and waist circumference (de Zwart et al., 2018), which is possibly due to differences in age of the study population, with the former being in a teenage population compared to adult populations in the first studies. As this current prospective evidence is still contradicting, the findings of this meta-analysis should be interpreted with caution.

In conclusion, despite substantial heterogeneity, social jetlag is associated with certain parameters of the metabolic syndrome and T2D, but not with prevalent metabolic syndrome or T2D. These findings should be interpreted with caution as the level of evidence is low and mostly based on cross-sectional data, longitudinal studies are needed to further assess the direction of causality.

AUTHOR CONTRIBUTIONS

Emma J. Bouman performed study selection, data extraction and quality assessment, made major revisions to the manuscript, performed the analyses and drafted tables and figures. Lenka Groeneveld performed the literature search, study selection, quality assessment and made revisions to the manuscript. Linda Schoonmade performed the literature search, provided methodology support, and made revisions to the manuscript. Rozemarijn S. de Kruijk performed study selection and made revisions to the manuscript. Joline W. J. Beulens, Petra J. M. Elders and Sharon Rimmelzwaal provided support in design and execution of the review and meta-analyses and made major revisions to the manuscript. Femke Rutters performed literature search, study selection, data extraction 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 is original and has not been submitted elsewhere.

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data, code and other materials that underlie the results reported in this article are available from hoornstudy@amsterdamumc.nl upon reasonable request to the Hoorn Steering Committee.

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