Mismatch of Sleep and Work Timing and Risk of Type 2 Diabetes

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OBJECTIVE

To examine whether a mismatch between chronotype (i.e., preferred sleep timing) and work schedule is associated with type 2 diabetes risk.

RESEARCH DESIGN AND METHODS

In the Nurses' Health Study 2, we followed 64,615 women from 2005 to 2011. Newly developed type 2 diabetes was the outcome measure (n = 1,452). A question on diurnal preference ascertained chronotype in 2009; rotating night shift work exposure was assessed regularly since 1989.

RESULTS

Compared with intermediate chronotypes, early chronotypes had a slightly decreased diabetes risk after multivariable adjustment (odds ratio 0.87 [95% CI 0.77–0.98]), whereas no significant association was observed for late chronotypes (1.04 [0.89–1.21]). Among early chronotypes, risk of type 2 diabetes was modestly reduced when working daytime schedules (0.81 [0.63–1.04]) and remained similarly reduced in women working <10 years of rotating night shifts (0.84 [0.72–0.98]). After ≥10 years of shift work exposure, early chronotypes had a nonsignificant elevated diabetes risk (1.15 [0.81–1.63], P_{trend} = 0.014). By contrast, among late chronotypes, the significantly increased diabetes risk observed among day workers (1.51 [1.13–2.02]) appeared largely attenuated if their work schedules included night shifts (<10 years: 0.93 [0.76–1.13]; ≥10 years: 0.87 [0.56–1.34]; P_{trend} = 0.14). The interaction between chronotype and shift work exposure was significant ($P_{interaction}$ = 0.0004). Analyses restricting to incident cases revealed similar patterns.

CONCLUSIONS

In early chronotypes, type 2 diabetes risk increased with increasing duration of shift work exposure, whereas late types had the highest diabetes risk working daytime schedules. These data add to the growing body of evidence that workers could benefit from shift schedules minimizing interference with chronotype-dependent sleep timing.

Laboratory studies have shown that sleep loss results in altered glucose metabolism, and large observational studies have shown that short and long sleep durations are associated with type 2 diabetes risk, supporting the link between sleep and metabolism (1,2). Sleep, however, is multidimensional. In addition to sleep duration and quality, sleep timing may be critical for metabolic processes (3). For example, studies have shown that late chronotypes (also referred to as owls), who generally tend to fall asleep and wake up later than earlier chronotypes (or larks) (4,5), exhibit higher HbA_{1c} levels (6), are at higher risk for the metabolic syndrome (7), and have a

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significantly higher risk for type 2 diabetes compared with early or intermediate chronotypes (8).

Sleep timing is largely regulated by the circadian clock (together with the sleep homeostat) (9); however, in our 24/7 society, it also heavily depends on work schedules: In a cross-sectional study, we showed that early chronotypes sleep worse and less and display the highest levels of circadian misalignment during night shift work, whereas late chronotypes' sleep and circadian system are most adversely affected by early morning shifts (10). Furthermore, among >60,000 day-working participants, work schedules constraining individual sleep timing were associated with obesity (11), suggesting that chronotype may interact with working times and thereby modulate sleep and ultimately health (12).

Experimental studies support independent effects of sleep timing and duration. When systematically varying sleep/wake episodes across the biological day and night in a laboratory setting (i.e., similar to what shift workers experience), Scheer et al. (13) observed that greater circadian misalignment is associated with impaired glucose metabolism, decreased insulin sensitivity, and reduced leptin levels. Taking this approach one step farther, Buxton et al. (14) mimicked shift schedule constraints on sleep in the laboratory, imposing both partial sleep deprivation and circadian misalignment on participants. They found that metabolic rates decreased and plasma glucose levels increased, suggesting inadequate insulin secretion.

We have previously demonstrated in the Nurses' Health Study 2 (NHS2) that type 2 diabetes risk increases monotonically with increasing years of shift work (15). In the current study, we first examined the association of chronotype with type 2 diabetes risk and then tested how rotating night shift work may modulate these associations. We hypothesized that night shift work adversely affects the risk of type 2 diabetes in early chronotypes but not in late chronotypes because night shifts interfere less with their sleep timing.

RESEARCH DESIGN AND METHODS

The NHS2 is a large prospective cohort study of women's health that began in 1989 when 116,434 U.S. registered nurses aged 25–42 years responded to a baseline questionnaire. Participants complete biennial follow-up questionnaires to update information on medical history, lifestyle factors, and newly diagnosed diseases. Follow-up rates are high, with ~90% participation at each 2-year cycle (16). This study was approved by the Brigham and Women's Institutional Review Board. Answering the self-administered questionnaire implies informed consent.

Chronotype Assessment

In 2009, we queried chronotype with a single question on the NHS2 main questionnaire, specifically, question 19 from the Morningness-Eveningness Questionnaire (17): "One hears about 'morning' and 'evening' types of people. Which one of these types do you consider yourself to be?" Response categories comprised definitely a morning type, rather more a morning than an evening type, rather more an evening than a morning type, definitely an evening type, and neither. This single-item measure of chronotype relates well with the overall score of the Morningness-Eveningness Questionnaire (r = 0.72) (18) and has previously been associated with sleep timing (19).

Night Shift Work Assessment

The assessment of night shift work history in NHS2 has been described in detail elsewhere (16). Briefly, women indicated in 1989 how many years of rotating night shift work (at least three night shifts per month in addition to days and evenings) they had worked until then, with updates in 1991, 1993, 1997, 2001, 2005, and 2009, and retrospective rotating night shift work assessments for 1997–1999 (in 2001), 2001–2003 (in 2005), and 2005–2007 (in 2009) were included in the next biennial questionnaire, respectively.

Ascertainment of Type 2 Diabetes

Type 2 diabetes has been queried biennially since 1989 in the NHS2. All women reporting the diagnosis of diabetes on any questionnaire received a supplemental questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy. A case of type 2 diabetes was considered confirmed if one of the following National Diabetes Data Group criteria (20) applied: *1*) one or more classic symptoms (i.e., excessive thirst, polyuria or frequent urination, weight loss, hunger) in addition to fasting plasma glucose levels of at least 7.8 mmol/L or random plasma glucose levels of at least 11.1 mmol/L, *2*) two or more measures of elevated plasma glucose concentrations at separate occasions in the absence of symptoms (≥7.8 mmol/L fastening, ≥11.1 mmol/L random plasma glucose, or oral glucose tolerance test of ≥11.1 mmol/L after 2 h), or *3*) hypoglycemia treatment (insulin or oral hypoglycemic agent). In line with American Diabetes Association recommendations (21), a level of 7.0 mmol/L was considered the threshold for fasting plasma glucose levels from 1998 onward.

Validation studies showed extremely high reliability of self-reported diabetes diagnoses in the NHS cohorts. Of 62 cases in the NHS, 61 were verified by medical records (22). A substudy evaluated the prevalence of undiagnosed diabetes by measuring plasma glucose and fructosamine in a random sample of nurses who had not reported diabetes previously. Only one woman (0.5%) had levels within the diabetic range, suggesting a very low level of false-positive findings in this highly medically trained population of nurses.

Assessment of Covariates

From 1989 onward, women were asked every 2 years to provide updated information on risk factors for chronic diseases, such as body weight, cigarette smoking, family history of diabetes, physical activity, menopausal status, and hormone intake. Census 2005 and 2009 data were used to assign median annual household income at the census tract level. Alcohol consumption and the Alternative Healthy Eating Index (AHEI) (23) were calculated based on food frequency questionnaire data collected in 2007. Average sleep duration was ascertained in 2009. Participants repeatedly answered questions regarding antidepressant medication use (1993, 1997, 1999, 2001, 2003, 2005, 2007, and 2009) as well as indicated whether they had a diagnosis of depression (2001–2009). We combined this information to account for potential depressive symptoms.

Population for Analysis

A total of 85,362 women completed the NHS2 questionnaire in 2005. Of these, 9,885 did not answer the chronotype question in 2009. We further excluded

participants with diabetes, heart disease, stroke, or cancer at baseline (n = 10,131). Finally, due to incomplete type 2 diabetes follow-up beyond May 2011, we excluded another 731 participants with diabetes. After all exclusions, the final population comprised 64,615 women.

Statistical Analyses

We defined definite morning types as early chronotypes, definite evening types as late chronotypes, and everyone else as intermediate chronotypes. We first used multivariable-adjusted logistic regression to calculate multivariable odds ratios (MVORs) and 95% CIs across these three chronotype categories. The referent group comprised the intermediate chronotypes in all analyses. To determine duration of rotating night shift work history, we generally used the midpoints of the respective response categories (0, 1–4, 5–9, 10–14, 15–19 months) and calculated the sum of all durations. For the last response category (i.e., ≥20-month category), we conservatively set the duration to 20 months. To then examine the combined effects of chronotype and rotating night shift work, we stratified by cumulative shift work (never worked rotating night shifts, 1–10 years, >10 years) and used a likelihood ratio test to evaluate the significance of the cross-product term between chronotype (continuous) and rotating night shift work (midpoints of categories). The primary analysis examining the associations among chronotype, shift work, and type 2 diabetes included all cases occurring between 2005 and 2011 (n = 1,472). In secondary analyses, we restricted to incident cases of type 2 diabetes (i.e., occurring between 2009 and 2011 [n = 319]).

We calculated age-adjusted estimates and multivariable-adjusted estimates, additionally adjusting for type 2 diabetes risk factors such as family history of diabetes, BMI (<25, 25–30, or >30 kg/m^2), diet [AHEI (23)], physical activity (MET-h/week, both in quintiles), smoking status (never, past, current 1–14 cigarettes/day, current ≥15 cigarettes/day), alcohol intake (0, 0.1–5, 5.1–10, 10.1–15, >15 g/day), oral contraceptive use (ever, never), menopausal status (pre-, postmenopause), postmenopausal hormone use (premenopause, ever, never), sleep duration during the current work schedule (<5, 6, 7, 8, >9 h), median annual household income ($, in tertiles), and history of depressive mood (defined as either regular antidepressant medication use or self-reported physician-diagnosed depression). The interaction between average sleep duration and age did not yield significance in our main analysis and thus was not included in the regression models.

In secondary analyses, we also examined potential effect modification by BMI of the association between chronotype and type 2 diabetes, stratifying by BMI (<25 and ≥25 kg/m^2) and adjusting for BMI continuously in each stratum to account for residual confounding. To minimize residual confounding by depressed mood, a potentially strong confounding factor (24,25), we performed a sensitivity analysis excluding women from the study population who reported either regular antidepressant medication use in any 2-year cycle or a physician diagnosis of depression (n = 20,586). We also restricted to cases occurring before 2009 (i.e., truly prevalent cases) to avoid overlap with the incident case analyses, potentially introducing bias. Finally, in sensitivity analyses, we excluded all women who *1*) currently indicated working permanent night shifts (in 2009) and *2*) ever indicated working permanent night shifts (1989–2011). We conducted all analyses with SAS 9.3 software (SAS Institute Inc., Cary, NC).

RESULTS

Table 1 shows age and age-adjusted characteristics across chronotype categories in the study population. Thirty-five percent of all women classified themselves as early chronotypes, 54% as intermediate, and 11% as late chronotypes.

Overall, women had very similar characteristics across chronotypes; however, we observed increasingly lower levels of physical activity and higher BMI when moving from early to intermediate to late chronotype categories. In addition, late chronotypes reported more extreme sleep durations (<5 and ≥9 h), reported physician-diagnosed depression more often, and had higher proportions of regular antidepressant medication use.

Table 2 shows the relationship between chronotype and type 2 diabetes. Compared with intermediate types, early chronotypes had a modestly lower risk of type 2 diabetes, and this effect remained after multivariable adjustment (model 3: MVOR 0.87 [95% CI 0.77–0.98]) (Table 2). By contrast, late chronotypes had a significantly increased risk of type 2 diabetes in age-adjusted models; however, this effect was attenuated and nonsignificant after multivariable adjustment (1.04 [0.89–1.21]).

Among women who had never worked rotating night shifts, early chronotypes had a nonsignificantly reduced type 2 diabetes risk (MVOR 0.81 [95% CI 0.63–1.04]) (Table 3) compared with intermediate types, whereas late chronotypes showed a significantly increased type 2 diabetes risk (1.51 [1.13–2.02]). Women who worked <10 years of rotating night shifts still had reduced risk estimates if they were early chronotypes (0.84 [0.72–0.98]). For late chronotypes, the association with type 2 diabetes was attenuated (0.93 [0.76–1.13]). Among women with ≥10 years of shift work exposure, neither early nor late chronotypes had an increased risk of type 2 diabetes compared with intermediate chronotypes (early chronotypes: 1.15 [0.81–1.63]; late chronotypes: 0.87 [0.56–1.34]). The trend across shift work categories was significant in early (P = 0.014) but not in late (P = 0.14) chronotypes. We observed a significant interaction between shift work exposure and chronotype [$\chi(1)$ = 12.4, $P_{interaction}$ = 0.0004].

The results of the secondary prospective analysis (n = 319 incident cases occurring between 2009 and 2011, i.e., after the 2009 chronotype assessment) reflected similar patterns (Tables 2 and 3), and the interaction between chronotype and cumulative rotating night shift work remained significant in these analyses [$\chi(1)$ = 4.0, $P_{interaction}$ = 0.045]. We examined whether the associations between chronotype and type 2 diabetes differed by BMI strata (<25, ≥25 kg/m^2). We did not find strong evidence for a significant effect modification by BMI, with odds ratios remaining largely similar among overweight and obese women and slightly stronger among normal weight women [early chronotypes: MVOR 0.80 (0.49–1.33); late chronotypes: 1.56 (0.85–2.88); $\chi(1)$ = 3.2; $P_{interaction}$ = 0.07] compared with intermediate chronotypes.

Table 1—Age-adjusted characteristics of women in the NHS2 by chronotype in 2009

	Chronotype		
	Early (*n* = 22,089)	Intermediate (*n* = 33,825)	Late (*n* = 7,029)
Age (years)[1]	54.3 (4.6)	54.2 (4.6)	54.2 (4.7)
Median annual family income ($)[2]	66,599 (24,714)	65,767 (23,883)	64,953 (23,393)
Family history of diabetes	37	37	38
BMI (kg/m^2)	26.4 (5.6)	27.3 (6.1)	28.6 (6.6)
Smoking status			
Never	67	67	64
Past	28	28	27
Current 1–14 cigarettes/day	3	3	5
Current ≥15 cigarettes/day	2	2	4
Alcohol consumption 2007 (g/day)	6.9 (10.4)	6.6 (10.4)	5.9 (10.5)
Physical activity (MET-h/week)[3]	28.2 (34.6)	23.1 (27.6)	19.8 (26.6)
Diet score (AHEI)[4]	56.8 (12)	55.0 (12.1)	53.4 (12.3)
Ever use of oral contraceptives	88	88	87
Postmenopausal	66	66	67
Ever use of postmenopausal hormones	39	40	39
Sleep duration in current work schedule			
≤5 h	5	5	8
6 h	20	21	25
7 h	40	41	34
8 h	32	29	26
≥9 h	3	4	7
Ever rotating night shift work	70	70	73
Cumulative night shift work exposure (years)[5]	3.3 (4.2)	3.4 (4.4)	4.2 (5.1)
Physician-diagnosed depression[6]	18	25	32
Ever regular antidepressive medication use[7]	28	35	43

Data are mean (SD) or %. [1]Value is not age adjusted. [2]At census tract level. [3]Weekly energy expenditure in MET-h from recreational and leisure-time activities. [4]AHEI 2010 [Chiuve et al. (23)] in 2007 (arbitrary units 0–100). [5]Restricted to women ever reporting rotating night shift work since 1989. [6]Self-reported from 2003 onward. [7]Self-reported; assessed in 1993, 1997, 2001, and 2003–2009.

In sensitivity analyses, we excluded women with an indication of depressed mood, and results among the remaining women (*n* = 44,029) were similar to those of the main analyses (Supplementary Table 1). Compared with intermediate chronotypes, early chronotypes had a significantly reduced risk of type 2 diabetes (MVOR 0.81 [95% CI 0.69–0.94]), and late chronotypes had a nonsignificantly increased type 2 diabetes risk (1.21 [0.97–1.50]). Among nondepressed women who worked daytime schedules, the type 2 diabetes risk was almost twofold increased for late versus intermediate chronotypes (1.97 [1.31–2.96]) (Supplementary Table 2). Estimates were attenuated for both early (0.82 [0.67–1.00]) and

Table 2—Analysis of the association between chronotype and type 2 diabetes in the NHS2

	Chronotype		
	Intermediate	Early	Late
Prevalence analysis: follow-up period 2005–2011	*n* = 34,686; 822 cases	*n* = 22,702; 413 cases	*n* = 7,227; 237 cases
Model 1[1]	1.00	0.74 (0.66–0.83)	1.39 (1.20–1.61)
Model 2[2]	1.00	0.82 (0.73–0.93)	1.17 (1.01–1.36)
Model 3[3]	1.00	0.87 (0.77–0.98)	1.04 (0.89–1.21)
Incidence analysis: follow-up period 2009–2011	*n* = 33,825; 177 cases	*n* = 22,089; 93 cases	*n* = 7,029; 49 cases
Model 1[1]	1.00	0.77 (0.60–0.99)	1.34 (0.98–1.84)
Model 2[2]	1.00	0.88 (0.68–1.13)	1.11 (0.81–1.53)
Model 3[3]	1.00	0.93 (0.73–1.20)	1.01 (0.73–1.38)

Data are MVOR (95% CI) in the prevalence analysis (*n* = 64,615; 1,472 cases) and hazard ratio (95% CI) in the incidence analysis (*n* = 62,943; 319 cases). [1]Age-adjusted model. [2]Additionally adjusted for family history of diabetes (yes/no), smoking status (never, past, current 1–14 cigarettes/day, current ≥15 cigarettes/day), alcohol intake (0, 0.1–5, 5.1–10, 10.1–15, >15 g/day), physical activity (quintiles of MET-h/week), diet score (quintiles, AHEI as assessed in 2007), oral contraceptive use (ever, never), menopausal status (pre-, postmenopause), postmenopausal hormone use (premenopause, ever, never), sleep duration (<5, 6, 7, 8, >9 h as assessed in 2009), median annual household income ($, in tertiles), depressive symptoms (yes/no based on regular medication use or self-reported physician diagnosis), and cumulative rotating night shift work exposure since 1989 (<1, 1–10, ≥10 years). [3]Additionally adjusted for BMI (<25, 25–30, 30–35, >35 kg/m^2).

Table 3—Risk for type 2 diabetes in the NHS2 by chronotype and stratified by cumulative rotating night shift work history

	Chronotype		
	Intermediate	Early	Late
Prevalence analysis: follow-up period 2005–2011			
No rotating night shift work	1.00 (*n* = 10,131; 198 cases)	0.81 (0.63–1.04) (*n* = 6,774; 99 cases)	1.51 (1.13–2.03) (*n* = 1,857; 68 cases)
<10 years	1.00 (*n* = 21,829; 528 cases)	0.84 (0.72–0.98) (*n* = 14,232; 255 cases)	0.93 (0.76–1.13) (*n* = 4,571; 138 cases)
≥10 years	1.00 (*n* = 2,726; 96 cases)	1.15 (0.82–1.63) (*n* = 1,696; 59 cases)	0.86 (0.56–1.33) (*n* = 799; 31 cases)
Incidence analysis: follow-up period 2009–2011			
No rotating night shift work	1.00 (*n* = 10,086; 44 cases)	0.75 (0.44–1.29) (*n* = 6,690; 19 cases)	1.43 (0.77–2.62) (*n* = 1,862; 14 cases)
<10 years	1.00 (*n* = 20,893; 116 cases)	0.91 (0.67–1.25) (*n* = 13,711; 60 cases)	0.86 (0.57–1.32) (*n* = 4,289; 27 cases)
≥10 years	1.00 (*n* = 2,846; 17 cases)	1.63 (0.79–3.34) (*n* = 1,688; 14 cases)	1.01 (0.43–2.37) (*n* = 878; 8 cases)

Data are MVOR (95% CI) in the prevalence analysis (*n* = 64,615; 1,472 cases) and hazard ratio (95% CI) in the incidence analysis (*n* = 62,943; 319 cases). The interaction between chronotype and cumulative shift work exposure is significant in both analyses. Models adjusted for age, family history of diabetes (yes/no), BMI (<25, 25–30, 30–35, >35 kg/m^2), smoking status (never, past, current 1–14 cigarettes/day, current ≥15 cigarettes/day), alcohol intake (0, 0.1–5, 5.1–10, 10.1–15, >15 g/day), physical activity (quintiles of MET-h/week), diet score (quintiles, AHEI as assessed in 2007), oral contraceptive use (ever, never), menopausal status (pre-, postmenopause), postmenopausal hormone use (premenopause, ever, never), self-reported sleep duration (<5, 6, 7, 8, >9 h as assessed in 2009), median annual household income ($, in tertiles), and depressive symptoms (yes/no based on regular medication use or self-reported physician diagnosis).

late (0.91 [0.68–1.21]) chronotypes when exposed to <10 years of rotating night shift work. Among women who worked ≥10 years of shift work, no significant association between chronotype and type 2 diabetes risk was detected (early chronotypes: 1.18 [0.75–1.84]; late chronotypes: 0.95 [0.51–1.76]). Risk estimates increased with increasing duration of shift work exposure in early chronotypes (P_{trend} = 0.02), whereas estimates in late chronotypes decreased significantly with increasing shift work exposure (P_{trend} = 0.03). Again, the interaction between chronotype and cumulative shift work history was significant [$\chi(1)$ = 9.6, $P_{interaction}$ = 0.002].

We conducted another set of analyses with cases occurring between 2005 and 2009 only (*n* = 64,111, 948 cases). The results in both analyses (i.e., the association between chronotype and type 2 diabetes risk as well as the patterns observed in the stratified analysis) remained largely unchanged (data not shown). Finally, we excluded women who indicated that they had ever (*n* = 14,226) or currently (*n* = 785) worked permanent night shifts (Supplementary Table 3). Multivariable adjusted models revealed similar patterns as in the main analysis. The interaction between chronotype and cumulative rotating night shift work exposure was significant in both analyses [ever: $\chi(1)$ = 6.9, *P* = 0.008; current: $\chi(1)$ = 14.9, *P* = 0.001].

CONCLUSIONS

The findings add to the growing body of evidence suggesting a chronotype-dependent association between work hours and metabolic disease risk among women. To our knowledge, this is the first large cohort study to explicitly probe the hypothesis of circadian misalignment by examining the interaction between chronotype and shift work (3). We consistently observed in women a significant interaction between chronotype and shift work, suggesting a slightly lower risk of type 2 diabetes among early chronotypes compared with intermediate chronotypes, which appeared to increase with increasing duration of rotating night shift work (no rotating night shift work: MVOR 0.81; <10 years: 0.84; ≥10 years: 1.15). This finding is a possible result of early sleep and wake times (4), leading to more circadian misalignment during night shifts (10). By contrast, late chronotypes experienced a significant increase in type 2 diabetes risk when their shift schedule did not involve night work, whereas this association was not observed if they worked any number of years of night shifts independent of the duration of exposure (no rotating night shift work: MVOR 1.51; <10 years: 0.93; ≥10 years: 0.86).

In line with the current findings, a previous cross-sectional analysis reported an up to two- to fivefold increased risk of type 2 diabetes among late compared with early chronotypes (8). However, covariate adjustment in that study was limited because no information on other important confounders such as diet, physical activity, or family history of diabetes was available.

Building on a large body of literature on shift work tolerance and interindividual differences (26–29) and more recent findings on the links among the circadian system, sleep, and metabolism, it is believed that in addition to sleep deprivation, circadian misalignment contributes to disease etiology (30). Thus, chronotype (a measure of internal biological time, which is most readily described through sleep timing) alone may not fully capture associations with disease that are driven by circadian misalignment. Rather, the interaction between chronotype and working times likely represents a better measure of a person's actual level of circadian misalignment. To explicitly address this hypothesis, we made use of the regularly updated shift work information in the NHS2, where from 1989 onward, women indicated how many months in the past 2-year period they worked three or more night shifts per month.

The findings support this hypothesis: Early chronotypes had a reduced type 2 diabetes risk when not exposed to night shift work, which tended to increase if they worked longer durations of night shift work. Future studies with more detailed information on number of night shifts worked per month in addition to years of night work may be able to further disentangle possible intensity and duration effects.

A breast cancer case-control study by Hansen and Lassen (31) reported similar interaction patterns between shift work and chronotype: Early chronotypes had an elevated risk for breast cancer if duration and frequency of night shift work was relatively high. Although the study had limited sample sizes, it recorded working times with relatively high precision. In the NHS2, shift work information is continuously assessed through follow-up but with only very limited information about the number of shifts worked per month; hence, more detailed working time assessments are essential in future studies. Such studies should also address the currently largely neglected effects of early morning shifts, which have also been associated with disturbed sleep and increased fatigue; albeit, most studies have focused on the more strenuous night shifts (32).

Women in the current study who were late chronotypes and without any history of rotating night shift work had a 1.5-fold increased risk of type 2 diabetes; this finding is novel and warrants confirmation. One potential explanation could be that working no night shifts may be indicative of exposure to early morning shifts, which have been shown to be the most strenuous for late chronotypes (10). Of note, the type 2 diabetes risk of late chronotypes was decreased if their work schedule involved night shifts compared with late chronotypes without night shift work. Because late chronotypes tend to fall asleep later than early types, even on work-free days (10), it appears plausible that working night shifts is more in line with their circadian phase than for early chronotypes. In a recent analysis, we showed that chronotype-adapted shift schedules (i.e., removing late chronotypes from morning shifts and early chronotypes from night shifts) can improve quality and quantity of workday sleep (33). In early chronotypes, the data qualitatively suggest an inverse association between daytime-oriented work schedules, which interfered less with the sleep/wake cycle, and longer exposure to rotating night shift work, which showed a consistent, albeit nonsignificant, risk elevation. This observation is in line with the hypothesis that night shift work is especially strenuous for early chronotypes. The results also suggest a different temporal relationship among shift work, sleep, and circadian misalignment and type 2 diabetes etiology in early versus late chronotypes. Overall, the pattern we observed supports the hypothesis that chronotype may also be an important modifier for the association between work schedules and type 2 diabetes risk.

Impaired glucose tolerance, insulin resistance, and elevated levels of oxidative stress and inflammation are among the hypothesized links among shift work, the circadian system, and type 2 diabetes risk (30). Shift work has been associated with metabolic disturbances, such as high triglyceride and low HDL cholesterol levels (34), and even though only few prospective studies exist, they have consistently linked shift work to an increased risk of type 2 diabetes (35). The current findings add to this growing body of literature by suggesting that the effects of shift work on type 2 diabetes risk vary depending on an individual's chronotype.

Diet may be another important explanation for why late chronotypes could have an elevated risk for type 2 diabetes. Late chronotypes appear to have more unhealthy dietary habits (36), and Reutrakul et al. (6) showed that poor glycemic control is partly related to higher caloric intake. However, it seems unlikely that diet quality in late chronotypes is solely responsible for the elevated risk of type 2 diabetes among non–night shift workers in the current study given that adjustment for diet quality using the AHEI, a score shown to reliably measure relevant dietary information in the context of chronic disease epidemiology (23), did not alter the estimates. Another facet of diet that has not been addressed in observational studies is the timing of food intake. Animal studies that varied diet quality and feeding and fasting times showed that the effects of poor diet on body weight and metabolism can be overridden by appropriate timing of feeding and fasting periods (37). Shift work not only induces light exposure and activity but also food intake at potentially all times of day, which may add to the strain associated with shift work.

This study has several strengths, including its large size (crucial for any examination of interactions by stratification) and that we were able to adjust for a wide variety of key health and lifestyle factors, which were potential confounders of the associations of interest. Furthermore, even though our definition of shift work was not detailed, it was continuously assessed since 1989, resulting in a powerful duration of exposure assessment. However, the intensity of exposure cannot be inferred from the continuous data collection in NHS2. In addition, no information on early morning and evening shifts has been gathered. Early morning shifts can induce circadian misalignment and sleep deprivation (32), especially in late chronotypes (10). Recommendations of an International Agency for Research on Cancer working group on quantifying shift work exposure stress the importance of assessing both intensity (number and timing of shifts) and duration of exposure (38). Further studies are needed to disentangle the respective contributions of intensity and duration of exposure to chronic disease epidemiology.

Another limitation of the current study is that chronotype was only assessed once. However, even though chronotype appears to change with age (39), existing evidence suggests that once adulthood is reached (40), changes occur at a very slow pace. Hence, it seems unlikely that noteworthy chronotype changes would have occurred within 6 years in this middle-aged cohort of women, which is why we deliberately chose this time frame. If changes had occurred during this time frame, and assuming that with age adult individuals tend to become earlier chronotypes, we anticipate this to have caused a nondifferential chronotype misclassification and therefore likely to have biased the results toward the null. Additionally, we cannot exclude the possibility that type 2 diabetes influences chronotype, but this possibility seems less likely given the similar patterns in both the incidence and the prevalence analyses. Nonetheless, how metabolic disorders may affect circadian phenotypes remains an open question and deserves further investigation.

Although we adjusted for antidepressant medication use, we had no information on potential antipsychotic medication use, another known risk factor for type 2 diabetes (41). Finally, we were unable to account for the role of sleep

quality in this study, another consistent predictor of type 2 diabetes (2) that may be especially important because it has been shown that chronotype modulates both quantity and quality of sleep in shift workers (10). Future prospective studies with repeated chronotype and objective sleep assessments (i.e., quality, timing, quantity) as well as longer durations of follow-up are needed to address these issues.

In conclusion, the results suggest that if work times interfere with sleep timing, shift and day workers may be at an increased risk for type 2 diabetes. More detailed working time assessments will allow for a better understanding of the interaction between chronotype and work schedules. Together with systematic sleep and chronotype assessments, they may provide a powerful approach to individualized risk assessments in shift workers and ultimately minimize adverse health effects.

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