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Chapter 5

The association between social jetlag, the metabolic syndrome and Type 2 Diabetes Mellitus in the general population: the New Hoorn Study.

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ABSTRACT

Only a few studies have investigated the metabolic consequences of social jetlag. Therefore, we examined the association of social jetlag with the metabolic syndrome and type 2 diabetes mellitus, in a population-based cohort. We used cross-sectional data from the New Hoorn study cohort (n=1585, 47% men, age 60.8±6 years). Social jetlag was calculated as the difference in mid-point sleep between week and weekend days (h). Poisson and linear regression models were used to study the associations and age was regarded as a possible effect modifier. We adjusted for sex, employment status, education, smoking, physical activity, sleep duration and BMI. In the total population, we only observed an association between social jetlag and the metabolic syndrome, with prevalence ratios adjusted for sex, employment status and educational levels of 1.64 (95%CI: 1.1; 2.4) for participants with >2h social jetlag, compared to participants with 0-1h social jetlag. We however observed an interaction effect of median age (<61y). In older participants (>=61y), no significant associations were observed between social jetlag status, the metabolic syndrome and (pre)diabetes. In the younger group (<61y), the adjusted prevalence ratios were 1.29 (95%CI: 0.9-1.9) and 2.13 (95% CI: 1.3; 3.4) for the metabolic syndrome and 1.39 (95%CI: 1.1; 1.9) and 1.75 (95% CI: 1.2; 2.5) for (pre-)diabetes, for participants with 1-2h and >2h of social jetlag, compared to participants with 0-1h social jetlag. In conclusion, in our population-based cohort social jetlag was associated with a 2-fold increased risk of the metabolic syndrome and (pre-)diabetes mellitus, especially in younger (<61y) participants.

INTRODUCTION

Despite vast efforts toward prevention, the metabolic syndrome and type 2 diabetes mellitus are still highly prevalent in developed countries [1]. Age, obesity, and lifestyle are well-known risk factors [1], and recently, disturbance of the circadian rhythm was added to this list [2]. Shift work and time zone travel are examples of disruption of our circadian rhythm, with light and activity during the circadian night and sleep during the circadian day [3], which are associated with a 2-fold higher risk of both the metabolic syndrome and type 2 diabetes mellitus [4-7].

A less known but more chronic disruption of the circadian rhythm is social jetlag. Social jetlag represents the discrepancy between circadian and social clocks; people often use alarm clocks and/or medication to align their sleep and wake times with social obligations (e.g., work and school schedules) rather than with their internally regulated sleep-wake times [8, 9]. Social jetlag is highly prevalent; 69% of adults reported at least 1 h of social jetlag [8-11] and it is suggested to disturb physiological processes, such as blood pressure and glucose metabolism.

To date, only a few studies have investigated the metabolic consequences of social jetlag. Social jetlag was associated with a higher body mass index (BMI) in an overweight population [9, 12] as well as increased heart rate and cortisol levels in the general population [11, 13]. To date, only 2 smaller cohorts (n < 1000) showed an increased prevalence of the metabolic syndrome with social jetlag [12, 14] among participants younger than 50 years. In addition, a study of the association between social jetlag and type 2 diabetes mellitus is still lacking. Therefore, the aim of this study was to examine the association of social jetlag with the metabolic syndrome and type 2 diabetes mellitus in a population-based cohort. As the prevalence of the social jetlag decreases with age [15], while the prevalence of the metabolic syndrome and diabetes or prediabetes increases with age, we assessed whether age was an effect modifier in this cohort of people aged 50 and older.

METHODS

Study population

The New Hoorn Study (NHS) is a population-based cohort that is representative of the general Dutch population. As depicted in figure 1, from 2006 to 2007, a population-based survey of glucose tolerance was carried out in the Dutch city of Hoorn, which is a medium-sized town of about 70,000 residents with a mixed rural and urban population. The eligible population of the NHS consisted of 6180 men and women aged 40 to 75 years

randomly selected from the municipal registry. Of the eligible participants, 45% agreed to participate, resulting in the NHS cohort of 2807 participants [16].

Between January 2013 and December 2015, 1734 participants agreed to participate in follow up. As the questionnaire on social jetlag was introduced in 2013-2015, for the current analysis we only use data from the 2013-2015 measurement. Of the 1734 participants, we excluded those performing shift work (n=94) and those with no information regarding sleep-related measures (n=47) or metabolic syndrome, diabetes, or prediabetes (n=8), leaving 1585 participants for analysis. The Ethics Committee of the VU University Medical Centre approved the New Hoorn Study, and written informed consent was obtained from all participants.

Study design

Participants were asked to refrain from eating and drinking (except drinking water) from 20:00 h the night before the visit and from drinking alcohol and smoking from 17:00 h the day before the visit. Participants did not follow these instructions were asked to reschedule their visit. Before the visit, participants were asked to fill out questionnaires about their physical activities, medical history, quality of life, diet, and sleeping behavior. During the visit, we determined anthropometrics and blood pressure, collected a fasting blood sample, administered questionnaires, and noted self-reported medication. All visits were scheduled on weekdays [16].

Social jetlag status

Social jetlag status was determined using an adapted version of the Munich ChronoType Questionnaire (MCTQ)[15], which questions typical bedtime and wake times on weekdays and weekend/free days [17]. This questionnaire has shown good validity and reliability, with actual sleep time on weekdays and weekend/free days correlating highly (r ~ 1, p<0.001) [9, 15]. Social jetlag was measured as the difference in hours in midpoint of sleep between workdays and free days [8]. For example, when a person sleeps from 22:00 h until 06:00 h on weekdays, the midpoint is 02:00 h, and when one sleeps from 00:00 h until 10:00 h on weekend/free days, the midpoint is 05:00 h, which results in a 3-h social jetlag. In our population, social jetlag ranged from 0 to 4.5 h, which resulted in a skewed distribution. After log transformation, the distribution was still skewed. We therefore stratified the participants per hour of social jetlag, resulting in 3 groups: no social jetlag (<1h), 1-2 h social jetlag, or >2 h social jetlag, as previously done by Roenneberg et al. and Rutters et al. [9, 11]. We could not make 4 groups, as only 0.4% of the population had >3 h social jetlag.
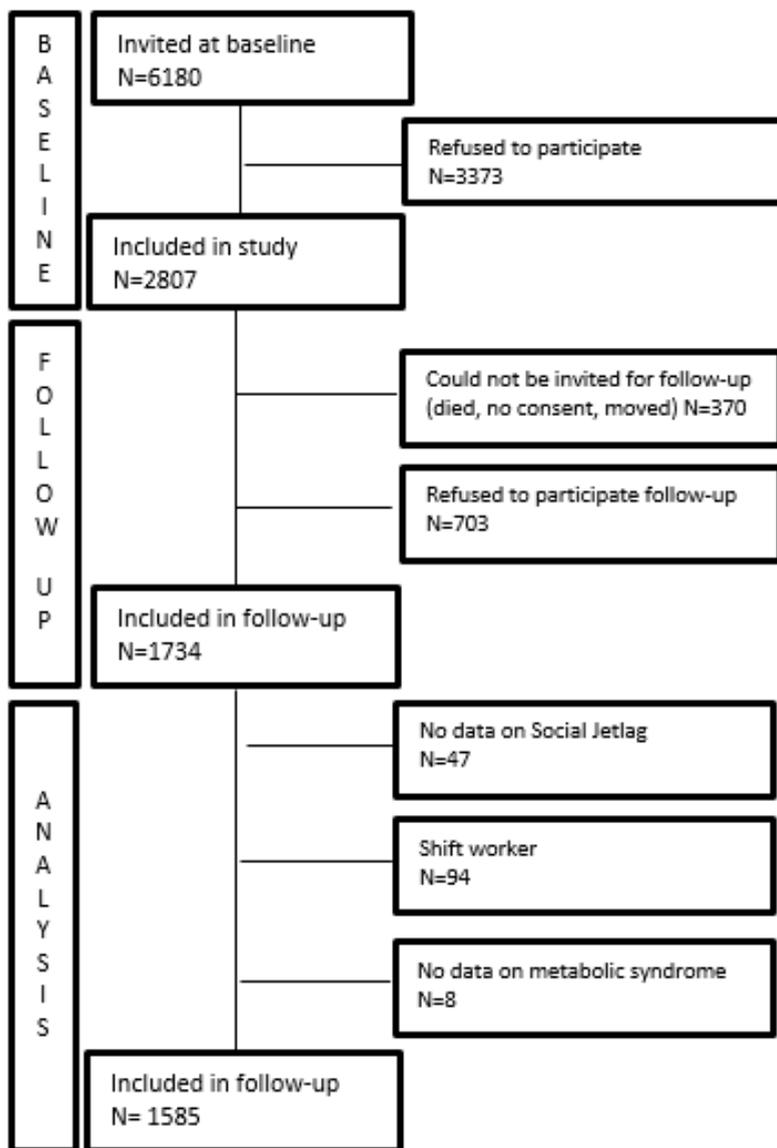
Figure 1. Flowchart of the study population of the New Hoorn Study cohort.

Metabolic syndrome

Metabolic syndrome status (yes/no) was defined according to the Adult Treatment Panel III of the National Cholesterol Education Program. That is, participants had to meet 3 or more of the following criteria: fasting plasma glucose levels ≥6.1 mmol/L, high-density lipoprotein (HDL) cholesterol levels <1.0 mmol/L in men or <1.3 mmol/L in women, triglyceride levels ≥1.7 mmol/L, waist circumference ≥102 cm in men or ≥88 cm in women, hypertension defined by ≥130/85 mmHg or use of hypertension medication [18].

Glucose levels (mmol/L) were determined from a fasting blood sample, using the glucose dehydrogenase method (Merck, Darmstad, Germany). Levels of HDL cholesterol (HDL-C, mmol/L) and triglycerides (mmol/L) were determined using enzymatic techniques (Boehringer Mannheim, Mannheim, Germany). Waist circumference (cm) was measured according to a standardized procedure [19]. Sitting blood pressure (mmHg) was measured 3 times on the right arm with a random-zero sphygmomanometer (Hawksley-Gelman, Lancing, UK), and the average between the 2 measures with the smallest difference between them was used in the statistical analyses.

Pre-diabetes and Type 2 diabetes mellitus

Prediabetes or type 2 diabetes mellitus status (yes/no) was classified according to the criteria of the WHO Consultation of 2011; prediabetes was defined as fasting plasma glucose levels ≥6.1 mmol/L and HbA1c levels ≥6.0% or ≥44 mmol/mol, and type 2 diabetes mellitus was defined as fasting plasma glucose levels ≥6.5 mmol/L, HbA1c levels ≥6.5% or ≥ 48 mmol/mol, and/or treatment for diabetes, including medication and diet [20]. Due to budget restraints, HbA1c levels were measured only in those with a higher risk for diabetes (n = 881), as determined using the DIRECT prediction model [21].

Covariates

Demographic factors were determined by questionnaires. Educational level was measured in 8 categories based on highest attainment; we stratified these categories into low educational level containing categories 1 and 2 (no education, primary school), middle educational level containing categories 3 to 5 (secondary education), and high educational level containing categories 6 to 8 (tertiary education). Job status was based on current status: having a job versus no job, the latter including unemployed people, housewives, and retirees. Smoking habits (current and previous smoking: yes/no) and physical activity were assessed using questionnaires. Low physical activity (yes/no) was defined as fewer than 5 days of 30 min of physical activity, the Dutch exercise norm. Average sleep duration (hours) was calculated as the difference between sleep onset until wake time from the MCTQ for weekdays and weekend days. Finally, weight and height were measured with participants wearing light clothes only, and we calculated BMI as weight divided by height squared (kg/m2).

Statistical analysis

First, to assess the participants' characteristics per social jetlag status, we determined the characteristics as percentages for dichotomous variables, as means and standard deviations for normally distributed continuous variables, and as medians and interquartile ranges for non-normal distributions. To address missing values for confounders, we used imputation via mean substitution. To assess possible bias, we used t-tests to compare participant characteristics for participants with and without follow-up as well as for participants with and without social jetlag data.

Second, we assessed the association between social jetlag and the metabolic syndrome as well as type 2 diabetes mellitus. As former and the latter are dichotomous outcome variables, we wanted to use logistic regression. However, as the high prevalence of the metabolic syndrome would have led to overestimation of relative risks, we used modified Poisson regression models [22, 23]. We reported the association between social jetlag and the metabolic syndrome as well as type 2 diabetes mellitus as prevalence ratios and 95% confidence intervals (CI) and p for trend.

Third, because the prevalence of social jetlag decreases with age [15] whereas the prevalence of the metabolic syndrome and diabetes/prediabetes increases with age, we assessed whether age was an effect modifier. A p value ≤ 0.10 was considered to be statistically significant for effect modification, in concordance with Twisk et al. [24]. In addition, we assessed possible confounding by sex, education, and employment status as well as possible confounding or mediating effects of smoking, physical activity, and BMI. We therefore corrected the association for these variables and reported 5 models, namely the unadjusted model (model 1); a model adjusted for sex, employment status, and educational level (model 2, the main model); a model adjusted for sex, employment status, educational level, smoking, and physical activity (model 3); a model adjusted for adjusted for sex, employment status, educational level, and BMI (model 4); and a model adjusted for adjusted for sex, employment status, educational level, and sleep duration (model 5).

Fourth, we assessed the association between social jetlag and the continuous parameters of the metabolic syndrome. We therefore used linear regression models and reported the unadjusted model and adjusted models as described above. Statistical analyses were performed with SPSS version 20.0 (SPSS Inc., Chicago, IL). Overall, a p-value ≤ 0.05 was considered to be statistically significant.

RESULTS

Our population-based cohort consisted of 1585 participants, of whom 47% were male, and had a mean age of 60.8 ± 6 years. Comparing participants at follow-up with those lost to follow-up, we observed no difference in sex (45% vs. 48%, p = 0.10), but participants without follow-up were slightly younger (53.0 vs. 53.6 years, p = 0.02) and less often had the metabolic syndrome (22% vs. 25%, p = 0.03) and more often had type 2 diabetes mellitus (10% vs. 4%, p = 0.01), compared with those included in our study. In addition, in those excluded due to having no social jetlag information (n = 47), we observed no significant difference in sex (47% vs. 58%, p = 0.12), age (60.6 vs. 61.9 years, p = 0.20), metabolic syndrome prevalence (19% vs. 18%, p = 0.78), or type 2 diabetes mellitus prevalence (11% vs. 19%, p = 0.07), compared with those with social jetlag information.

The baseline characteristics for the participants included in our analyses are described in Table 1, stratified for social jetlag. In our cohort, 61% of the participants reported not having social jetlag (<1 h social jetlag), 31% reported having 1-2 h social jetlag, and 8% reported having >2 h social jetlag. We observed differences between the social jetlag groups regarding age, those participants with 1-2 h and >2 h social jetlag being younger compared with participants without social jetlag (57 ± 5 years and 57 ± 5 years vs. 64 ± 6 years, p < 0.001). In addition, in the older participants (median age split, ≥61 years) only 24% and 19% had 1-2 h or >2 h social jetlag. As the prevalence of the metabolic syndrome and diabetes/prediabetes increases with age (stratified for median age, 61 years), 18% versus 22% and 26% versus 38%, respectively, we assessed whether age was an effect modifier.

First, we assessed the associations between social jetlag status and prevalence of the metabolic syndrome and diabetes/prediabetes, as depicted in Table 2. We observed no significant association between social jetlag status and diabetes/prediabetes. Additionally, we observed that social jetlag was associated with an increased prevalence of metabolic syndrome. After adjustment for sex, employment status, and educational level, prevalence ratios of 1.15 (95% CI 0.9-1.5) were observed for participants with 1-2 h social jetlag and 1.64 (95% CI 1.1-2.4) for participants with >2 h social jetlag, compared with participants with <1 h social jetlag (p for trend = 0.04). We observed confounding effects in model 2 and models 3-5, which showed that the association was confounded or mediated by BMI.

We observed effect modification by age (p = 0.01 for metabolic syndrome and p = 0.02 for diabetes/prediabetes) and therefore stratified the analyses for median age (≥61 years). In the participants older than 61 years, no significant associations were observed between social jetlag status and prevalence of the metabolic syndrome and diabetes/prediabetes (Tables 3 and 4). However, in the younger group (<61 years), social jetlag was associated with an increased risk of metabolic syndrome and diabetes/prediabetes. After adjustment for sex, employment status, and educational level,

prevalence ratios of 1.29 (95% CI 0.9-1.9) were observed for participants with 1-2 h social jetlag and 2.13 (95% CI 1.3-3.4) for participants with >2 h social jetlag, compared with participants with <1 h social jetlag (Table 3) for the metabolic syndrome. In addition, we observed prevalence ratios of 1.39 (95% CI 1.1-1.9) for participants with 1-2 h social jetlag and 1.75 (95% CI 1.2-2.5) for participants with >2 h social jetlag, compared with participants with <1 h social jetlag (Table 4) for diabetes/prediabetes. We observed confounding effects in model 2 and confounding/mediating effects in model 3-5, but the association remained significant.

Table 1. Participant characteristics stratified for social jetlag (n= 1585).

	Social jetlag <1 h	Social jetlag 1-2h	Social jetlag
Demographic variables			
Number (%) participants (n / %)	971/ 61	497/ 31	117/ 8
Sex (men %)	46	47	59
Age (years)	64 ± 6	57 ± 5	57 ± 5
Median age (≥61y %)	68	24	19
Education level (low %)	6	3	2
Job status (paid job %)	27	78	87
Behavioural variables			
Social jetlag (min)	21.7 ± 17	78.9 ± 17	139.6 ± 24
Average sleep duration (h)	8.2 ± 1	7.8 ± 1	7.8 ± 1
Smoking (current/previous, %)	59	58	62
Low physical activity (%)	31	38	38
Metabolic variables			
Fasting glucose (mmol/l)	5.9 ± 1	5.8 ± 1	5.9 ± 1
High-density lipoprotein cholesterol	1.57 ± 0.5	1.59 ± 0.5	1.53 ± 0.4
Triglycerides (mmol/l)	1.35 [0.9-1.6]	1.33 [0.8-1.6]	1.37 [0.8-1.9]
Waist circumference (cm)	91.2 ± 11	90.9 ± 12	93.8 ± 11
Systolic blood pressure (mmHg)	133 ± 19	127 ± 18	129 ± 17
Diastolic blood pressure (mmHg)	79 ± 8	78 ± 9	80 ± 9
Use hypertension medication (%)	33	23	23
Body mass index (kg/m^2)	26.5 ± 4	26.4 ± 4	27.1 ± 4
HbA1c (mmol/mol) n=920	42.4 ± 6	41.5 ± 5	42.8 ± 6
HbA1c (%) n=920	6 ± 2.7	5.9 ± 2.6	6 ± 2.7
Metabolic syndrome (%)	21	18	26
Pre-diabetes and type 2 diabetes	33/14	30/8	34/11

Characteristics are presented as percentage, mean ± standard deviation, or median [interquartile range].

Table 2. Prevalence Ratios (with 95% CIs) of the metabolic syndrome and diabetes/prediabetes per social jetlag groups in the New Hoorn Study cohort (n= 1585).

		Model 1	Model 2	Model 3	Model 4	Model 5
Metabolic syndrome	Social jetlag <1 h	[ref]	[ref]	[ref]	[ref]	[ref]
	Social jetlag 1-2 h	0.87 (0.7; 1.1)	1.15 (0.9; 1.5)	1.04 (0.8; 1.4)	1.03 (0.8; 1.3)	1.11 (0.9; 1.5)
	Social jetlag >2 h	1.23 (0.9; 1.7)	**1.64 (1.1; 2.4)**	**1.51 (1.1; 2.2)**	1.25 (0.9; 1.8)	**1.62 (1.1; 2.4)**
P for trend		0.14	0.04	0.10	0.47	0.10
Diabetes/prediabetes	Social jetlag <1 h	[ref]	[ref]	[ref]	[ref]	[ref]
	Social jetlag 1-2 h	0.89 (0.8; 1.1)	0.99 (0.8; 1.2)	0.99 (0.8; 1.2)	0.96 (0.8; 1.2)	0.99 (0.8; 1.2)
	Social jetlag >2 h	1.02 (0.8; 1.3)	1.11 (0.8; 1.5)	1.10 (0.8; 1.5)	0.98 (0.8; 1.3)	1.10 (0.8; 1.5)
P for trend		0.76	0.75	0.77	0.92	0.75

Model 1: unadjusted; Model 2: adjusted for sex, employment status and educational level; Model 3: adjusted for sex, employment status, educational level, smoking and physical activity; Model 4: adjusted for sex, employment status, educational level and BMI; Model 5: adjusted for employment status, educational level and sleep duration. [ref]=reference category

Table 3. Prevalence Ratios (with 95% CIs) of the metabolic syndrome per social jetlag groups stratified for age in the New Hoorn Study cohort (n= 1585).

		Model 1	Model 2	Model 3	Model 4	Model 5
Metabolic syndrome, <61 years	Social jetlag <1 h	[ref]	[ref]	[ref]	[ref]	[ref]
	Social jetlag 1-2 h	1.13 (0.8; 1.6)	1.29 (0.9; 1.9)	1.15 (0.8; 1.7)	1.13 (0.8; 1.6)	1.22 (0.8; 1.8)
	Social jetlag >2 h	**1.91 (1.3; 2.9)**	**2.13 (1.3; 3.4)**	**1.83 (1.1; 2.9)**	**1.55 (1.0; 2.4)**	**2.06 (1.3; 3.3)**
	P for trend	0.01	0.01	0.04	0.13	0.01
Metabolic syndrome, ≥61 years	Social jetlag <1 h	[ref]	[ref]	[ref]	[ref]	[ref]
	Social jetlag 1-2 h	0.86 (0.6; 1.3)	1.04 (0.7; 1.6)	0.94 (0.6; 1.5)	0.99 (0.6; 1.5)	1.04 (0.7; 1.6)
	Social jetlag >2 h	0.39 (0.1; 1.5)	0.56 (0.2; 2.2)	0.64 (0.2; 2.5)	0.51 (0.1; 1.9)	0.58 (0.2; 2.2)
	P for trend	0.29	0.70	0.79	0.61	0.70

Model 1: unadjusted; Model 2: adjusted for sex, employment status and educational level; Model 3: adjusted for sex, employment status, educational level, smoking and physical activity; Model 4: adjusted for sex, employment status, educational level and BMI; Model 5: adjusted for employment status, educational level and sleep duration. [ref]=reference category

Table 4. Prevalence Ratios (with 95% CIs) of diabetes/prediabetes per social jetlag groups stratified for age in the New Hoorn Study cohort (n= 1585).

		Model 1	Model 2	Model 3	Model 4	Model 5
Diabetes/ prediabetes, <61 years	Social jetlag <1 h	[ref]	[ref]	[ref]	[ref]	[ref]
	Social jetlag 1-2 h	**1.35 (1.0; 1.8)**	**1.39 (1.1; 1.9)**	**1.40 (1.0; 1.9)**	**1.34 (1.0; 1.8)**	**1.39 (1.0; 1.9)**
	Social jetlag >2 h	**1.79 (1.3; 2.5)**	**1.75 (1.2; 2.5)**	**1.67 (1.1; 2.5)**	**1.50 (1.1; 2.1)**	**1.73 (1.2; 2.5)**
	P for trend	0.01	0.01	0.02	0.05	0.01
Diabetes/ prediabetes, ≥61 years	Social jetlag <1 h	[ref]	[ref]	[ref]	[ref]	[ref]
	Social jetlag 1-2 h	0.94 (0.7; 1.2)	0.89 (0.7; 1.2)	0.88 (0.7; 1.2)	0.88 (0.7; 1.2)	0.89 (0.7; 1.2)
	Social jetlag >2 h	0.58 (0.3; 1.3)	0.54 (0.3; 1.2)	0.59 (0.3; 1.2)	0.50 (0.3; 1.1)	0.54 (0.3; 1.2)
	P for trend	0.36	0.21	0.28	0.11	0.21

Model 1: unadjusted; Model 2: adjusted for sex, employment status and educational level; Model 3: adjusted for sex, employment status, educational level, smoking and physical activity; Model 4: adjusted for sex, employment status, educational level and BMI; Model 5: adjusted for employment status, educational level and sleep duration. [ref]=reference category

We also assessed the association between social jetlag and the parameters of metabolic syndrome factors separately (Tables 5 and 6). In the participants ≥61 years old, after adjustment for sex, employment status, and educational level, no significant associations were observed between social jetlag status and the parameters of the metabolic syndrome. In the younger group (<61 years old), after correcting for sex, employment level, and educational level, we observed 0.33 mmol/L (95% CI 0.1-0.5) higher glucose levels as well as 2.94 cm (95% CI 0.2-5.7) higher waist circumference in participants with >2 h social jetlag, compared with those without (<1 h) social jetlag. The association between social jetlag, glucose levels, and waist circumference was confounded by employment status, educational level, and sleep duration, decreasing the association, but still being significant. No differences were observed with regard to the parameters of the metabolic syndrome in participants with 1-2 h social jetlag, compared with those without social jetlag.

Table 5. Unstandardized betas (with 95% CIs) for the association between social jetlag and parameters of the metabolic syndrome for participants <61 years old.

<61y		Model 1	Model 2	Model 3
Glucose (mmol/l)	Social jetlag <1 h	[ref]	[ref]	[ref]
	Social jetlag 1-2 h	0.07 (-0.1; 0.2)	0.09 (-0.1; 0.2)	0.10 (-0.1; 0.2)
	Social jetlag >2 h	**0.34 (0.1; 0.5)**	**0.33 (0.1; 0.5)**	**0.34 (0.1; 0.5)**
HDL cholesterol (mmol/l)	Social jetlag <1 h	[ref]	[ref]	[ref]
	Social jetlag 1-2 h	-0.02 (-0.1; 0.1)	-0.01 (-0.1; 0.1)	-0.01 (-0.1; 0.1)
	Social jetlag >2 h	-0.08 (-0.2; 0.1)	-0.02 (-0.2; 0.1)	-0.02 (-0.1; 0.1)
Log triglycerides (mmol/l)	Social jetlag <1 h	[ref]	[ref]	[ref]
	Social jetlag 1-2 h	-0.01 (-0.1; 0.1)	-0.01 (-0.1; 0.1)	-0.01 (-0.1; 0.1)
	Social jetlag >2 h	0.02 (-0.1; 0.1)	0.02 (-0.1; 0.1)	0.02 (-0.1; 0.1)
Waist circumference (cm)	Social jetlag <1 h	[ref]	[ref]	[ref]
	Social jetlag 1-2 h	0.89 (-0.9; 2.6)	0.93 (-0.9; 2.6)	0.66 (-1.2; 2.5)
	Social jetlag >2 h	**3.93 (1.2; 6.7)**	**2.94 (0.2; 5.7)**	**2.78 (0.1; 5.6)**
Systolic blood pressure	Social jetlag <1 h	[ref]	[ref]	[ref]
	Social jetlag 1-2 h	0.65 (-1.9; 3.3)	0.73 (-2.0; 3.5)	0.57 (-2.2; 3.4)
	Social jetlag >2 h	2.17 (-1.8; 6.2)	1.79 (-2.4; 5.9)	1.69 (-2.5; 5.9)

Model 1: unadjusted; Model 2: adjusted for sex, employment status and educational level; Model 3: adjusted for employment status, educational level and sleep duration. [ref]=reference category

Table 6. Unstandardized betas and confidence intervals for the association between social jetlag and parameters of the metabolic syndrome for participants ≥61 years old.

>=61y		Model 1	Model 2	Model 3
Glucose	Social jetlag < 1h	[ref]	[ref]	[ref]
(mmol/l)	Social jetlag 1-2h	-0.19 (-0.4; 0.1)	-0.19 (-0.4; 0.1)	-0.19 (-0.4; 0.1)
	Social jetlag >2h	-0.41 (-0.8; 0.1)	-0.44 (-0.9; 0.1)	**-0.43 (-0.8; -0.1)**
HDL	Social jetlag < 1h	[ref]	[ref]	[ref]
cholesterol	Social jetlag 1-2h	0.05 (-0.1; 0.1)	0.03 (-0.1; 0.1)	0.03 (-0.1; 0.1)
(mmol/l)	Social jetlag >2h	-0.05 (-0.2; 0.1)	-0.03 (-0.2; 0.1)	-0.03 (-0.2; 0.1)
Log	Social jetlag < 1h	[ref]	[ref]	[ref]
triglycerides	Social jetlag 1-2h	-0.01 (-0.1; 0.1)	-0.01 (-0.1; 0.1)	-0.01 (-0.1; 0.1)
(mmol/l)	Social jetlag >2h	-0.04 (-0.1; 0.1)	-0.03 (-0.1; 0.1)	-0.03 (-0.1; 0.1)
Waist	Social jetlag < 1h	[ref]	[ref]	[ref]
circumference	Social jetlag 1-2h	0.93 (-0.9;2.7)	0.37 (-1.8;2.5)	0.37 (-1.8;2.6)
(cm)	Social jetlag >2h	**2.94 (0.2; 5.7)**	1.92 (-2.45; 6.3)	1.92 (-2.5; 6.2)
Systolic blood	Social jetlag < 1h	[ref]	[ref]	[ref]
pressure	Social jetlag 1-2h	**-5.83 (-9.6; -2.1)**	-4.04 (-8.1; 0.1)	-4.01 (-8.1; 0.1)
	Social jetlag >2h	-1.58 (-9.7; 6.5)	-0.11 (-8.3; 8.2)	-0.1 (-8.4; 8.1)

Model 1: unadjusted; Model 2: adjusted for sex, employment status and educational level; Model 3: adjusted for employment status, educational level and sleep duration. [ref]=reference category

DISCUSSION

The aim of this study was to examine the association of social jetlag with the metabolic syndrome and type 2 diabetes mellitus, in a population-based cohort. In our total cohort, we observed an association between social jetlag and the metabolic syndrome only for participants with >2 h social jetlag, compared with participants with <1 h social jetlag. However, we observed an interaction effect of median age (<61 years). We observed that having >2 h social jetlag was associated with an approximate 2-fold increased risk of the metabolic syndrome and diabetes mellitus or prediabetes, compared with participants without social jetlag in the younger (<61 years) group. This association was mainly driven by the increased glucose levels and higher waist circumference associated with >2 h social jetlag. In contrast, in the older (≥61 years) group we observed no significant associations between social jetlag status, parameters of metabolic syndrome, and diabetes/prediabetes.

We showed an association between social jetlag and a higher prevalence of diabetes/prediabetes. These results are congruent with earlier studies that showed similar directionality of the association between social jetlag and diabetes markers [12, 14].

However, in contrast to Wong et al. [14], we did not observe a positive association between social jetlag and triglycerides. This contradiction to the only other study that investigated the association between social jetlag and metabolic syndrome parameters might be caused by differences in study population. Wong et al. included a younger group of more homogenous participants: 500 healthy, working participants, aged 30 to 54 years, while our population was population-based and thus more heterogeneous.

Second, our analysis showed effect modification for age. This modification is due to the lower prevalence of social jetlag in our older (≥61 years) participants: only 24% and 19% of them had 1-2 h or >2 h social jetlag, respectively, while the prevalence of the metabolic syndrome and diabetes/prediabetes increases in this group. The lower prevalence of social jetlag in the older participants confirms the results from Roenneberg et al. [9], who showed a decrease in social jetlag with age. In the younger (<61 years) participants, we observed similar effect sizes and direction of the association between social jetlag and metabolic syndrome, when compared with literature studying even younger (<50 years) populations [12, 14]. However, no such association was observed in our older (≥61 years) participants. This lack of association might be due to social jetlag being driven by work obligations, which decline after age 61 years due to retirement. The absence of social clocks might decrease social jetlag in these older participants, creating a group of people who had social jetlag for more than 40 years and other people who never had social jetlag, resulting in a mixed group in which the associations cannot be determined.

Overall, the findings from the current study suggest the association between social jetlag and metabolic syndrome to be driven by higher glucose and waist circumference. This is congruent with our hypotheses on how social jetlag can lead to adverse health outcomes. First, circadian misalignment is suggested to disrupt the endogenous circadian rhythm controlled by the suprachiasmatic nucleus (SCN) [25], which controls the hypothalamus pituitary adrenal (HPA) axis and thus alters its regulation [25]. In concordance with the Bjorntorp hypothesis, disturbance of the HPA axis is associated with the development of visceral obesity and the metabolic syndrome [6, 26]. Second, the SCN also controls the peripheral clocks, which in turn control glucose homeostasis. By disturbing the SCN and peripheral clocks, circadian misalignment also alters glucose homeostasis [25, 27]. Overall, these data suggested that the effect of social jetlag is driven by visceral obesity and glucose homeostasis rather than cardiovascular parameters.

In the literature, several pathways have been proposed that would mediate the association between social jetlag and metabolic syndrome. For example, changes in circadian rhythm deregulate appetite and physical activity [28]. Aside from altering health behaviors, changes in the circadian rhythm could also affect metabolic syndrome via several physiologic pathways, such as hyperactivation of the HPA axis and autonomic nervous system [29]. We do not have data to study this; however, proxy measurements of these systems (i.e., blood pressure) were not associated with social jetlag. A recent experimental

study by Rao et al. showed a role for nonesterified fatty acid (NEFA) levels in the decrease of whole body insulin sensitivity after sleep alterations [30]. In general, it is believed that all these different pathways add up the metabolic syndrome. However, future studies need to include measures of these potential pathways.

Our study has some limitations that warrant discussion. First, our data were cross-sectional, which makes it difficult to determine cause, effect, and the possible mediating effect of risk factors. Second, we used data from a follow-up measurement that was not completely representative of the baseline cohort: Participants at the earlier visit were slightly older and had a higher prevalence of the metabolic syndrome and a lower prevalence of type 2 diabetes. Third, we used an adapted version of the Munich ChronoType Questionnaire from 2003 to assess social jetlag [8, 15]. This version questions sleep and wake times on weekdays and weekend/free days and does not question use of an alarm clock on weekend/free days, which might lead to an underestimation of social jetlag, while our current estimates of sleep and wake times on weekend/free days would be earlier compared with days that entail unrestricted sleep and wake times. Fourth, we did not measure information on dietary intake, which could have affected or mediated the association between social jetlag and metabolic outcomes. Fifth, we did not measure HbA1c levels in the whole cohort, but only in those with an increased risk of having developed diabetes (55%), which might result in an underestimation of the prevalence of diabetes/prediabetes. Strengths of our study are that we diagnosed metabolic syndrome and diabetes/prediabetes, instead of using self-reported measures, and that we collected the data in a large, middle-aged, population-based cohort with comprehensive information on relevant confounders.

From our current study, we conclude that in our population-based cohort, social jetlag was associated with a 2-fold increased risk of the metabolic syndrome and diabetes mellitus or prediabetes, especially in younger (<61 years) participants. These results confirm that even small changes of circadian misalignment are associated with adverse health outcomes, such as metabolic syndrome and even diabetes/prediabetes. Possible interventions targeting social jetlag, including simple behavioral modifications such as keeping a regular sleep-wake schedule, could therefore have beneficial effects on the development of the metabolic syndrome and type 2 diabetes mellitus, especially in younger (<61 years) people. However, more in vivo research in prospective cohorts is necessary to confirm these findings.

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