REVIEW

Chronotype Differences in Energy Intake, Cardiometabolic Risk Parameters, Cancer, and Depression: A Systematic Review with Meta-Analysis of Observational Studies

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ABSTRACT

Chronotype is a behavioral manifestation of the internal circadian clock system. It refers to the specific activity-rest preference of an individual over a 24-h period and can be assessed using different methodologies that classify individuals into morning or evening chronotype. In recent years, several studies have suggested a relation between individual chronotype, eating habits, and the risk of developing obesity and other conditions. Our aim was to evaluate the association between chronotype, energy intake, and health status through a meta-analytic approach. A comprehensive search of MEDLINE, Embase, Scopus, Web of Science, and Cochrane Database was conducted. Observational studies that reported a measure of association between chronotype, energy intake, and health indicators were considered eligible. Overall, 39 observational studies (37 cross-sectional studies, 2 prospective cohort studies) were included in the systematic review, with a total of 377,797 subjects. By comparing morning and evening subjects, pooled analyses of cross-sectional studies showed significantly ($P < 0.001$) higher concentrations of blood glucose [mean difference (MD): 7.82; 95% CI: 3.18, 12.45], glycated hemoglobin (MD: 7.64; 95% CI: 3.08, 12.21), LDL cholesterol (MD: 13.69; 95% CI: 6.84, 20.54), and triglycerides (MD: 12.62; 95% CI: 0.90, 24.35) in evening subjects. Furthermore, an association between evening type and the risk of diabetes (OR: 1.30; 95% CI: 1.20, 1.41), cancer (OR: 1.18; 95% CI: 1.08, 1.30), and depression (OR: 1.86; 95% CI: 1.20, 2.88) was reported. Regarding the other outcomes examined, no significant differences were observed between the groups in terms of energy intake, anthropometric parameters, blood pressure, insulin, total and HDL cholesterol, and hypertension risk. In conclusion, evening chronotype was associated with a worse cardiometabolic risk profile and higher risk of diabetes, cancer, and depression. Further studies are needed to confirm these results and to better elucidate the interplay between chronotype, nutrition, and health status.This systematic review was registered at www.crd.york.ac.uk/prospero/ as CRD42021231044. *Adv Nutr* 2022;13:269–281.

Statement of Significance: This study includes all available observational studies to provide a comprehensive overview of the association between chronotype, nutritional parameters, and multiple health outcomes.

Keywords: chronotype, health, energy intake, risk factors, meta-analysis

Introduction

Circadian rhythms, controlled by the master circadian clock located in the suprachiasmatic nuclei of the hypothalamus, regulate daily sleep/wake rhythms, feeding behavior, and hormone secretions (1). Individual circadian typology has been summarized under the concept of chronotype, which refers to the specific activity-rest preference of an individual over a 24-h period (2). Early risers who are preferentially active in the mornings are said to have a morning chronotype, whereas late risers with more nocturnal activities are said to have an evening chronotype (61). Different methods can be used to assess chronotype; the most common is the administering of validated questionnaires, such as the "Morningness-Eveningness Questionnaire" (MEQ) (3).

In recent years, chrono-nutrition—the science that combines elements of nutritional research with elements of chronobiology—has received increasing attention given the growing literature revealing a possible association between chronotype, dietary habits, and health (4–6). In fact, many studies suggest that evening subjects have worse eating habits and consume more alcoholic beverages and sweets and less whole grains, fish, vegetables, and fruit (4). Furthermore, a

possible relation between the evening chronotype and higher BMI; higher concentrations of triglycerides, total cholesterol, LDL cholesterol, and glucose; and lower concentrations of HDL cholesterol has been reported (7, 8). Also, in terms of disease risk, the evening chronotype has been associated with an increased risk of metabolic disorders (5), type 2 diabetes (9), cardiovascular disease (10), and depression (11).

Although the most accredited hypothesis is that evening subjects have a higher risk of cardiometabolic and chronic diseases, no conclusive data have been obtained and no systematic reviews and meta-analyses have been conducted so far. The aim of this study was to carry out a comprehensive systematic review with meta-analysis of all cross-sectional and prospective cohort studies hitherto published in order to obtain an estimate of the association between chronotype, energy intake, and health status.

Methods

Search strategy

The review protocol has been registered on PROSPERO (CRD42021231044). According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (12), all potentially relevant articles were identified through a computerized search of the main electronic databases: MEDLINE, Embase, Scopus, Web of Science, and Cochrane Database, from inception to 1 April, 2021. Reference lists of the identified studies and previous reviews were also screened. Search terms included the following key words, used in combination as Medical Subject Headings (MeSH) terms and text words: "chronotype," "diurnal preference," "nocturnal preference," "circadian typology," "morningness," "eveningness," and their variants, in combination with words relating to dietary intake and health status: "energy intake," "plasma lipids," "cholesterol," "glycemia," "cardiovascular disease∗," "cancer," "obesity," "body mass index," "diabetes," "metabolic syndrome," "depression," "mortality," "health," "health status," and their variants. **Supplemental Table 1** provides a more exhaustive search strategy list, for each database. No language limitations were applied.

Data selection

Two authors (SL and MD) independently assessed potentially relevant articles for eligibility. Observational studies (cross-sectional and prospective cohort studies) that reported a measure of association between chronotype, energy intake, and/or health indicators were considered eligible for inclusion. Eligibility criteria are summarized in **Supplemental Table 2**, by following the PECOS (Population, Exposure, Comparator, Outcomes, Study design) framework. Inclusion criteria were as follows: *1*) Population: adults (≥18 y old); *2*) Exposure: evening chronotype; *3*) Comparator: morning chronotype; *4*) Outcomes: energy intake, cardiometabolic parameters [BMI, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, insulin, glycated hemoglobin (HbA1c), systolic blood pressure, diastolic blood pressure], chronic degenerative diseases (e.g., cardiovascular diseases, cancer, depression); *5*) Study design: cross-sectional and prospective cohort studies.

Exclusion criteria were as follows: *1*) Population: nonadults (<18 y old), pregnancy, and postpartum; *2*) Exposure: intermediate chronotype; *3*) Outcomes: outcomes assessed with questionnaires (e.g., anxiety, depressive moods); *4*) Study design: case-control studies (to minimize bias in recall and selection), review articles, letters to the editor, comments, case reports, and randomized controlled trials. Studies not reporting sufficient data to allow calculation of differences between subjects with evening preference and subjects with morning preference were excluded as well. When multiple articles for a single cohort were present, the most recent publication was considered. Missing data or necessary additional information were requested from the corresponding authors of the articles.

The decision to include studies was initially based on the title, the abstract, and full-text screening. In case of disagreement between the 2 reviewers, a third reviewer (FS) was consulted to reach consensus.

Data extraction

Two authors (SL and MD) independently extracted data from each study using a standardized form. Disagreements were resolved by consensus, or by a third investigator (FS) if consensus could not be reached. The spreadsheet was elaborated in Microsoft Excel® for Windows (2007) and was prepiloted, on 5 randomly selected articles, to ensure methodological concordance among the authors. The following data were extracted: first author and year of publication, study design, country of study population, age, sex, length of follow-up (when applicable), method used to assess individual chronotype, number of participants with morning chronotype, number of participants with evening chronotype, definition of outcome of interest, measures of effect size and CIs, and details of adjustment for confounding factors in the multivariate model (when available). If the results were reported separately for women and men, they were included in the analysis as separate populations.

Continuous outcomes were reported as follows: energy intake (kcal), body weight (kg), BMI (in kg/m^2), fat percentage (%), systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), glucose (mg/dL), insulin (μU/mL), HbA1c (%), insulin resistance score (HOMA-IR), total cholesterol (mg/dL), LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), and triglycerides (mg/dL). When data were provided in mmol/L, they were transformed into mg/dL for consistency of results.

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Supplemental Figure 1 and Supplemental Tables 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
Address correspondence to SL (e-mail: sofia.lotti@unifi.it).
Abbreviations used: HbA1c, glycated hemoglobin; MCTQ, Munich Chronotype Questionnaire; MD, mean difference; MEQ, Morningness-Eveningness Questionnaire; NOS, Newcastle-Ottawa Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Quality assessment

Two authors (SL and MD) independently assessed the methodological quality of the included studies using the Newcastle-Ottawa Scale (NOS) (13). Any incongruity was discussed and resolved with a third reviewer (FS). This scale assesses each study in 3 domains: the selection of the participants for each group, the comparability between the study groups, and the ascertainment of the outcome. We considered high-quality studies those that achieved ≥7 points, medium-quality studies those with 4–6 points, and poor-quality studies those with ≤3 points.

Statistical analysis

All data were analyzed using Review Manager (RevMan; version 5.4 for Macintosh). Pooled results were reported as mean difference (MD), OR, or HR and presented with 95% CIs with 2-sided P values. A random-effects model (DerSimonian and Laird method), which accounts for interstudy variation and provides a more conservative effect than the fixed model, was used. Meta-analysis was conducted if ≥2 studies were available for an outcome. When available, the results of the original studies with the most complete adjustment for potential confounders were used.

The chi-square Cochran's Q test with the I^2 statistic was calculated to assess the statistical heterogeneity between studies. The I^2 value determined the appropriateness of pooling the individual study results and provided a variance estimation across studies based on heterogeneity rather than chance (14). Where I^2 was >50%, heterogeneity was defined as substantial and subgroup analyses were performed to establish the source of the heterogeneity (15). We assessed whether there were differences related to geographical region [Northern compared with Southern countries, as defined by Brandt (16)], study populations (clinically healthy subjects compared with patients, i.e., subjects with a clinical diagnosis of disease), and study quality (low = studies with scores ≤ 3 on the NOS; moderate = studies with scores ranging from 4 to 6 on the NOS; high = studies with scores ≥ 7 on the NOS). To establish the robustness of the results, a sensitivity analysis was conducted by removing each study one-by-one from the meta-analysis and recalculating the summary estimate (the "leave-one-out" approach). If >10 studies were available, the possibility of publication bias was investigated by visual inspection of a funnel plot of effect size against SE. A P value < 0.05 was considered statistically significant.

Results

Literature search and study characteristics

Figure 1 shows the selection process, in accordance with PRISMA guidelines. Initial databases and other searches yielded 7194 articles. After review and elimination of duplicates, 251 articles were identified as potentially relevant for analysis. Of these, 212 were excluded based on full-text evaluation. At the end of the selection process, 39 articles with a total of 377,797 subjects (75% morning types, 25% evening types) met the inclusion criteria and were included in the analysis. Most of the studies had a cross-sectional design (n = 37), and **Tables 1** and **2** summarize their characteristics. As for the prospective cohort studies, only 2 studies were identified, and **Table 3** shows their characteristics.

Overall, 18 studies were conducted in Europe (of which 8 were in Scandinavian countries), 12 studies in Asia, and 9 studies in the United States. Most of the studies (n = 37; 95%) used the MEQ (in its full or reduced form) to assess chronotype, whereas only 2 studies used the Munich Chronotype Questionnaire (MCTQ). Six studies (15%) were conducted only in women and 2 (5%) only in men. Nine studies (22.5%) were conducted on subjects with a clinical diagnosis of disease. Regarding adjustment for possible confounders, only 10 studies (25.6%) reported adjusted results, and in some cases only few factors were considered. Based on the NOS assessment, 9 studies (23.1%) were of high quality, 25 (64.1%) of medium quality, and 5 (12.8%) of low quality. **Supplemental Tables 3** and **4** give a detailed description of the quality assessment of the cross-sectional and prospective cohort studies, respectively.

Chronotype, energy intake, and cardiometabolic risk factors

Table 1 shows the characteristics of cross-sectional studies that investigated the association between chronotype, energy intake, and cardiometabolic risk factors. In particular, the following outcomes were examined: energy intake (n = 16), body weight (n = 7), BMI (n = 33), fat mass percentage (n = 5), systolic blood pressure (n = 9), diastolic blood pressure (n = 9), fasting blood glucose (n = 8), HbA1c (n = 7), insulin (n = 2), HOMA-IR (n = 2), total cholesterol (n = 6), HDL cholesterol (n = 9), LDL cholesterol (n = 6), and triglycerides (n = 8).

Figure 2 shows the forest plot of cross-sectional studies summarizing the association between chronotype, energy intake, and cardiometabolic risk factors. By comparing evening and morning subjects, pooled analysis of 8 studies (5, 7, 8, 18, 19, 21, 28, 42) showed significantly higher concentrations of fasting blood glucose in evening subjects than in morning subjects (MD: 7.82; 95% CI: 3.18, 12.45), with substantial heterogeneity between studies (I^2 = 94%, P < 0.00001). Another significant difference between groups was observed for HbA1c, where the pooled analysis of 7 studies (1, 5, 8, 17, 19, 42, 43) showed significantly higher concentrations of HbA1c in evening subjects than in morning subjects (MD: 7.64; 95% CI: 3.08, 12.21). Again, heterogeneity was high (I^2 = 98%, P < 0.00001). Finally, evening subjects reported significantly higher concentrations than morning subjects of LDL cholesterol (MD: 13.69; 95% CI: 6.84, 20.54) and triglycerides (MD: 12.62; 95% CI: 0.90, 24.35) in 6 (8, 18, 21, 17, 30, 40) and 8 studies (5, 7, 8, 17–19, 21, 30), respectively, with substantial heterogeneity between studies in both cases (I^2 = 85%; P < 0.00001 and I^2 = 100%; P < 0.00001, respectively). No significant differences between the groups were reported for energy intake, anthropometric parameters, blood pressure, insulin, HOMA-IR, total cholesterol, and HDL cholesterol.

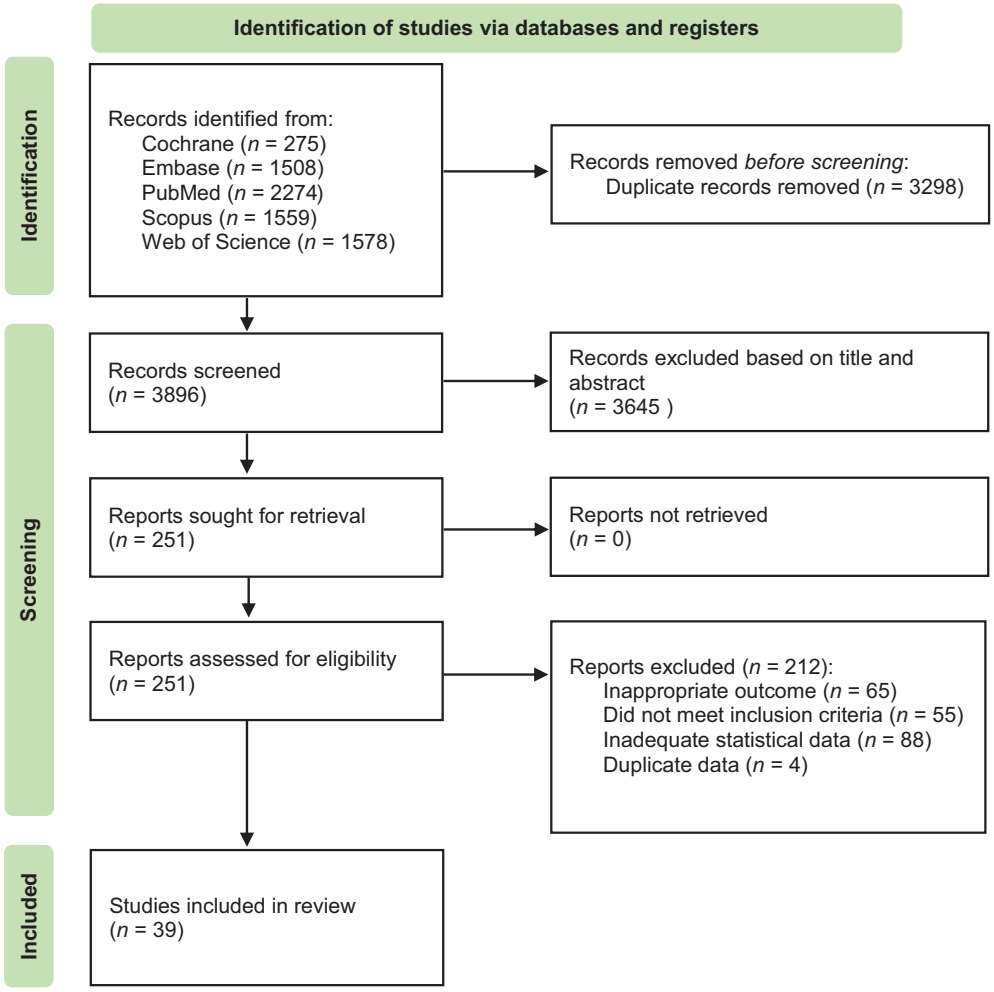

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for search strategy.

Chronotype and risk of diseases

Table 2 summarizes the characteristics of cross-sectional studies that investigated the association between chronotype and the risk of hypertension ($n = 5$), diabetes ($n = 7$), cancer ($n = 3$), depression ($n = 2$), cardiovascular disease ($n = 1$), myocardial infarction ($n = 1$), stroke ($n = 1$), and metabolic syndrome ($n = 1$). As depicted in **Figure 3**, meta-analytic pooling under a random-effects model showed an increased risk of diabetes (OR: 1.30; 95% CI: 1.20, 1.41; $I^2 = 39\%$; $P = 0.13$), cancer (OR: 1.18; 95% CI: 1.08, 1.30; $I^2 = 0\%$; $P = 0.82$), and depression (OR: 1.86; 95% CI: 1.20, 2.88; $I^2 = 62\%$; $P = 0.11$) among evening subjects, with nonsignificant ($P > 0.05$) heterogeneity between studies. In contrast, no association with hypertension emerged.

Subgroup analyses and publication bias

To examine the potential sources of heterogeneity, subgroup analyses were conducted (**Table 4**). For fasting blood glucose and HbA1c, the heterogeneity disappeared ($I^2 = 6\%$; $P = 0.37$ and $I^2 = 0\%$; $P = 0.99$, respectively) when populations with a clinical diagnosis of disease, which were also the studies reporting the greatest difference between evening and morning subjects, were excluded. The opposite was observed for triglycerides, where the heterogeneity disappeared ($I^2 = 0\%$; $P = 0.96$) when only patients were considered. A significant difference according to geographical region was observed for LDL cholesterol and triglycerides, with no heterogeneity among studies conducted in Southern countries ($I^2 = 0\%$; $P = 0.53$ and $I^2 = 0\%$; $P = 0.43$, respectively). Finally, heterogeneity was reduced to 9% ($P = 0.30$) for blood glucose when only medium-quality studies were considered, and it disappeared for blood glucose and HbA1c when only high-quality studies were considered, suggesting that the quality of the original studies may influence the results.

To confirm that our findings were not driven by any single study, a leave-one-out sensitivity analysis was performed. In this case, little change in the quantitative summary measures of MD or OR with the 95% CI was reported, with no study influencing results for all outcomes. Publication bias was assessed for energy intake and BMI, the outcomes assessed in >10 studies, using the funnel plot (**Supplemental Figure 1**).

TABLE 1 Characteristics of cross-sectional studies evaluating chronotype, energy intake, and cardiometabolic risk factors[1]

Study	Country	Sex	Age, y2	Study population	Morning type, *n*	Definition of morning type	Evening type, *n*	Definition of evening type	Outcome	Mean difference (95% CI)	Study quality
Energy intake											
Iwasaki et al. (17)	Japan	M	53.9 ± 7.1	Diabetic population	32	MES > 59 points (MEQ)	11	MES < 41 points (MEQ)	Energy intake, kcal/d	− 29.90 (−373.20, 313.40)	Medium
Kanerva et al. (4)	Finland	M/F	25–74	General population	995	5th quintile of rMEQ	826	1st quintile of rMEQ	Energy intake, kcal/d	0.00 (−27.68, 27.68)	Medium
Lucassen et al. (18)	USA	M/F	41.7 ± 5.9	Obese population	80	MES > 50 points (MEQ)	39	MES < 49 points (MEQ)	Energy intake, kcal/d	147.00 (−143.77, 437.77)	Medium
Reutrakul et al. (19)	USA	M/F	18–85	Diabetic population	51	1st quartile of MSF (MCTQ)	48	4th quartile of MSF (MCTQ)	Energy intake, kcal/d	− 19.00 (−256.49, 218.49)	Low
Osonoi et al. (20)	Japan	M/F	57.8 ± 8.6	Diabetic population	117	MES > 65 points (MEQ)	184	MES < 52 points (MEQ)	Energy intake, kcal/d	31.00 (−87.96, 149.96)	Medium
Maukonen et al. (21)	Finland	M	25–74	General population	839	MES 19–27 points (MEQ)	568	MES 5–12 points (MEQ)	Energy intake, kcal/d	42.75 (26.99, 58.51)	High
Maukonen et al. (21)	Finland	F	25–74	General population	816	MES 19–27 points (MEQ)	669	MES 5–12 points (MEQ)	Energy intake, kcal/d	− 23.88 (−34.52, − 13.24)	High
Munoz et al. (22)	Spain	M/F	30–60	General population	80	MES ≥ 52 points (MEQ)	91	MES ≤ 51 points (MEQ)	Energy intake, kcal/d	165.00 (106.38, 223.62)	Medium
Ruiz-Lozano et al. (23)	Spain	M/F	52 ± 11	Obese population	124	MES > 64 points (MEQ)	128	MES < 53 points (MEQ)	Energy intake, kcal/d	31.00 (−225.47, 287.47)	Medium
Basnet et al. (24)	Finland	M/F	51.6 ± 13.8	General population	1935	MES 19–27 points (MEQ)	595	MES 5–12 points (MEQ)	Energy intake, kcal/d	− 17.59 (−42.00, 6.82)	High
Maukonen et al. (25)	Finland	M/F	25–74	General population	904	MES 19–27 points (MEQ)	224	MES 5–12 points (MEQ)	Energy intake, kcal/d	17.44 (−12.21, 47.09)	High
Teixeira et al. (26)	Brazil	M/F	≥18	General population	151	MES > 59 points (MEQ)	124	MES < 41 points (MEQ)	Energy intake, kcal/d	140.10 (88.98, 191.22)	High
Vera et al. (7)	Spain	M/F	40 ± 13	General population	1110	MES > 59 points (MEQ)	1016	MES < 41 points (MEQ)	Energy intake, kcal/d	− 54.26 (−121.50, 12.98)	High
Yoshizaki et al. (27)	Japan	F	20–59	Nurses	270	MES > 60 points (MEQ)	336	MES < 53 points (MEQ)	Energy intake, kcal/d	− 29.00 (−105.35, 47.35)	Medium
Yazdinezhad et al. (28)	Iran	F	≥20	General population	25	MES > 52 points (MEQ)	16	MES < 51 points (MEQ)	Energy intake, kcal/d	− 73.00 (−249.62, 103.62)	Medium
Yazdinezhad et al. (28)	Iran	F	≥20	Obese population	39	MES > 52 points (MEQ)	16	MES < 51 points (MEQ)	Energy intake, kcal/d	− 114.00 (−322.89, 94.89)	Medium
Kayacan and Tokay (29)	Turkey	M	39.7 ± 14.9	Patients with IBD	8	MES > 59 points (MEQ)	6	MES < 41 points (MEQ)	Energy intake, kcal/d	520.60 (306.07, 735.13)	Medium
Kayacan and Tokay (29)	Turkey	F	39.7 ± 14.9	Patients with IBD	4	MES > 59 points (MEQ)	8	MES < 41 points (MEQ)	Energy intake, kcal/d	− 220.60 (−305.38, − 135.82)	Medium
Cardiometabolic risk factors											
Gaspar-Barba et al. (30)	Mexico	M/F	34.0 ± 11.7	Patients with major depressive disorder	21	MES > 59 points (MEQ)	18	MES < 41 points (MEQ)	Body weight, kg	− 1.76 (−8.96, 5.44)	Medium
									BMI, kg/m^2	− 2.50 (−4.91, −0.09)	
Selvi et al. (31)	Turkey	M/F	≥18	Patients after AMI	63	MES > 59 points (MEQ)	40	MES < 41 points (MEQ)	Total cholesterol, mg/dL	− 2.08 (−18.18, 14.02)	Medium
									HDL-C, mg/dL	− 1.40 (−5.24, 2.44)	
									LDL-C, mg/dL	2.32 (−18.07, 22.71)	
									Triglycerides, mg/dL	14.98 (−25.12, 55.08)	
Iwasaki et al. (17)	Japan	M	53.9 ± 7.1	Diabetic population	32	MES > 59 points (MEQ)	11	MES < 41 points (MEQ)	BMI, kg/m^2	0.70 (−1.82, 3.22)	Medium
									Systolic BP, mm Hg	− 7.00 (−17.57, 3.57)	
									Diastolic BP, mm Hg	− 0.60 (−6.26, 5.06)	
									HbA1c, %	12.00 (1.01, 22.99)	
									HDL-C, mg/dL	− 7.70 (−14.65, −0.75)	
									LDL-C, mg/dL	29.00 (12.78, 45.22)	
									Triglycerides, mg/dL	24.70 (−24.97, 74.37)	
Kanerva et al. (4)	Finland	M/F	25–74	General population	995	5th quintile of rMEQ	826	1st quintile of rMEQ	BMI, kg/m^2	− 0.20 (−0.76, 0.36)	High
Meule et al. (32)	Germany	M/F	23.1 ± 2.7	General population	35	MES ≥ 55 points (MEQ)	31	MES ≤ 44 points (MEQ)	BMI, kg/m^2	− 0.80 (−2.92, 1.32)	Low
Roeser et al. (33)	Germany	F	23.2 ± 4	General population	27	MES > 59 points (MEQ)	28	MES < 41 points (MEQ)	BMI, kg/m^2	0.07 (−1.36, 1.50)	Medium
									Systolic BP, mm Hg	4.48 (−0.02, 8.98)	
									Diastolic BP, mm Hg	2.62 (−0.55, 5.79)	
Lucassen et al. (18)	USA	M/F	41.7 ± 5.9	Obese population	80	MES > 50 points (MEQ)	39	MES < 49 points (MEQ)	BMI, kg/m^2	0.90 (−1.59, 3.39)	High
									Blood glucose, mg/dL	1.50 (−2.29, 5.29)	
									Insulin, μU/mL	1.00 (0.13, 1.87)	
									Total cholesterol, mg/dL	− 1.80 (−15.54, 11.94)	
									HDL-C, mg/dL	1.00 (−0.24, 2.24)	
									LDL-C, mg/dL	10.00 (6.02, 13.98)	
									Triglycerides, mg/dL	− 16.00 (−21.58, − 10.42)	

(*Continued*)

TABLE 1 (*Continued*)

Study	Country	Sex	Age, y2	Study population	Morning type, *n*	Definition of morning type	Evening type, *n*	Definition of evening type	Outcome	Mean difference (95% CI)	Study quality
Merikanto et al. (9)	Finland	M/F	25–74	General population	3242	MES 19–27 points (MEQ)	809	MES 5–12 points (MEQ)	Body weight, kg	− 0.20 (−1.49, 1.09)	High
									Fat percentage, %	− 0.20 (−0.89, 0.49)	
Reutrakul et al. (19)	USA	M/F	18–85	Diabetic population	51	1st quartile of MSF (MCTQ)	48	4th quartile of MSF (MCTQ)	BMI, kg/m^2	2.30 (−0.76, 5.36)	Low
									HbA1c, %	14.00 (12.01, 15.99)	
Osonoi et al. (20)	Japan	M/F	57.8 ± 8.6	Diabetic population	117	MES > 65 points (MEQ)	184	MES < 52 points (MEQ)	BMI, kg/m^2	2.20 (1.30, 3.10)	Medium
									Systolic BP, mm Hg	1.00 (−2.30, 4.30)	
									Diastolic BP, mm Hg	2.00 (−1.08, 5.08)	
									Blood glucose, mg/dL	10.00 (2.38, 17.62)	
									HbA1c, %	6.00 (3.63, 8.37)	
									Total cholesterol, mg/dL	− 3.00 (−9.35, 3.35)	
									HDL-C, mg/dL	− 5.00 (−8.07, −1.93)	
									Triglycerides, mg/dL	18.00 (13.65, 22.35)	
Kim et al. (34)	Brazil	M/F	20–80	General population	446	MES > 59 points (MEQ)	72	MES < 41 points (MEQ)	BMI, kg/m^2	− 0.50 (−2.00, 1.00)	Medium
Merikanto et al. (35)	Finland	M/F	25–74	General population	4851	MES 19–27 points (MEQ)	1204	MES 5–12 points (MEQ)	Body weight, kg	− 1.10 (−2.15, −0.05)	Medium
									BMI, kg/m^2	− 0.60 (−0.92, −0.28)	
									Systolic BP, mm Hg	− 8.90 (−10.03, −7.77)	
									Diastolic BP, mm Hg	− 3.30 (−3.99, −2.61)	
Vetter et al. (36)	USA	F	25–42	Nurses	22,089	Question no. 19 of MEQ	7029	Question no. 19 of MEQ	BMI, kg/m^2	2.20 (2.03, 2.37)	Medium
Yu et al. (5)	Republic of Korea	M/F	47–59	General population	480	MES > 59 points (MEQ)	95	MES < 41 points (MEQ)	BMI, kg/m^2	0.20 (−0.54, 0.94)	High
									Systolic BP, mm Hg	− 3.60 (−6.73, −0.47)	
									Diastolic BP, mm Hg	3.40 (1.32, 5.48)	
									Blood glucose, mg/dL	2.00 (−0.54, 4.54)	
									HbA1c, %	1.00 (0.62, 1.38)	
									HOMA-IR	0.20 (0.01, 0.39)	
									Total cholesterol, mg/dL	8.00 (6.05, 9.95)	
									HDL-C, mg/dL	0.00 (−0.70, 0.70)	
									Triglycerides, mg/dL	27.00 (26.56, 27.44)	
Antypa et al. (37)	Netherlands	M/F	19–68	Depressed patients	409	1st quintile of MSF (MCTQ)	387	5th quintile of MSF (MCTQ)	BMI, kg/m^2	− 1.50 (−2.15, −0.85)	Medium
Dickerman et al. (38)	Finland	M/F	40 ± 12.1	Twins	3159	Question no. 19 of MEQ	1117	Question no. 19 of MEQ	BMI, kg/m^2	− 1.00 (−1.21, −0.79)	High
Maukonen et al. (21)	Finland	M	25–74	General population	839	MES 19–27 points (MEQ)	568	MES 5–12 points (MEQ)	BMI, kg/m^2	− 0.30 (−0.71, 0.11)	High
									Fat percentage, %	− 0.20 (−0.81, 0.41)	
Maukonen et al. (21)	Finland	F	25–74	General population	816	MES 19–27 points (MEQ)	669	MES 5–12 points (MEQ)	BMI, kg/m^2	− 0.10 (−0.57, 0.37)	High
									Fat percentage, %	0.10 (−0.55, 0.75)	
Munoz et al. (22)	Spain	M/F	30–60	General population	80	MES ≥ 52 points (MEQ)	91	MES ≤ 51 points (MEQ)	Body weight, kg	5.00 (−0.27, 10.27)	Medium
									BMI, kg/m^2	0.30 (−1.50, 2.10)	
									Fat percentage, %	0.40 (−1.93, 2.73)	
									Systolic BP, mm Hg	− 4.00 (−8.50, 0.50)	
									Diastolic BP, mm Hg	− 4.00 (−6.55, −1.45)	
									Blood glucose, mg/dL	3.00 (0.29, 5.71)	
									HDL-C, mg/dL	− 6.00 (−6.98, −5.02)	
									Triglycerides, mg/dL	20.00 (18.46, 21.54)	
Ruiz-Lozano et al. (23)	Spain	M/F	52 ± 11	Obese population	124	MES > 64 points (MEQ)	128	MES < 53 points (MEQ)	Body weight, kg	6.20 (1.43, 10.97)	Medium
									BMI, kg/m^2	2.30 (0.84, 3.76)	
Suh et al. (39)	Republic of Korea	M/F	58 ± 7.1	General population	1138	MES > 59 points (MEQ)	146	MES < 41 points (MEQ)	BMI, kg/m^2	− 0.18 (−0.87, 0.51)	High
Basnet et al. (24)	Finland	M/F	51.6 ± 13.8	General population	1935	MES 19–27 points (MEQ)	595	MES 5–12 points (MEQ)	Body weight, kg	− 1.00 (−2.45, 0.45)	High
									BMI, kg/m^2	− 0.70 (−1.16, −0.24)	
									Fat percentage, %	− 0.06 (−0.88, 0.76)	
									Systolic BP, mm Hg	0.99 (−0.77, 2.75)	
									Diastolic BP, mm Hg	1.31 (0.28, 2.34)	

(*Continued*)

TABLE 1 (*Continued*)

Study	Country	Sex	Age, y[2]	Study population	Morning type, *n*	Definition of morning type	Evening type, *n*	Definition of evening type	Outcome	Mean difference (95% CI)	Study quality
Maukonen et al. (25)	Finland	M/F	25–74	General population	904	MES 19–27 points (MEQ)	224	MES 5–12 points (MEQ)	BMI, kg/m^2	0.50 (−0.21, 1.21)	High
Teixeira et al. (26)	Brazil	M/F	≥18	General population	151	MES > 59 points (MEQ)	124	MES < 41 points (MEQ)	BMI, kg/m^2	−0.40 (−1.21, 0.41)	High
Knutson and Schantz (10)	United Kingdom	M/F	38–73	General population	117,224	Question no. 19 of MEQ	38,867	Question no. 19 of MEQ	BMI, kg/m^2	0.30 (0.24, 0.36)	High
Vera et al. (7)	Spain	M/F	40 ± 13	General population	1110	MES > 59 points (MEQ)	1016	MES < 41 points (MEQ)	BMI, kg/m^2	0.32 (−0.12, 0.76)	High
									Fat percentage, %	−0.05 (−0.57, 0.47)	
									Systolic BP, mm Hg	0.00 (−1.26, 1.26)	
									Diastolic BP, mm Hg	−0.30 (−1.10, 0.50)	
									Blood glucose, mg/dL	0.25 (−1.00, 1.50)	
									Insulin, μU/mL	0.22 (−0.40, 0.84)	
									HOMA-IR	0.07 (−0.09, 0.23)	
									HDL-C, mg/dL	−1.50 (−2.80, −0.20)	
									Triglycerides, mg/dL	4.37 (3.88, 4.86)	
Yoshizaki et al. (27)	Japan	F	20–59	Nurses	336	MES > 60 points (MEQ)	400	MES < 53 points (MEQ)	BMI, kg/m^2	−0.10 (−0.50, 0.30)	Medium
Kwon et al. (8)	Republic of Korea	M/F	19–81	General population	145	MES > 59 points (MEQ)	145	MES < 41 points (MEQ)	BMI, kg/m^2	0.00 (−0.77, 0.77)	High
									Systolic BP, mm Hg	−1.00 (−4.14, 2.14)	
									Diastolic BP, mm Hg	−0.80 (−3.38, 1.78)	
									Blood glucose, mg/dL	0.20 (−3.53, 3.93)	
									HbA1c, %	1.00 (−0.63, 2.63)	
									Total cholesterol, mg/dL	9.90 (2.11, 17.69)	
									HDL-C, mg/dL	−1.40 (−4.29, 1.49)	
									LDL-C, mg/dL	9.20 (1.80, 16.60)	
									Triglycerides, mg/dL	18.70 (4.23, 33.17)	
Sun et al. (40)	USA	M/F	48.2 ± 5.3	General population	498	3rd tertile of rMEQ	131	1st tertile of rMEQ	BMI, kg/m^2	2.80 (1.02, 4.58)	Medium
Tomizawa et al. (41)	Japan	M	28.2	Shift workers	32	MES > 59 points (MEQ)	17	MES < 41 points (MEQ)	BMI, kg/m^2	−0.50 (−2.03, 1.03)	Medium
									Total cholesterol, mg/dL	5.50 (−12.07, 23.07)	
									HDL-C, mg/dL	0.30 (−6.74, 7.34)	
									LDL-C, mg/dL	8.00 (−8.96, 24.96)	
Yazdinezhad et al. (28)	Iran	F	≥20	General population	25	MES > 52 points (MEQ)	16	MES < 51 points (MEQ)	BMI, kg/m^2	1.10 (−4.68, 6.88)	Medium
Yazdinezhad et al. (28)	Iran	F	≥20	Obese population	39	MES > 52 points (MEQ)	16	MES < 51 points (MEQ)	BMI, kg/m^2	2.20 (−3.32, 7.72)	Medium
De Amicis et al. (42)	Italy	M/F	50 ± 13	General population	135	3rd tertile of rMEQ	38	1st tertile of rMEQ	BMI, kg/m^2	−0.30 (−2.46, 1.86)	Medium
Hashemipour et al. (43)	Iran	M/F	40.7 ± 3.3	Diabetic population	42	MES > 59 points (MEQ)	58	MES < 41 points (MEQ)	BMI, kg/m^2	1.90 (0.66, 3.14)	Low
									Blood glucose, mg/dL	31.80 (20.58, 43.02)	
									HbA1c, %	20.00 (15.46, 24.54)	
Henson et al. (44)	United Kingdom	M/F	63.8 ± 8.4	Diabetic population	159	MES ≥ 65 points (MEQ)	146	MES ≤ 52 points (MEQ)	BMI, kg/m^2	1.80 (0.59, 3.01)	Low
									HbA1c, %	3.00 (0.06, 5.94)	
Muscogiuri et al. (45)	Italy	M/F	51.8 ± 15.7	Obese population	100	MES > 59 points (MEQ)	22	MES < 41 points (MEQ)	Body weight, kg	0.80 (−5.61, 7.21)	Medium
									BMI, kg/m^2	1.20 (−1.36, 3.76)	
Thapa et al. (46)	Republic of Korea	M/F	≥70	General population	56	MES > 59 points (MEQ)	46	MES < 41 points (MEQ)	BMI, kg/m^2	3.00 (1.94, 4.06)	Low
Kayacan and Tokay (29)	Turkey	M/F	39.7 ± 14.9	Patients with IBD	12	MES > 59 points (MEQ)	14	MES < 41 points (MEQ)	Blood glucose, mg/dL	27.70 (21.68, 33.72)	Medium

[1] AMI, acute myocardial infarction; BP, blood pressure; HbA1c, glycated hemoglobin; HDL-C, HDL cholesterol; IBD, inflammatory bowel disease; LDL-C, LDL cholesterol; MCTQ, Munich Chronotype Questionnaire; MEQ, Morningness-Eveningness Questionnaire; MES, Morningness–Eveningness Score calculated from the Morningness-Eveningness Questionnaire items; MSF, Mid Sleep on Free Days; rMEQ, reduced Morningness-Eveningness Questionnaire.[2]Values are reported as mean ± SD

TABLE 2 Characteristics of cross-sectional studies evaluating chronotype and diseases[1]

Study	Country	Sex	Age, y[2]	Study population	Morning type, *n*/total *n*	Definition of morning type	Evening type, *n*/total *n*	Definition of evening type	Outcome	OR (95% CI)	Adjustment	Study quality
Selvi et al. (31)	Turkey	M/F	≥18	Patients after AMI	24/63 10/63	MES > 59 points (MEQ)	16/40 7/40	MES < 41 points (MEQ)	Hypertension Diabetes	1.08 (0.48, 2.44) 1.35 (0.39, 2.39)	—	Medium
Merikanto et al. (9)	Finland	M/F	25–74	General population	NA/3242	MES 19–27 points (MEQ)	NA/809	MES 5–12 points (MEQ)	Hypertension Diabetes Myocardial infarction Stroke	1.3 (1.0, 1.8) 2.6 (1.5, 4.4) 0.8 (0.3, 2.1) 1.4 (0.7, 2.8)	Sex, age, education level, civil status	High
Ramin et al. (47)	USA	F	52.9	Nurses	647/25,038	Question no. 19 of MEQ	238/8542	Question no. 19 of MEQ	Breast cancer	1.15 (0.98, 1.34)	Age, family history of breast cancer, age at menarche, history of rotating night-shift work, smoke, BMI, alcohol, history of benign breast disease, oral contraceptive use, menopausal status, age at menopause, parity, and age at first birth and postmenopausal hormone use	High
Yu et al. (5)	Republic of Korea	M/F	47–59	General population	97/480 148/480 111/480	MES > 59 points (MEQ)	27/95 22/95 29/95	MES < 41 points (MEQ)	Hypertension Diabetes MetS	0.68 (0.40, 1.13) 1.73 (1.01, 2.95) 1.74 (1.05, 2.87)[3]	Age, sex, BMI, smoking, alcohol, exercise, occupation, sleep duration, use of antihypertensive, antidiabetic, or antilipid drugs	High
Antypa et al. (37)	Netherlands	M/F	19–68	Depressed patients	139/409	1st quintile of MSF (MCTQ)	171/387	5th quintile of MSF (MCTQ)	Depression	1.54 (1.15, 2.05)	—	Medium
Basnet et al. (24)	Finland	M/F	51.6 ± 13.8	General population	NA/1935 NA/1935 NA/1935 NA/1935	MES 19–27 points (MEQ)	NA/595 NA/595 NA/595 NA/595	MES 5–12 points (MEQ)	Hypertension Diabetes Cancer Depression	1.05 (0.72, 1.51) 1.01 (0.51, 1.98) 1.51 (0.53, 4.33) 2.43 (1.52, 3.90)	Age, BMI, sex, marital status, education, region, smoking, alcohol intake, physical activity	High
Knutson and Schantz (10)	United Kingdom	M/F	38–73	General population	6330/117,224 45,014/117,224	Question no. 19 of MEQ	2417/38,867 13,309/38,867	Question no. 19 of MEQ	Diabetes CVD	1.30 (1.24, 1.36) 1.07 (1.04, 1.10)	Age, sex	High
Hurley et al. (48)	USA	F	40–89	Postmenopausal women	955/15,175	5th quintile of rMEQ	392/5027	1st quintile of rMEQ	Breast cancer	1.20 (1.06, 1.35)	Age, race, family history of breast cancer, age at menarche, smoking pack-years, BMI, alcohol consumption, physical activity, age at first full-term pregnancy, breastfeeding history, age at menopause, ever use of hormone therapy	Medium
Kwon et al. (8)	Republic of Korea	M/F	19–81	General population	38/145 10/145	MES > 59 points (MEQ)	31/145 10/145	MES < 41 points (MEQ)	Hypertension Diabetes	0.77 (0.44, 1.32) 1.00 (0.40, 2.48)	Age, sex, BMI	High
Tan et al. (49)	Sweden	M/F	40–69	General population	NA/79,955	Question no. 19 of MEQ	NA/26,016	Question no. 19 of MEQ	Diabetes	1.25 (1.17, 1.33)	Age, sex, self-reported chronotype, self-reported sleep duration, insomnia, BMI, systolic BP, smoking, alcohol intake, test center, principal components of ancestry, Townsend index	Medium

[1] AMI, acute myocardial infarction; BP, blood pressure; CVD, cardiovascular disease; MCTQ, Munich Chronotype Questionnaire; MEQ, Morningness-Eveningness Questionnaire; MES, Morningness–Eveningness Score calculated from the Morningness-Eveningness Questionnaire items; MetS, metabolic syndrome; NA, not available. [2] Values are reported as mean ± SD. [3] Not adjusted.

TABLE 3 Characteristics of prospective cohort studies evaluating chronotype and diseases[1]

Study	Country (cohort, length of follow-up)	Sex	Age, y[2]	Study population	Morning type, *n*/total *n*	Definition of morning type	Evening type, *n*/total *n*	Definition of evening type	Outcome	HR (95% CI)	Adjustment	Study quality
Vetter et al. (36)	USA (NHSII, 6 y)	F	25–42	Nurses	93/22,089	Question no. 19 of MEQ	49/7029	Question no. 19 of MEQ	Diabetes	1.01 (0.73, 1.38)	Age, family history of diabetes, smoking, alcohol intake, physical activity, diet score, oral contraceptive use, menopausal status, postmenopausal hormone use, sleep duration, median annual household income, depressive symptoms, cumulative rotating night-shift work exposure since 1989, BMI	Medium
Dickerman et al. (38)	Finland (OFTC, 30 y)	M	40 ± 12.1	Twins	208/3159	Question no. 19 of MEQ	181/1117	Question no. 19 of MEQ	Prostate cancer incidence	1.3 (1.1, 1.6)	Age, education, BMI, physical activity, social class, smoking status, alcohol use, snoring, zygosity	High

[1] MEQ, Morningness-Eveningness Questionnaire; NHSII, Nurses' Health Study II; OFTC, Older Finnish Twin Cohort. [2] Values are reported as mean ± SD.

For both outcomes, the shape of the funnel plot showed little asymmetry, suggesting little evidence of publication bias.

Discussion

To our knowledge, this is the first systematic review with meta-analysis including all available cross-sectional and prospective cohort studies estimating the association between chronotype, energy intake, and multiple health outcomes. The overall analysis included 39 studies with a total of 377,797 subjects. Evening subjects were found to be associated with a worse cardiometabolic profile. In fact, they showed significantly higher concentrations of fasting blood glucose, HbA1c, LDL cholesterol, and triglycerides than morning individuals, and a significantly higher risk of diabetes, cancer, and depression.

Because a wide range of physiological and metabolic functions are set and programmed by the time of day, the interaction between circadian rhythms, food intake, and health status has been increasingly studied in recent years. Circadian rhythms are cyclical endogenous processes that occur with a periodicity of ∼24 h and play an important role in regulating sleep/wake cycles, metabolism, hormonal secretions, immune function, and cell cycle control (47, 49). Despite the regulation of the master circadian clock, humans living in modern industrialized societies often engage in behaviors that are inappropriately timed relative to their endogenous circadian system, or chronotype (19). The 24-h access to light, irregular eating patterns, and social rhythms imposed by professional obligations and school schedules can result in a timing mismatch, defined "circadian misalignment" or "chrono-disruption" (50). As reported by a growing body of evidence, this misalignment can disrupt the natural oscillations of physiologic processes such as the regulation of blood pressure and glycemic and lipid metabolism, resulting in an increased risk of obesity and chronic degenerative diseases (6). Furthermore, it seems that the evening chronotype is associated with a higher risk of chrono-disruption and consequently with developing pathological conditions (40), probably because the circadian phase of such individuals is shifted by as much as 2–3 h (6).

In this meta-analysis, both daily energy intake and anthropometric parameters were evaluated. Previous studies have suggested that evening subjects consume more calories during the day (18, 21, 29, 51) and have a lower-quality diet (4, 22, 52) than morning subjects. One possible explanation for this behavior is that disruption of the circadian system affects appetite, energy expenditure, and several determinants of obesity (53). However, no significant differences in energy intake, body weight, BMI, and fat mass percentage were observed between the 2 chronotypes in our analysis, probably owing to the high heterogeneity in terms of study population and sample size of the studies included in the meta-analysis.

On the other hand, significantly higher concentrations of fasting blood glucose, HbA1c, LDL cholesterol, and triglycerides were reported in evening subjects than in morning subjects. From a chronobiological perspective, glucose

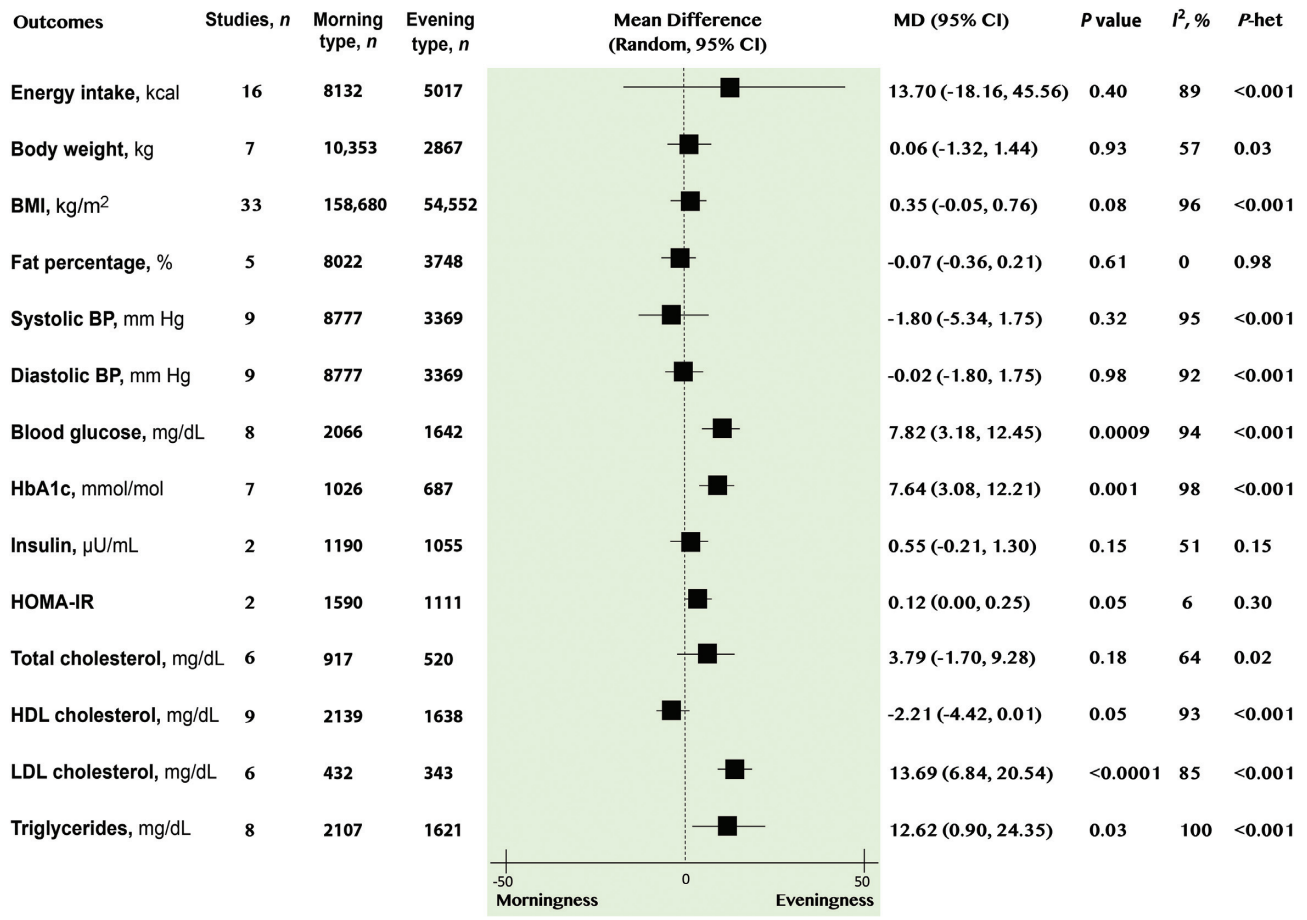

FIGURE 2 Forest plot summary of the association between chronotype, energy intake, and cardiometabolic risk factors assessed in cross-sectional studies. MD, mean difference; *P*-het, probability of the null hypothesis that there is no heterogeneity between studies.

metabolism in humans follows a circadian rhythm through diurnal variation in glucose tolerance, which typically peaks during the daytime hours, when food consumption usually occurs, and declines during the nighttime hours, when fasting usually occurs (54). As previously reported, evening subjects tend to eat later than morning ones (1, 18) and this may be associated with poorer glycemic control and increased risk of type 2 diabetes (1, 9). In addition, it has been reported that plasma triglyceride concentrations are elevated during the biological nighttime, and that the postprandial

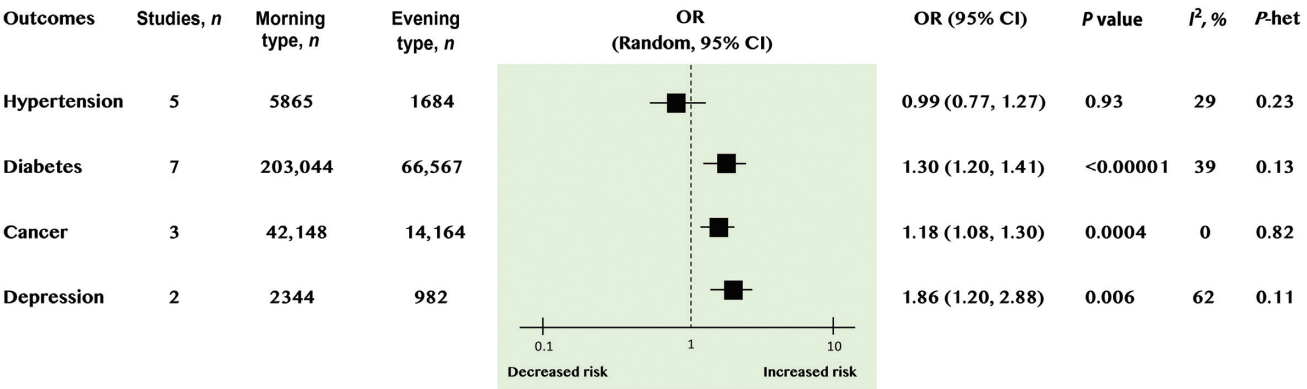

FIGURE 3 Forest plot summary of the association between chronotype and disease risk assessed in cross-sectional studies. *P*-het, probability of the null hypothesis that there is no heterogeneity between studies.

TABLE 4 Subgroup analyses[1]

	Blood glucose			HbA1c			LDL cholesterol			Triglycerides		
	n	MD (95% CI)	I^2 (*P*-het)	*n*	MD (95% CI)	I^2 (*P*-het)	*n*	MD (95% CI)	I^2 (*P*-het)	*n*	MD (95% CI)	I^2 (*P*-het)
Geographical region												
Northern	4	2.25 (−0.39, 4.88)	66% (0.03)	4	8.37 (2.34, 14.40)	94% (<0.00001)	4	16.22 (8.19, 24.26)	88% (<0.00001)	5	7.54 (−3.37, 18.45)	99% (<0.00001)
Southern	4	14.58 (2.14, 27.02)	97% (<0.00001)	3	6.47 (1.08, 11.86)	97% (<0.00001)	2	8.40 (1.44, 15.36)	0% (0.53)	3	26.99 (26.55, 27.43)	0% (0.43)
Study population												
Clinically healthy subjects	5	1.01 (−0.04, 2.05)	6% (0.37)	2	1.00 (0.63, 1.37)	0% (0.99)	4	12.80 (5.22, 20.37)	90% (<0.00001)	5	10.68 (−2.96, 24.33)	100% (<0.00001)
Patients[2]	3	22.88 (9.85, 35.92)	87% (0.0004)	5	10.77 (4.87, 16.68)	94% (<0.00001)	2	16.40 (−9.70, 42.52)	75% (0.04)	3	18.02 (13.71, 22.33)	0% (0.96)
Study quality												
Low (≤3 points, NOS)	1	31.80 (20.58, 43.02)	—	3	12.22 (3.46, 20.98)	96% (<0.00001)	—			—		
Medium (4–6 points, NOS)	5	7.91 (1.33, 14.49)	95% (<0.00001)	2	6.50 (3.25, 9.75)	9% (0.30)	5	14.84 (7.11, 22.56)	85% (<0.0001)	5	9.62 (−6.75, 26.00)	97% (<0.0001)
High (7–9 points, NOS)	2	1.43 (−0.67, 3.53)	0% (0.43)	2	1.00 (0.63, 1.37)	0% (0.99)	1	9.20 (1.80, 16.60)	—	3	16.57 (−2.08, 35.21)	100% (<0.00001)

[1] HbA1c, glycated hemoglobin; I^2, magnitude of heterogeneity; MD, mean difference; *n*, number of studies; NOS, Newcastle-Ottawa Scale; *P*-het, probability of the null hypothesis that there is no heterogeneity between studies.
[2] Subjects with a clinical diagnosis of disease (diabetes, inflammatory bowel disease, acute myocardial infarction).

response after a night meal is amplified compared with the same meal consumed during the day (55). Our results reinforce this hypothesis, because both glycemic and lipid profiles were worse in evening subjects.

Consistent with a worse cardiometabolic risk profile, evening subjects also reported an increased risk of developing diseases such as diabetes, cancer, and depression. Regarding cancer, evidence suggests that the direct disruption of the functions of circadian clock genes that control cell proliferation, or disruptions of clock-controlled settings such as sleep disturbances, may increase the risk (56, 57). Another hypothesis, called light-at-night, places the hormone melatonin at the center of the cancer disease process. It argues that melatonin is a major scavenger of reactive oxygen species (1). Because melatonin is primarily produced at night and suppressed by light, oncogenesis becomes more likely when people are exposed to light at night (1). Regarding depression, our results are in line with a previous meta-analysis that investigated the relation between chronotype and mood disorders such as depression, bipolar, and seasonal disorders (2). Indeed, evening subjects seem to be potentially associated with major depressive disorder (1, 2, 24, 37, 58), likely owing to a change in the rhythmic activity of neurotransmitter systems involved in mood regulation, including dopamine and serotonin secretion (58).

There are some limitations that should be discussed. First, in the included studies, chronotypes were assessed through self-reported questionnaires (the MEQ, reduced MEQ, the 19th question of the MEQ, and MCTQ), which are generally accepted, but are susceptible to bias. To date, the most reliable circadian phase marker in humans is the dim light melatonin onset, but the cost of this test is relatively high to allow its use in epidemiologic studies. Other reliable and valid methods to detect the circadian rhythm in humans are polysomnography or actigraphy, but their use in epidemiologic studies also has limitations owing to high costs and the specific expertise required. To consolidate our findings and to better examine how chronotype may affect the association between chrono-nutrition and health, further research on the best methods to assess chronotype is required. Second, the overall analysis for several outcomes such as insulin, HOMA-IR, cancer, and diabetes was performed in a limited number of studies, thus reducing the statistical power of the analysis. Furthermore, the possibility of publication bias could only be assessed for the 2 outcomes with >10 available studies. In this regard, publication bias is known to be a major threat to the validity of meta-analyses. Indeed, a higher probability of including statistically significant positive results generally causes an increase in the false-positive rate. Therefore, further well-conducted studies are needed to confirm these results and to better elucidate the interplay between chronotype, nutrition, and health status. Third, most of the included studies were cross-sectional. Although useful for identifying associations, these studies cannot infer causality or analyze behavior over time. Additional longitudinal or experimental studies are needed to investigate a possible cause-and-effect relation. Fourth, most of the included studies did not account for

confounders. Given that previous researchers have suggested that morning people tend to be more persistent, cooperative, conscientious, proactive, and less likely to procrastinate than evening people (59, 60), we cannot rule out that chronotype differences are due to subject characteristics and behaviors that lead to the morning instead of the evening state rather than a disruption of circadian rhythms. Finally, the high heterogeneity among the studies in terms of country, population, sample size, and chronotype assessment introduces a limitation in the interpretation of the results. Despite all these limitations, however, our study has several strengths, such as a rigorous search and selection strategy that identified all available cross-sectional and prospective cohort studies examining the relation between chronotype and health status, and the fact that most of the included studies were of good methodological quality.

In conclusion, we report, to our knowledge for the first time in a systematic review with meta-analysis, the possible association between evening chronotype, worse cardiometabolic risk profile, and increased risk of cardiovascular diseases, diabetes, cancer, and depression. The limitations of the available literature and the methods used to define individual chronotype, which need improving, reduce the applicability of these results to the general population. In addition, the underlying biological mechanisms that explain the link between chronotype, dietary habits, and health status need to be better understood and future experimental designs capable of drawing causal inferences are needed. Further research is also needed to better understand how to effectively apply the concept of chrono-nutrition in communities and in clinical practice. Nonetheless, these results provide a greater understanding of the relation between chronotype, diet, and health, and contribute to developing chronobiological approaches for the prevention and treatment of cardiometabolic and chronic disorders.

Acknowledgments

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