Association between chronotype and cardio-vascular disease risk factors: A systematic review and meta-analysis

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ARTICLE INFO
Keywords:
Chronotype
Diabetes
Morning-type
Evening-type
Body mass index
Morningness
Eveningness
Circadian rhythm

ABSTRACT
Introduction: Circadian rhythm influences individuals’ chronotype or morning-evening preferences. Chronotype affects an individual’s lifestyle behaviors, social and work pattern, and even development of cardiovascular risk factors and diseases. This review aimed to examine the association between the chronotype and cardio-vascular risk factors.

Methods: We systematically reviewed the association between chronotype and type 2 diabetes mellitus (T2DM). We searched relevant observational studies in PubMed, Embase, Scopus databases and adhered to the PRISMA guidelines and meta-analysis was performed to get the pooled odds ratios and mean differences using the random effects model.

Results: Thirteen eligible studies were systematically reviewed, of which six studies were included in meta-analysis. Evening chronotype was significantly associated with higher odds of T2DM (OR 1.17; 95% CI: 1.13 to 1.22) and a higher Hemoglobin A1c level (Mean difference: 0.35; 95% CI: 0.06 to 0.65) as compared to the morning chronotype participants. Sensitivity analysis showed 53% higher odds of T2DM in evening chronotype participants when Morningness -Eveningness Questionnaire was applied in the studies, however, the result was statistically not significant.

Conclusion: Evening chronotype was significantly associated with T2DM and higher HbA1c level than with morning-type. We need future large scale experimental or prospective longitudinal studies to explore the causal association between chronotype and T2DM.

1. Introduction
Circadian rhythm is cyclical changes with multiple oscillators that repeat approximately once every 24 h organized hierarchically in cellular, molecular, and biological processes generated and maintained by endogenous circadian clocks. It is an adaptive mechanism to the environmentally visible transition of day and night. The circadian rhythm is controlled by the hypothalamus, which is determined by the body’s feeding cycles, temperature rhythms and blood borne signals and external photoperiod. The circadian physiology coordinates with the body’s vigilance states, metabolism, endocrine functions and cardio-vascular activity and plays a central role in the endocrine rhythms, behavioral traits and sleep–wake cycles. The natural circadian clock may be misaligned to meet the needs of the modern society, for instance, professional obligations, educational schedules and familial commitments. The circadian clock might alter and affect the body’s metabolism, sleep - wake cycle, feeding behavior and hormonal secretions.

Individuals differ in their preferred sleep and activity time based on their inherent circadian rhythm; this is known as chronotype. In humans, circadian rhythmicity is reflected by a complex phenotype that is developed from distinct genetic factors that determine the chronotype. Inter-individual variations can be noticed between those who get active early in the day and those who become active later in the day; described as ‘Morningness’ and ‘Eveningness’ respectively. The degree of circadian misalignment further depends on the individuals’ chronotype or ‘morning-evening’ preferences. The misalignment because of variations in the chronotype leads to changes in the meal timing and or/sleep, which leads to desynchrony between external (light - dark) cycle and internal cycle (e.g. change in the cyclical release of hormones).

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https://doi.org/10.1016/j.cegh.2022.101108
Received 20 January 2022; Received in revised form 21 June 2022; Accepted 30 June 2022
Available online 6 July 2022
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The misalignment in the circadian influences the patterns of glucose metabolism by the body. Individuals with preferential evening chronotype have exhibited reduced glucose tolerance and increased inflammatory markers, increasing one’s cardio metabolic risk. The increased risk among evening chronotype is attributed to their reduced physical activity, unhealthy eating habits during late hours and altered sleeping habits.

Several studies in humans have showed differential performances with interindividual differences because of their chronotype, with certain studies even negating the above findings. In the past decade, evidence suggested that various health hazards were attributed to the interindividual diurnal preferences, evening-type individuals often consume alcohol, comparatively smoke more tobacco, do less physical activities. Besides the non-modifiable risk factors for cardiovascular diseases (CVD) like age, sex, race, and family history, some of the modifiable risk factors are smoking, unhealthy diet, lack of physical activity, high blood pressure, high cholesterol levels, overweight or obesity, and diabetes. The association of obesity and CVD is well evident from several reported studies.

Previous studies have documented evidence for the increased risk of diabetes among evening chronotype as compared to the morning chronotype. Further independent studies reported an association between evening chronotype and clinical parameters of diabetes such as elevated insulin resistance and glucose tolerance. Perhaps there is yet no systematic review investigating the association between the variant of chronotypes and the risk of diabetes. Therefore, the current study aimed to examine the association between the chronotype and cardiovascular risk factors such as type 2 diabetes mellitus, raised body mass index, fasting blood glucose and glycosylated hemoglobin (HbA1c).

2. Methods

We performed the review according to PRISMA (Preferred Reporting Items of Systematic reviews and Meta-Analysis) guidelines and registered at International Prospective Register of Systematic Reviews (PROSPERO) (Registration ID: CRD42020143484). The registered protocol includes evaluation of the association between chronotype and diabetes and cardiovascular risk factors, however in view of vastness and timely dissemination of results, the present study results are restricted to diabetes. While the part of the proposal involving cardiovascular illness and its associated risk factors is being pursued and would be disseminated later to completion. Cross-sectional, longitudinal, case control and cohort studies of observational nature reporting the risk of diabetes among adults (>18 years) with preferential chronotype (as evaluated by ‘morningness evenness scale’ or its equivalent) available at PubMed-Medline, Scopus, and EMBASE databases, published between January 1990 and March 2020, and published in English language were considered for the present systematic review. The last search was performed on 31 March 2020.

Studies reporting of recruiting participants without major neuropsychological disturbances or sleep disturbances were included. While animal studies, cell-line based studies, study subjects with known neuropsychiatric or sleep disorders or on medications altering sleep cycle, studies conducted among adolescents and shift workers, preclinical studies, case reports, case series, reviews, commentaries, letters to editors, conference abstracts, editorialials, methodological papers, clinical studies involving participants with major neuropsychological or sleep disorders or on treatment for these conditions, and dual/multiple publications were excluded from the present review. The PICOS (Participants, Intervention, Comparator, Outcome and Study design) approach was used to construct the search (key) terms. Additional keywords discovered during review were considered. We adopted sensitivity and precision maximizing strategy to identify the relevant studies during the review. The detailed description of the keywords is available in Appendix (Supplementary Table 1, Box1).

2.1. Screening and reviewing of studies

Two reviewers (DB, BSB) independently screened the titles and abstracts of studies selected from the electronic database search for their potential inclusion using the Rayyan-web app for systematic reviews. The authors (DB, BSB) independently reviewed the full text of the identified articles. Any disagreement arising in the process was resolved by discussion and on a mutual consensus of the authors (DB, BSB, BR). The final list of the included studies that met the inclusion and exclusion criteria was prepared.

2.2. Data collection, extraction, analysis and management

A data extraction form (DEF) was developed on Microsoft Excel (Version 2016) and relevant information required to achieve the proposed objectives including participant details and characteristics (study design, sample size, age, gender, body mass index [BMI], presence of diabetes mellitus, glycosylated hemoglobin [HbA1c], fasting blood glucose [FBG], chronotype etc.) from the selected studies. Details of author names, study title, year of publication, study period, sample size, and contact details of the corresponding author were recorded in the data extraction form.

The chronotype characteristic was assessed by three instruments, viz. Morningness Eveningness Questionnaire or MEQ questionnaire. Munich chronotype questionnaire (MCTQ) and Composite Scale of Morningness (CSM). Individuals scoring 22 or below in CSM and 41 or below in MEQ were identified as evening type, those scoring above 44 and 59 in CSM and MEQ respectively, were identified as morning type, and those with scores in between were classified as intermediate. However, the chronotype using MCTQ was classified using the mid-sleep time (derived by a complex calculation of responses collected in the questionnaire) as continuous variable and categorized the score into two groups: more evening (score >53) and more morning (score >53). Whereas Wong et al., 2015 didn’t categorize CSM score, only reported CSM score as a continuous variable. MCTQ is a 17 items questionnaire consisting of the domains of work schedule, weekend sleep schedule, free day sleep schedule, and self-assessment of chronotype.

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Participants were asked about their usual bedtime, wake-up time, sleep onset latency and actual sleep duration on weekdays and weekends. The mid-sleep time separately for weekdays and weekends was calculated as the midpoint between sleep onset and wake time. Then the mid-sleep time on free days (MSFsc) was derived from mid-sleep time on weekend nights adjusted for the sleep debt. The formula is: MSFsc = mid-sleep time on weekend night – 0.5 * (SDF - (5*SDF + 2*SDF/7)), where SDF is the calculated sleep duration on weekend nights and SDW is the calculated sleep duration on weekday night.

Data on central tendency (mean/median) and dispersion (standard deviation (SD)/Standard Error (SE)/Inter quartile range/95% confidence interval (CI)) for the available parameters were independently extracted from included studies by the reviewers (DB & BSB). The data were checked for consistency and confirmed for further analysis. For studies reporting outcome variables other than the conventional units/standard units, the outcome parameters were converted to uniform units using standard conversion factors.
We performed meta-analysis with Stata version 16 software (StataCorp, College Station, TX, USA). Mean and SD of HbA1c, FBG, and BMI of the participants between morning and evening type were pooled for evening chronotype and morning chronotype groups to determine their pooled quantitative difference (meta-analysis). The laboratory values of HbA1c and FBG were converted to the standardized units. We calculated the pooled estimates of the association between chronotype and T2DM from the odds ratios (OR) and 95% confidence intervals (CI) of the individual studies by Der Simonian and Laird method in Stata. Heterogeneity among the included studies was assessed using visual inspection of forest plots, Cochran-Q test, and I squared ($I^2$) statistic. The heterogeneity was considered where $I^2$ value was greater than 25% or Cochran- $Q < 0.1$. Heterogeneity was graded as low, moderate, and high to $I^2$ values of less than 25%, 25%–50%, and more than 75% respectively. In case of heterogeneity, a random effects model with DerSimonian and Laird was used, else a fixed effect model was used. Sensitivity analysis was performed to examine whether the type of questionnaire used to assess chronotype influenced the diabetes outcome. We conducted Peto odds ratio (POR) to examine the association between T2DM and chronotype. Lastly, publication bias was assessed using funnel plot and Egger’s test of the effect measures. Publication bias was considered present when the funnel plot showed asymmetry or the p value from Egger test was less than 0.05. In case of asymmetry the source of asymmetry was explored using contour-enhanced funnel plot. Two-sided $p < 0.05$ was considered statistically significant except for the heterogeneity test, in which $p < 0.10$ was used.

2.3. Assessment of risk of bias in individual studies

The quality and risk of bias in cross-sectional studies were assessed using the Appraisal Tool for Cross-Sectional Studies (AXIS), a quality assessment tool for cross-sectional studies. This tool contains 20 items covering introduction, methods, results, discussion, funding, and ethical components of a study report. Each question was judged as yes, no, or do not know. Observational studies (cohort and case control study) were assessed by Newcastle-Ottawa quality assessment scale (NOS). This tool was used to judge a non-randomized observational study (cohort or case control) on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest. Each question under these domains was marked as a ‘star’ for affirmative response. The tool contains eight items out of them, four items on selection category, one on comparability, and three items on outcome category. Within the selection and exposure categories a study can be awarded a maximum of one star for each numbered item. A maximum of two stars can be given for the domain of comparability. Even though recent researches showed no definitive choice between Newcastle-Ottawa scale and AXIS for the methodological quality assessment of cross-sectional studies, we chose to apply AXIS tool in this review for cross-sectional studies as it judges the study methodology in details compared to NOS and was primarily prepared for assessing the quality of the cross-sectional study.

3. Results

Out of total 5726 studies searched from the databases, 222 full-text articles assessed for eligibility, and 13 studies were identified as
Table 1
Summary and Characteristics of the articles.

<table>
<thead>
<tr>
<th>Study author (Publication year)</th>
<th>Country</th>
<th>Type of study</th>
<th>Sample size</th>
<th>Age (years)</th>
<th>Participants</th>
<th>Chronotype assessment tool</th>
<th>Outcomes assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan et al. (2020)</td>
<td>United Kingdom</td>
<td>Cross-sectional</td>
<td>337083</td>
<td>56.9 (8.0)</td>
<td>Men and women of 40–69 years</td>
<td>A single question of “Do you consider yourself to be?”</td>
<td>T2DM: A validated algorithm based on self-reported disease, medication, and medical history.</td>
</tr>
<tr>
<td>Mokhlesi et al. (2019)</td>
<td>United States</td>
<td>Cross-sectional</td>
<td>962</td>
<td>52.2 (9.5)</td>
<td>Overweight/obese Men and women of 20–65 years with prediabetes or recently diagnosed, untreated T2DM</td>
<td>Munich chronotype questionnaire. Mean mid sleep time on free days (MSFsc) time in 24-h clock time – 03:31 (02:33)</td>
<td>T2DM was assessed by standard laboratory assessment.</td>
</tr>
<tr>
<td>Knutson et al. (2018)</td>
<td>United Kingdom</td>
<td>Cross-sectional Cohort (Mean follow up time 6.5 years)</td>
<td>433268</td>
<td>56.5 (8.1)</td>
<td>Men and women of 37–73 years</td>
<td>A single question, “Do you consider yourself to be?” Chronotype was grouped into 4 categories: definite morning; moderate morning; moderate evening and definite evening types. BMI and sleep duration were measured.</td>
<td>Primary: all-cause mortality and mortality due to CVD. Secondary: Self-reported T2DM, endocrine disorders, neurological disorders, renal disorders, respiratory disorders, musculoskeletal disorders, gastrointestinal/abdominal disorders. T2DM: Medical records BMI was calculated using the standard formula. Most recent HbA1c values (assessed within the prior 3 months) was extracted from medical records. Depressive symptoms were assessed using the Thai version of CES-D Scale.</td>
</tr>
<tr>
<td>Nimitphong (2018.b)</td>
<td>Thailand</td>
<td>Cross-sectional</td>
<td>163</td>
<td>54.7 (10.4)</td>
<td>Non-night shift working adult men and women with a clinical diagnosis of prediabetes and type 2 diabetes mellitus</td>
<td>Composite Scale of Morningness (CSM). Mean score - 44.2 (5.4)</td>
<td>T2DM assessed by medical records</td>
</tr>
<tr>
<td>Vera (2018)</td>
<td>Spain</td>
<td>Cross-sectional</td>
<td>2126</td>
<td>40 (13)</td>
<td>Overweight &amp; obese men and women</td>
<td>MEQ (Hone &amp; Ostberg, 1976) questionnaire. ME score was expressed continuously. Median ME score – 53. Chronotype was categorized as: more evening (score &lt;53) and more morning (score ≥ 53).</td>
<td>Fasting glucose measured with the glucose oxidase method. Fasting insulin measured by a solid-phase, two-site chemiluminescent immunometric assay (IMMULITE 2000 Insulin). Insulin resistance (IR) assessed by Homeostasis model assessment of insulin resistance (HOMA-IR). MetS score was computed as per the International Diabetes Federation criteria. BMI, WC were calculated standard measurement technique. Other outcome: Genetic risk score assessed by DNA isolation and genotyping.</td>
</tr>
<tr>
<td>Anothaisintawee (2017)</td>
<td>Thailand</td>
<td>Cross-sectional</td>
<td>1014</td>
<td>62.4 (8.7)</td>
<td>Men and women with a diagnosis of prediabetes, defined as fasting plasma glucose (FPG) between 100 and 125 mg/dL (5.6 and 6.9 mmol/L) or HbA1c between 5.70% and 6.49% (38.80–47.44 mmol/mol)</td>
<td>Munich chronotype questionnaire. Chronotype was assessed as a continuous variable measured by the Mean mid sleep time on free days (MSFsc) time in 24-h clock time, Mean mid sleep time on free days (MSFsc) time in 24-h clock time - 01:57 (1:11).</td>
<td>Most recent HbA1c was retrieved from the retrieved from clinical laboratory databases.</td>
</tr>
<tr>
<td>Yu (2015)</td>
<td>Korea</td>
<td>Cohort (Mean follow up time 10 years)</td>
<td>1620</td>
<td>53.0 (3.2)</td>
<td>Men and women of 47–59 years</td>
<td>A self-assessment questionnaire - MEQ (Hone &amp; Ostberg, 1976) questionnaire. Mean ME score – 53.9 (9.5) Chronotype categorized as: morning (score 59–86); neither (score 42–58); and evening (score 16–41).</td>
<td>T2DM was diagnosed when fasting plasma glucose (FPG) was 7.0 mmol/L, or 2-h plasma glucose was 11.1 mmol/L after a 75-g oral glucose tolerance test, or when participants took antidiabetic medication. Other factors assessed: BMI, WC, FBG, HbA1c, (continued on next page)</td>
</tr>
</tbody>
</table>
3.1. Characteristics of included studies

A total of 782,402 participants from the 13 studies were part of the present synthesis. Details of the included studies, such as year of publication, study site, sample size, type of scale used for assessment of chronotype, average age of the participants and the procedure adopted for diagnosing diabetes are described in Table 1. All studies included both men and women participants. Only one study\(^{25}\) diagnosed T2DM based on the self-reported declaration of T2DM, all other studies evaluated the outcome of interest (T2DM) either by laboratory assessment, or combination of medical records, self-reported symptoms, laboratory assessment. Three studies (Knutson 2018, Tan 2020 and Yu 2015) reported DM and non-DM cases in the morning and evening chronotype individuals. However, Iwasaki 2013, Osonoi 2014 and Yu et al. 2015 reported plasma glucose after overnight fast. Whereas Reutrakul et al. 2013 and Nimipthong et al., 2018\(^{45}\) extracted the most recent HbA1c values from the patient medical records, and the HbA1c assays were done under the certification of National Glycohemoglobin Standardization Program (NGSP). The major study findings were summarized in Table 2.

### Table 1 (continued)

<table>
<thead>
<tr>
<th>Study author (Publication year)</th>
<th>Country</th>
<th>Type of study</th>
<th>Sample size</th>
<th>Age (years) Mean (SD)</th>
<th>Participants</th>
<th>Chronotype assessment tool</th>
<th>Outcomes assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong (2015)</td>
<td>United States</td>
<td>Cross-sectional</td>
<td>447</td>
<td>42.7 (7.4)</td>
<td>Men and women of 30–54 years and working at least 25 h per week outside the home</td>
<td>Composite Scale of Morningsness (CSM) Chronotype was examined as a continuous score. Mean score 39.3 (7.2)</td>
<td>Serum lipids, High-sensitivity C-reactive protein (hsCRP), metabolic syndrome (MetS), sarcopenia, and visceral obesity.</td>
</tr>
<tr>
<td>Osonoi (2014)</td>
<td>Japan</td>
<td>Cross-sectional</td>
<td>725</td>
<td>57.8 (8.6)</td>
<td>Men and women of 25–69 years of age with type 2 diabetes mellitus</td>
<td>A self-assessment questionnaire - MEQ (Hone &amp; Ostberg, 1976). Chronotype was categorized as: Evening type (Scores 16–52), neither type (scores 53–64), and morning type (scores 65–86). Mean ME score 57.4 (7.3)</td>
<td>Metabolic (T2DM, fasting insulin, insulin resistance) and cardiovascular variables (blood pressure, waist circumference, BMI, serum lipids).</td>
</tr>
<tr>
<td>Iwasaki (2013)</td>
<td>Japan</td>
<td>Cross-sectional</td>
<td>101</td>
<td>53.7 (7.1)</td>
<td>Male workers of 41–64 years with type 2 diabetes mellitus</td>
<td>MEQ (Hone &amp; Ostberg, 1976) questionnaire. Chronotype was categorized as: morning type (score 59–86); neither type (score 42–58); and evening type (score 16–41). Mean ME score 53.7 (8.4)</td>
<td>T2DM: Laboratory assessment of blood in morning after a 12-h overnight fast.</td>
</tr>
<tr>
<td>Merikanto (2013)</td>
<td>Finland</td>
<td>Cross-sectional</td>
<td>4589</td>
<td>51.7 (14.5)</td>
<td>Men and women of 25–74 years</td>
<td>A Modified MEQ consisted of six items derived from original 19-item MEQ (Hone &amp; Ostberg, 1976) questionnaire. The internal consistency of six items -Cronbach’s alpha of .80. The M-E score was divided into three categories, definitely or moderately E-types (score 5–12), T-type (score 13–18), and definitely or moderately M-types (score 19–27). Mean ME score 57.3 (8.4)</td>
<td>T2DM and cardiovascular diseases were self-reported.</td>
</tr>
<tr>
<td>Reutrakul (2013)</td>
<td>United States</td>
<td>Cross-sectional</td>
<td>94</td>
<td>58.4 (13.0)</td>
<td>Men and women of 18–85 years with type 2 diabetes mellitus</td>
<td>Munich chronotype questionnaire. Chronotype was assessed as a continuous variable measured by the Mean midsleep time on free days (MSFsc) time in 24-h clock time. Mean midsleep time on free days (MSFsc) time in 24-h clock time 3:29 (1:46)</td>
<td>T2DM diagnosed based on the most recent HbA1c values from the patient medical records and self-reported history of diabetes.</td>
</tr>
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</table>

\(^{a}\)T2DM – Type 2 Diabetes mellitus, BMI – Body mass index, CVD - Cardiovascular disease, CES-D - Center for Epidemiologic Studies-Depression scale, WC - Waist circumference, FBG - Fasting blood glucose, HbA1c – Glycosylated haemoglobin, HDL-C - High-density lipoprotein cholesterol, LDL-C - Low-density lipoprotein cholesterol.
3.2. Risk of bias in included studies

Out of two cohort studies Yu et al. 2015,28 addressed the selection of cohorts, comparability, and outcome ascertainment better compared to Knutson et al. 2018,23 as judged by the reviewers (Table 3). The study by Yu et al., 2015 addressed all the domains of Newcastle-Ottawa Scale and appeared to be of high quality study compared to the other study.

The quality of assessed cross-sectional studies appeared to range from low-to-moderate quality as judged by AXIS criteria. Six out of eleven studies were judged as low-quality study as rated below the median score of 13.5 (Range 7–16). Out of 11 studies, only one study conducted by Anothaisintawee et al. 2017,27 addressed sample size justifiﬁcation, while others had included variable size (ranges from 94 to 433,268) of study participants without justifiﬁcation. Most of the studies did not mention the measure to address or describe the non-responders.12,28,43–45,47–50 (Supplementary Table 1)

3.3. Type2 diabetes mellitus (T2DM)

Six of the included studies (Iwasaki 2013, Osonoi 2014, Yu 2015, Knutson 2018, Nimitphong 2018 and Tan 2020)23,25,26,41–43 reported diabetes among different chronotype. The results from these studies were pooled to determine the association of diabetes among participants classiﬁed as morning chronotype as compared to that of the evening chronotype. The participants with evening chronotype had 17% greater odds of T2DM (OR 1.17; 95% CI: 1.13 to 1.22) than morning chronotype, this estimated increase in odds could be as small as 13% and as large as 22% (Fig. 2). Whereas the participants with morning chronotype showed 15% lesser odds of T2DM than morning chronotype, the estimated decrease in odds could be as small as 12% and as large as 18% (OR 0.85; 95% CI: 0.82 to 0.88) (Fig. 3).

Among the six studies, Iwasaki 2013, Osonoi 2014 and Nimitphong 2018 did not report nondiabetic control groups. The pooled result from these three studies found a similar association between evening chronotype and T2DM (OR 1.17; 95% CI: 1.13 to 1.22).

3.4. Glycosylated haemoglobin (HbA1c)

Five of the included studies13,28,43–45 reported HbA1c values in participants with morning and evening chronotype. We compared the values in both these groups. Pooled results exhibited signiﬁcantly higher HbA1c among participants identiﬁed as evening chronotype (Mean difference: 0.35; 95% CI: 0.06 to 0.65) as compared to the morning chronotype participants (Fig. 4a). However, substantial heterogeneity (I² = 77.83%) existed among the studies.

3.5. Fasting blood glucose (FBG)

Only two studies28,44 among the six studies reported the FBG. Both the studies reported independently higher mean FBG in evening type participants (Osonoi 2014: 142 mg/dl and Yu 2015: 99 mg/dl) when compared to morning type participants (Osonoi 2014: 132 mg/dl, Yu 2015: 97.2 mg/dl). The pooled results showed a non-signiﬁcantly higher level of fasting blood sugar in evening chronotype participants than morning chronotype participants (Mean difference: 6.2; 95% CI: –1.82 to 14.21) (Fig. 4b).

3.6. Body mass index (BMI)

Further six of the included studies13,23,25,26,41–43 reported BMI. Pooled results reveal relatively higher BMI among evening chronotype participants as compared to the other chronotype (Mean difference: 0.39; 95% CI: –0.65 to 1.43). However, the difference was not statistically signiﬁcant and further the heterogeneity among the studies was unacceptably high (I² = 82.12%) (Fig. 4c).

We conducted a sensitivity analysis of three studies (Knutson 2018,
Tan 2020 and Yu 2015)\(^{25,27,28}\) that reported both morning and evening chronotype among T2DM and no T2DM participants using Peto odds ratio (POR) in the random effect model. The findings showed a similar magnitude of association between evening chronotype and T2DM (OR 1.17; 95% CI: 1.13 to 1.22).

We conducted another sensitivity analysis by pooling the results of studies that evaluated chronotype using MEQ in this review among three studies\(^{28,43,44}\) that applied the full 19 items MEQ questionnaire for chronotype assessment. Sensitivity analysis showed that participants with evening chronotype had 53% higher chances of having T2DM than the participants with morning chronotype (OR 1.53; 95% CI: 0.94 to 2.50). The funnel plot showed asymmetry suggestive of publication bias. However, because of limited number of studies in the review one must be cautious while interpreting.

4. Discussion

This is the first review that has systematically and quantitatively explored the association between chronotype and T2DM. The study found a significant association between T2DM and chronotype preferences. Individuals with evening preference had 17% greater likelihood of having T2DM than morning type participants. Whereas morning chronotype participants had 15% lesser chances of having T2DM than evening chronotype participants.

In this review, we explored the association between T2DM and different chronotype. However, very few studies had measured the association between T2DM and chronotype. The meta-analysis findings in our review showed that the participants of the evening chronotype had higher odds of being T2DM than the morning chronotype group. Several studies have shown that adolescents or adults with evening preferences and shift workers have unhealthy diets, smoking habit\(^{16}\) or consume alcohol,\(^{17}\) less engage with physical activity,\(^{19}\) and have poorer sleep quality.\(^{51-53}\) These health behaviors collectively are risk factors for T2DM. Previous studies have already explained the diurnal variation of normal glucose metabolism is modulated by the sleep and circadian rhythmicity.\(^{54}\) The individuals with evening preference usually have later sleep onset, wake-up time, and shorter duration of sleep.\(^{55}\) As a result, the misalignment of circadian rhythm may alter the glucose regulation in the body.\(^{11,56}\) In a study in Quebec city, Canada adults sleeping 5–6 h per day had higher odds for T2DM or impaired glucose tolerance than adults with 7–8 h of sleep.\(^{57}\) Besides prior studies have shown that chronotype or peoples preferences for morning or evening was partly determined by genetics\(^{58,59}\) and influenced by demographic such age, sex, geographic region, environmental like exposure to light-dark, temperature modifying technology, solar irradiation, and social activities.\(^{2,60,61}\)

In our review, we found a significant increase of HbA1c level in evening type participants than in morning type participants. In a cross-
sectional study of 140 patients with T2DM observed that evening chronotype individuals had an independent association with poorer glycemic control compared to morning type, even after adjusting for age, body mass index, and various sleep-related factors. In a healthy young individual, higher glucose response is observed after meals in the afternoon, evening, and most of the night compared to the morning meals. In addition, insulin response depends upon the time of consumption of meals. Studies have demonstrated that the plasma insulin level in normal individuals receiving three identical meals is higher and maximal in the morning, minimal in the afternoon, and lasted longer in the evening. These mechanisms might explain the higher likelihood of T2DM in individuals with evening preferences.

In the present review, we noticed that the BMI, an indicator of overweight and obesity, is marginally higher in the participants with evening preference than morning group individuals (Fig. 4b). This finding is consistent with the study that has explained the role of circadian rhythmicity in dietary intake. Several studies have showed the association between shorter duration of sleep and increased body fat,
weight gain, and obesity. Hypothalamic-pituitary functions are strongly associated with circadian rhythms and are integrated with the sleep regulatory process. Aberration of circadian rhythm can influence metabolic effects in the body. Disruption of orexin neuronal pathways in the hypothalamus might be a cause for weight gain. Besides this, late night sleep and shorter duration sleep reduces the satiety promoting leptin and, in contrast, increase ghrelin secretion entrains increased appetite and hunger. In our review, some of the risk factors of type 2 diabetes mellitus could be an independent risk factors for cardio-vascular diseases. Therefore, the results of this review should be interpreted cautiously.

 Previous studies have shown that individuals with shorter sleep duration are inclined to greater intake of energy, preferably from fats. Evening type of chronotype individuals who preferred to sleep late night are at a greater risk of obesity because of the factor of increased duration are inclined to greater intake of energy, preferably from fats.

However, a recent study confirmed a link between evening type of chronotype and unhealthy diet, but the chronotype was not associated with obesity.

Further studies have shown that the relatively higher energy intake in morning among morning chronotype individuals was associated with lower odds of being overweight or obese. Increased fast food consumption was observed in adolescents with delayed sleep timing. However, a recent study confirmed a link between evening type of chronotype and unhealthy diet, but the chronotype was not associated with obesity.

To our best of knowledge, this review is the first that systematically summarized the association between chronotype and T2DM. Our review included a substantial number of participants from different countries. However, our review has certain limitations as well. First, the demographic, environmental and social factors such as age, sex, region, country, artificial light, delayed work hours, social interactions in urban communities, enhanced social media may influence individuals’ preference for morning or eveningness.
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