Night Shift Work, Genetic Risk, and Type 2 Diabetes in the UK Biobank

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

To examine the effects of past and current night shift work and genetic type 2 diabetes vulnerability on type 2 diabetes odds.

RESEARCH DESIGN AND METHODS

In the UK Biobank, we examined associations of current (*N* = 272,214) and lifetime (*N* = 70,480) night shift work exposure with type 2 diabetes risk (6,770 and 1,191 prevalent cases, respectively). For 180,704 and 44,141 unrelated participants of European ancestry (4,002 and 726 cases, respectively) with genetic data, we assessed whether shift work exposure modified the relationship between a genetic risk score (comprising 110 single-nucleotide polymorphisms) for type 2 diabetes and prevalent diabetes.

RESULTS

Compared with day workers, all current night shift workers were at higher multivariable-adjusted odds for type 2 diabetes (none or rare night shifts: odds ratio [OR] 1.15 [95% CI 1.05–1.26]; some nights: OR 1.18 [95% CI 1.05–1.32]; and usual nights: OR 1.44 [95% CI 1.19–1.73]), except current permanent night shift workers (OR 1.09 [95% CI 0.93–1.27]). Considering a person's lifetime work schedule and compared with never shift workers, working more night shifts per month was associated with higher type 2 diabetes odds (<3/month: OR 1.24 [95% CI 0.90–1.68]; 3–8/month: OR 1.11 [95% CI 0.90–1.37]; and >8/month: OR 1.36 [95% CI 1.14–1.62]; P_{trend} = 0.001). The association between genetic type 2 diabetes predisposition and type 2 diabetes odds was not modified by shift work exposure.

CONCLUSIONS

Our findings show that night shift work, especially rotating shift work including night shifts, is associated with higher type 2 diabetes odds and that the number of night shifts worked per month appears most relevant for type 2 diabetes odds. Also, shift work exposure does not modify genetic risk for type 2 diabetes, a novel finding that warrants replication.

Shift work has become increasingly common since industrialization, with ~10% of the workforce in the Western world exposed to night work, including permanent night shifts, rotating shifts, and irregular schedules (1). Shift work, particularly night shifts, disrupts social and biological rhythms, as well as sleep, and through those pathways has been suggested to increase the risk of metabolic disorders and specifically type 2 diabetes (2–6). With the prevalence of type 2 diabetes on the rise, understanding which aspects of shift work schedules might be most disruptive, and for whom, is

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critical for designing targeted primary and secondary prevention strategies, which ultimately could help reduce disease-related societal burden and economic cost (7).

A recent meta-analysis of the association between shift work and type 2 diabetes, including eight prospective cohort studies and four cross-sectional studies (N = 226,652) (8), reported that shift workers had an overall 9% higher type 2 diabetes risk than day workers. However, results differed significantly across studies, possibly because of heterogeneous work schedule definitions. Further, using limited shift work information, the same meta-analysis observed that specifically rotating shifts with night shifts, mixed shifts, and rotating shifts without night shifts was associated with a 40–73% higher type 2 diabetes risk. Recent evidence also suggests that late chronotypes (i.e., individuals synchronizing later to the 24-h light/dark cycle, so that peaks and troughs in physiology and behavior occur later within the 24-h day) will suffer less from circadian and sleep disruption when working night shifts, as compared with early types (9). Accounting for chronotype may therefore better delineate acute and chronic health effects of shift work (10–13). Data from the Nurses' Health Study II (NHSII) showed that, compared with intermediate chronotypes, early types, but not late ones, had an increasing type 2 diabetes risk with longer durations of night shift work (14). Given the potentially important role of chronotype for individually tailored prevention strategies (15), replication of those initial findings is necessary.

In addition to environmental factors such as shift work, genetics also play a role in type 2 diabetes risk. Genome-wide association studies have identified >120 independent loci associated with type 2 diabetes (16). Because lifestyle and environmental factors may modify genetic predisposition to chronic disease (e.g., Khera et al. [17]), we also examined whether lifetime night work exposure modifies the association of genetic predisposition and type 2 diabetes risk, a question currently unexplored.

In this study of >270,000 participants, we tested the hypothesis that current and past shift work, especially involving night shifts, is associated with higher odds of type 2 diabetes. Using lifetime employment reports, we examined whether longer duration and more frequent night shift work are associated with higher type 2 diabetes odds. Finally, among those participants with genetic information, we also explored whether shift work modifies the genetic type 2 diabetes predisposition.

RESEARCH DESIGN AND METHODS

UK Biobank

From 2006 to 2010, the UK Biobank recruited 502,620 individuals from across the U.K. At this baseline assessment, participants reported on their lifestyle, medical conditions, work hours, and demographic information; medical history, health status, and medication intake were queried by trained health professionals. The UK Biobank and current validation efforts have been described in detail elsewhere (18). We restricted our analyses to participants in paid employment or who were self-employed at baseline (N = 287,222). We excluded individuals with prevalent chronic disease at baseline (i.e., breast, prostate, bowel, or lung cancer, heart disease, or stroke; N = 15,008), so that our analytic sample consisted of 272,214 participants (38–71 years, 180,704 with genetic data). Out of those, 70,480 participants provided in-depth lifetime employment information by filling out an online follow-up questionnaire in 2015, which was e-mailed to all ~330,000 UK Biobank participants with known e-mail addresses, regardless of employment status and shift work at baseline (19); a subgroup of 44,141 participants of European descent also had genetic data available. The UK Biobank study was approved by the National Health Service National Research Ethics Service (ref. 11/NW/0382), and all participants provided written informed consent to participate in the UK Biobank study.

Exposure and Outcome Assessment

Shift Work Assessment

Participants employed at baseline were asked to report whether their current main job involved shift work (i.e., a schedule falling outside of 9:00 A.M. to 5:00 P.M.; by definition, such schedules involved afternoon, evening, or night shifts or rotating through these shifts). If yes, participants were further asked whether their main job involved night shifts, defined as "...a work schedule that involves working through the normal sleeping hours, for instance, working through the hours from 12:00 A.M. to 6:00 A.M." For both questions, response options were "never/rarely," "sometimes," "usually," or "always" and included additional options: "prefer not to answer" and "do not know." Based on those two questions, we derived participants' current shift work status, categorized as "day workers," "shift workers, but only rarely, if ever night shifts," "irregular or rotating shifts with some night shifts," "irregular or rotating shifts with usual night shifts," and "permanent night shifts."

In the lifetime employment assessment, individuals reported each job ever worked, the number of years in each job, and the number of night shifts per month each job entailed. Using that information, we aggregated duration (i.e., number of years working night shifts) and frequency (i.e., the average number of night shifts per month) of night shift work. We also derived cumulative lifetime night shift exposure (i.e., a count of all night shifts worked throughout lifetime).

Polygenic Risk Score for Type 2 Diabetes

Genotyping in the UK Biobank was performed on two arrays, UK BiLEVE and UK Biobank Axiom. Genotyping, quality control, and imputation procedures have been previously described in detail (20). A total of 488,377 participants in the UK Biobank were genotyped. In total, 180,704 unrelated samples of European ancestry with high-quality genotyping, work, and covariate data were used for these analyses, of which 44,141 also reported on lifetime employment. We derived a genetic risk score (GRS) for type 2 diabetes using those 110 single-nucleotide polymorphisms (SNPs), which passed quality control, out of the 128 recently reported to be associated with type 2 diabetes at genome-wide significance in Europeans (16). Individual participant scores were created by summing the number of risk alleles at each genetic variant, which were weighted by the respective allelic effect sizes on type 2 diabetes risk reported by Scott et al. (16). A second GRS (GRS_{10}) was derived from a subset of 10 SNPs with a reported odds ratio (OR) >1.2 for type 2 diabetes (16).

Ascertainment of Cases of Type 2 Diabetes

We used the algorithms by Eastwood et al. (21) to determine type 2 diabetes

status. In brief, the algorithm uses self-reported and trained health professional queried medical history and medication use at baseline to derive case status. It was validated in a subset of UK Biobank participants against primary and secondary medical records, with 96% accuracy.

Chronotype Ascertainment

Participants self-reported chronotype on a touch-screen questionnaire at baseline by answering a question taken from the Morningness-Eveningness questionnaire (question 19; [22]). The question asks: "Do you consider yourself to be. . ." with response options "Definitely a 'morning' person," "More a 'morning' than 'evening' person," "More an 'evening' than a 'morning' person," "Definitely an 'evening' person," "Do not know," and "Prefer not to answer." Subjects who responded "Do not know" or "Prefer not to answer" were set to missing. This single item has been shown to correlate with sleep timing and dim-light melatonin onset (23–25).

Statistical Analyses

We used age- and multivariable-adjusted logistic regression models to estimate ORs and 95% CI across current shift work status ("day workers," "shift workers, but only rarely, if ever, night shifts," "irregular or rotating shifts with some night shifts," "irregular or rotating shifts with usual night shifts," and "always night shifts"). For participants who reported on lifetime employment, we examined associations of cumulative night shift work duration (none, 1–4.9, 5–9.9, and ≥10 years) and average monthly frequency of night shifts (none, <3 nights/month, 3–7 nights/month, or ≥8 nights/month) with type 2 diabetes odds. Day workers served as the reference category in all analyses. *P* values for trend were calculated with continuous values of the duration, frequency, and cumulative lifetime variables; the reported *P* value was based on the Wald test.

We considered the following covariates in multivariable models: age (continuous), sex (male/female), ethnicity (European, South Asian, African-Caribbean, and other/mixed), family history of diabetes (yes/no), the Townsend Deprivation Index (continuous [26]), BMI (continuous, in kilograms per square meter), physical activity (continuous, metabolic equivalents [MET], and total MET-h/week), smoking (current/past/never), alcohol consumption (never, once/week, two to three times/week, four to six times/week, or daily), habitual sleep duration (continuous, in hours per day), sleep apnea (yes/no), self-reported depressive symptoms (yes/no), hypertension status (yes/no), antihypertensive medication use (yes/no), elevated cholesterol levels (yes/no), cholesterol-lowering medication use (yes/no), and statin and steroid use (yes/no). If covariate information was missing, we imputed sex-specific median values for continuous variables (i.e., BMI, sleep duration, Townsend Deprivation Index, and physical activity, all <7% missing) or used a missing indicator approach for categorical variables (i.e., alcohol consumption and ethnicity, <1% missing). Model 1 was adjusted for age and sex. We used a change in estimate approach with forward selection for additional covariate selection (27), and resulting multivariable adjusted models are presented in model 2. As BMI can also be considered a potential mediator of the association between shift work and type 2 diabetes, we report BMI adjustments in addition to model 2 covariates separately in model 3.

In secondary analyses, we tested whether chronotype modified the association between current/lifetime shift work and type 2 diabetes odds using a log likelihood ratio test to compare models with and without cross-product interaction terms; corresponding *P* values were based on χ^2 statistics. We further examined a priori–defined potential effect modification by sex (male/female), ethnicity-specific obesity status (nonobese/obese [28], adjusting for continuous BMI within each stratum), weekly work hours (<48 h/week or ≥48 h/week, adjusting for continuous weekly work hours), sleep duration (<7 h, 7 to 8 h, or >8 h), and physical activity (median split, with additional adjustment for continuous MET-h/week) and used the same procedure described above to evaluate potential interactions.

Finally, we examined whether shift work exacerbated type 2 diabetes odds associated with genetic predisposition to type 2 diabetes. To do so, we first tested whether the GRS is positively associated with type 2 diabetes odds by estimating OR and 95% CIs across GRS quartiles (i.e., top and bottom quartile represent high and low genetic risk); linear trends were examined using the GRS continuously. We then stratified initial observational shift work associations for those currently employed and those with lifetime employment information by GRS category and tested whether the genetic predisposition modified the association between current shift work, lifetime night shift work duration, or lifetime night shift frequency with type 2 diabetes odds. We report results based on a log likelihood ratio test comparing models with and without cross-product interaction terms (using continuous GRS, duration and frequency night shift data, and current shift work category). We further tested for a linear trend using the continuous GRS within each shift work category; the reported *P* value was based on the Wald test. All genetic analyses were adjusted for age, sex, BMI, 10 principal components of ancestry, and genotyping array. All analyses were repeated for GRS_{10}.

The a priori hypothesis was that current and past rotating night shift work increased type 2 diabetes odds, and all secondary analyses were preplanned. Analyses were conducted with R 3.1 (29) with a two-sided significance threshold of $P < 0.05$.

RESULTS

We observed 6,770 prevalent cases of type 2 diabetes in the sample of 272,214 participants; Table 1 shows the baseline characteristics of this analytic sample. Overall, shift workers were younger, were more materially deprived, worked longer hours, and were more physically active compared with day workers. Shift workers were also more likely to be male, be of non-European ancestry, have a family history of type 2 diabetes, smoke, and consume alcohol daily. Late chronotypes were twice as common in permanent night shift workers than in day workers. No differences are evident between the overall analytic sample and the sample with lifetime employment history (Supplementary Table 1); however, the genetic sample, which is restricted to participants of European descent, were likely to be more physically active (Supplementary Tables 2 and 3).

In the age- and sex-adjusted model 1, shift workers had higher type 2 diabetes odds than day workers, with those working irregular, rotating shifts with usual night shifts having the highest odds

Table 1—UK Biobank participants' characteristics by current night shift work exposure (*N* = 272,214)

	Current work schedule				
	Day workers	Shift work, but only rarely, if ever, nights	Irregular or rotating shifts with some nights	Irregular/rotating shifts with usual nights	Permanent night shifts
N	224,928	23,172	13,559	3,754	6,801
Age (years)	52.7 (7.1)	52.3 (7.0)	51.0 (6.8)	50.8 (6.6)	51.3 (6.8)
Sex (% male)	46	47	62	64	61
European (%)	95	91	88	85	87
Single (%)	16	19	18	19	18
Townsend Index*	−2.2 (−3.7 to 0.2)	−1.3 (−3.2 to 1.6)	−1.3 (−3.2 to 1.8)	−1.2 (−3.2 to 1.8)	−1.1 (−3.0 to 2.0)
Weekly work hours	34.9 (12.5)	35.7 (12.2)	40.4 (13.0)	40.4 (12.7)	40.0 (13.0)
Family history of type 2 diabetes† (%)	21.5	24.7	24.9	25.1	25.8
BMI (kg/m^2)	27.0 (4.6)	27.7 (5.0)	28.2 (4.9)	28.2 (4.9)	28.4 (4.8)
Never smoker (%)	58.6	54.4	53.1	54.2	52.7
Physical activity (MET-h/week)	25.3 (12.6–48.1)	29.7 (17.2–75.7)	33.3 (19.0–81.3)	33.3 (19.0–79.5)	34.8 (21.8–91.4)
Daily alcohol consumption (%)	20	17	16	14	10
Sleep duration (h)	7.1 (0.94)	7.0 (1.0)	6.9 (1.1)	6.9 (1.1)	6.8 (1.2)
Late chronotype (%)	8.0	7.8	9.2	11.6	16.6
Hypertension (%)	18.9	20.6	20.5	21.1	21.6
Antihypertensive medication use (%)	12.3	13.5	13.4	14.5	14.4
Elevated cholesterol levels (%)	7.0	7.6	7.6	7.8	8.2
Lipid-lowering medication use (%)	8.6	9.5	9.5	10.2	10.0
Statin use (%)	7.5	8.4	8.4	8.8	8.8
Corticosteroid use (%)	0.4	0.4	0.4	0.3	0.3

Data are mean (SD), median (interquartile range), or percentages. *Positive values of the index will indicate areas with high material deprivation, whereas those with negative values will indicate relative affluence. †Biological father, mother, or sibling.

(OR 2.10 [95% CI 1.79–2.46]) (Table 2). The covariates retained in model 2 were family history of type 2 diabetes, ethnicity, Townsend Deprivation Index, alcohol consumption, physical activity, hypertension, hypertension medication use, hypercholesterolemia, and lipid-lowering medication intake. Type 2 diabetes odds associated with current shift work were attenuated by those covariates, but remained significantly elevated for all shift workers, except for permanent night shift workers. Model 3 additionally adjusted for BMI, and although estimates were further attenuated, results were overall comparable to model 2.

We then examined associations between lifetime night shift work duration and type 2 diabetes odds (*N* = 70,480; 1,191 cases). Although the age- and sex-adjusted model suggested that longer night shift work exposure was associated with higher type 2 diabetes odds ($P_{trend} < 0.001$) (Table 3), multivariable adjustment attenuated this association: only participants who worked schedules including night shifts for <10 years had a significantly higher type 2 diabetes likelihood than those who never worked night shifts (model 2, <5 years: OR 1.37 [95% CI 1.11–1.68]; and 5–10 years: 1.38 [1.05–1.81]), whereas those with >10 years of exposure did not (1.15 [0.95–1.38]). Additional adjustment for BMI further attenuated estimates, so that lifetime night shift work duration was only associated with type 2 diabetes odds for exposure durations of <5 years (1.26 [1.02–1.56]).

Average lifetime night shift frequency was associated with type 2 diabetes odds, even after multivariable adjustment

Table 2—Current night shift work and type 2 diabetes odds in the UK Biobank (*N* = 272,214)

	Current night shift work				
	Day workers	Shift work, but never or rarely night shifts	Irregular, rotating shifts with some night shifts	Irregular, rotating shifts with usual night shifts	Permanent night shift work
Total cases	5,173	730	461	169	237
Total sample size	224,928	23,172	13,559	3,754	6,801
Model 1: age- and sex-adjusted OR (95% CI)	1.00	1.43 (1.32–1.55)	1.54 (1.39–1.70)	2.10 (1.79–2.46)	1.58 (1.38–1.80)
Model 2: multivariable-adjusted OR (95% CI)*	1.00	1.15 (1.05–1.26)	1.18 (1.05–1.32)	1.44 (1.19–1.73)	1.09 (0.93–1.27)
Model 3: + BMI OR (95% CI)	1.00	1.11 (1.02–1.22)	1.13 (1.01–1.22)	1.37 (1.13–1.65)	1.09 (0.93–1.27)

*Additionally adjusted for ethnicity, family history of type 2 diabetes, alcohol consumption, Townsend Deprivation Index, physical activity, hypertension, antihypertensive medication use, elevated cholesterol levels, and lipid-lowering and statin medication use.

Table 3—Lifetime duration of night shift work involving night shifts and type 2 diabetes odds (*N* = 70,480)

	Lifetime duration of night shift work				*P* for trend
	None	<5 years	5–10 years	>10 years	
Total cases	806	131	72	182	
Total sample size	52,867	5,841	3,095	7,486	
Model 1: age- and sex-adjusted OR (95% CI)	1.00	1.37 (1.13–1.65)	1.57 (1.22–1.99)	1.47 (1.24–1.73)	<0.001
Model 2: Multivariable-adjusted OR (95% CI)*	1.00	1.37 (1.11–1.68)	1.38 (1.05–1.81)	1.15 (0.95–1.38)	0.07
Model 3: + BMI OR (95% CI)	1.00	1.26 (1.02–1.56)	1.28 (0.96–1.68)	0.97 (0.80–1.17)	0.86

*Additionally adjusted for ethnicity, family history of type 2 diabetes, alcohol consumption, Townsend Deprivation Index, physical activity, hypertension, antihypertensive medication use, elevated cholesterol levels, and lipid-lowering and statin medication use.

(P_{trend} = 0.001) (Table 4). Participants who, on average, worked more than eight night shifts per month had a significant 36% higher likelihood of type 2 diabetes compared with participants who never worked night shifts. Again, BMI adjustment attenuated the association, but overall patterns remained similar.

Stratified analyses by sex, chronotype, and obesity status were not suggestive of a differential association between current shift work and type 2 diabetes odds as a function of sex ($P_{interaction}$ = 0.34) (Supplementary Table 4), obesity status ($P_{interaction}$ = 0.21) (Supplementary Table 5), or chronotype ($P_{interaction}$ = 0.48) (Supplementary Table 6). We observed a significant interaction between levels of physical activity and current shift work on type 2 diabetes odds ($P_{interaction}$ = 0.03) (Supplementary Table 7): compared with day workers, individuals reporting low physical activity levels (i.e., <26.57 MET-h/week, median split) had a consistently higher type 2 diabetes likelihood when working any night shift schedules, whereas individuals reporting higher physical activity levels only had higher type 2 diabetes odds when working shift schedules that usually include night shifts. However, associations between frequency and duration of lifetime night shift work and type 2 diabetes odds did not differ by chronotype ($P_{interaction}$ > 0.35), sex ($P_{interaction}$ > 0.15), obesity status ($P_{interaction}$ > 0.15) or physical activity ($P_{interaction}$ > 0.2). In addition, associations did not differ by current weekly work hours or sleep duration in either sample (all $P_{interaction}$ > 0.3).

As expected, higher genetic risk for diabetes was associated with a higher type 2 diabetes likelihood (P_{trend} < 0.001). Participants at intermediate and high genetic risk had 1.91 (1.72–2.12) and 3.81 (3.44–4.23) higher type 2 diabetes odds compared with those at low genetic risk. When stratifying associations of current work schedule with type 2 diabetes odds by genetic risk, similar patterns were observed among day workers and shift workers ($P_{interaction}$ = 0.26). Independent SNP associations with type 2 diabetes are presented in Supplementary Table 8. We also did not observe an interaction between the GRS and lifetime duration ($P_{interaction}$ = 0.42) or frequency of night shift work ($P_{interaction}$ = 0.20).

When restricted to the 10 variants of larger effect on type 2 diabetes (GRS_{10}; OR >1.2), there remained an association between genetic risk for type 2 diabetes with a higher likelihood of type 2 diabetes (P_{trend} < 0.001). Participants at intermediate and high genetic risk had 1.14 (0.98–1.3) and 1.77 (1.65–1.90) higher odds of type 2 diabetes compared with those at low genetic risk, respectively (*P* = 0.09 and *P* < 0.001). Furthermore, no interaction was observed between current work schedule ($P_{interaction}$ = 0.55), lifetime duration of night shift work ($P_{interaction}$ = 0.31), or lifetime night shifts ($P_{interaction}$ = 0.60) with type 2 diabetes odds by GRS_{10}.

CONCLUSIONS

In this comprehensive study of >270,000 men and women in the UK Biobank linking shift work patterns to 6,770 prevalent type 2 diabetes cases, we show that *1*) rotating night shift workers were more likely to have type 2 diabetes than day workers, and this association remained significant after adjustment for BMI and other established risk factors; *2*) only shorter durations of shift work exposure, (i.e., <10 years) were associated with higher type 2 diabetes odds, as compared with day workers, perhaps because sicker participants (including those who developed diabetes) might quit night shift work; *3*) frequency of night shifts matters, as increasing average night shift frequency per month was associated with an increase in diabetes odds, also after adjustment for risk factors and lifetime duration of night shift work; and *4*) current and past night shift work did not interact with genetic type 2 diabetes predisposition and did not exacerbate type 2 diabetes odds.

Our findings extend those recently reported by Wyse et al. (30), who examined the association between current shift

Table 4—Association of average lifetime number of night shifts worked across all reported jobs and type 2 diabetes odds (*N* = 70,480)

	Average lifetime night shift frequency				*P* for trend
	None	<3/month	3–8/month	>8/month	
Total cases	804	52	125	210	
Total sample size	52,782	2,209	6,844	7,454	
Model 1: age- and sex-adjusted OR (95% CI)	1.00	1.35 (1.01–1.78)	1.21 (1.00–1.46)	1.66 (1.41–1.93)	<0.001
Model 2: multivariable-adjusted OR (95% CI)*	1.00	1.24 (0.90–1.68)	1.11 (0.90–1.37)	1.36 (1.14–1.62)	0.001
Model 3: + BMI OR (95% CI)	1.00	1.16 (0.83–1.58)	1.02 (0.82–1.26)	1.21 (1.02–1.45)	0.08

*Additionally adjusted for ethnicity, family history of type 2 diabetes, alcohol consumption, Townsend Deprivation Index, physical activity, hypertension, antihypertensive medication use, elevated cholesterol levels, and lipid-lowering and statin medication use.

work and a range of outcomes, including BMI, type 2 diabetes, sleep, and mental health in the UK Biobank. They reported a 7% higher likelihood of type 2 diabetes for shift workers, as compared with nonshift workers, after multivariable adjustment. Our results show that this elevated risk is especially related to working rotating and irregular night shift schedules, but does not generalize to current permanent night shift workers in this population. Additionally, our novel findings based on lifetime employment reports highlight the role of night shift frequency. That the frequency of night shifts might be detrimental to health has been suggested previously by work from Hansen and Lassen (31); their case-control study reported that the total number of night shifts worked was associated with a higher risk of breast cancer. In line with this observation, we showed that participants who worked rotating schedules with infrequent night shift had lower type 2 diabetes risk estimates than those with a higher proportion of night shifts. A prospective study by Pan et al. (32) in the Nurses' Health Studies, in which female nurses were regularly asked to indicate for how long they had been working a rotating schedule with at least three night shifts per month, showed that longer duration of rotating night shift work was associated with higher risk for incident type 2 diabetes and that estimates were attenuated by BMI adjustment. We did not observe a linear relationship between duration of night shift work and prevalent type 2 diabetes, potentially because of differences in study design or because participants in the UK Biobank might be more prone to transition to other less strenuous work schedules over time (also referred to as the healthy worker effect); our findings, however, do suggest that the monthly frequency of night shifts worked is key for type 2 diabetes risk. Future shift work studies should, as recommended previously (33), systematically assess frequency of shifts when collecting work hours information. The healthy worker effect, and the resulting selection of a certain work schedule, might also be relevant for the observation that current permanent night shift workers were not more likely to have type 2 diabetes as compared with dayworkers. Although permanent night shift workers were twice as likely to be late chronotypes, a solely chronotype-based self-selection seems to be insufficient to explain those results, especially as a complete circadian adaptation, as, for example, evidenced by an alignment of melatonin rhythms with sleep/wake behavior, is rarely achieved in this population (34). Worth noting is that permanent night shift workers exhibit some healthier lifestyle characteristics, including lower levels of alcohol intake and higher levels of physical activity, than other groups, which might further explain our results. Furthermore, the overall prevalence of type 2 diabetes in the present analytic sample (~2.5%) is lower than that in the overall UK Biobank (4.1%) (21).

Circadian misalignment causes adverse cardiometabolic outcomes, including glucose intolerance (5,35–39), even in long-time shift workers (40,41). One key assumption in the current study is that especially night shift work induces circadian misalignment. To model individual exposure levels of circadian misalignment more directly, we also examined a potential interaction between chronotype and night shift work, as it had been described that late chronotypes suffer from less circadian misalignment and sleep deprivation when working night shifts than early ones (9). A previous report from the NHSII indeed suggested that type 2 diabetes risk was dependent on both chronotype and rotating night shift work exposure (14). Yet our findings are not supportive of such an interaction. Further sensitivity analyses restricting to women only (because in Vetter et al. [14], participants were all female) resulted in similar overall patterns. It is noteworthy that in the present analyses, we used the same chronotype assessment method as in the NHSII study. This single question explains the highest fraction of variance in preferences in sleep–wake timing (25) and is an accepted measure of chronotype. Differences in study designs, response rates, and population characteristics are thus more likely to contribute to the discrepancy in findings. Further prospective studies are needed to better understand the potential interaction between chronotype and shift work and its effect on metabolic health.

The meta-analysis by Gan et al. (8) of observational studies suggested that men were at higher type 2 diabetes risk when working shifts than women. However, compared with the studies including men, those including women were more likely to be part of studies that adjusted for other risk factors, pointing toward potential overestimation due to residual confounding in men. Our study, which included a more homogeneous assessment of both exposure and covariate information and included both men and women, does not support the notion of sex differences in the association between shift work and type 2 diabetes risk.

This is the first study investigating the interaction between shift work and a cumulative GRS for type 2 diabetes. Current or past shift work did not modify genetic type 2 diabetes risk, with no evidence of interaction, even when restricted to genetic variants with known larger genetic risk. This could be related, at least in part, to epistatic interaction among the genetic variants or a healthy worker effect, as discussed earlier. It is also noteworthy that this analysis was limited to participants of European ancestry. Further work will be necessary to examine the interaction of individual genetic variants with shift work on glucose homeostasis and risk of type 2 diabetes.

Our results, together with the existing body of literature (e.g., Proper et al. [42]), are in line with suggestions that both intervention on body weight and work schedules might be useful in improving metabolic health in all individuals, independent of their genetic type 2 diabetes predisposition. A review of intervention studies in shift work settings (43) concluded that work schedule changes can improve chronic disease risk factors, and a recent pilot study eliminating night shifts for early chronotypes and early morning shifts for late ones improved sleep and reduced circadian misalignment (44).

Our study has several strengths. First, it has a large sample size of >270,000 individuals with detailed medical history, lifestyle information, and demographic information, which was collected in a uniform manner. Second, case definition was based on an extensively validated algorithm (21), with up to 96% accuracy for prevalent cases of type 2 diabetes. Third, >70,000 participants provided in-depth reports of shift work exposure history, allowing the derivation of a unique set of exposure categories. Although retrospective self-reports can be erroneous, a recent report comparing payroll data to self-reports (45) showed

moderate to high levels of sensitivity and specificity, with the exception of reports of shift work without night shifts, which were recalled with least accuracy (i.e., 62% sensitivity). The lifetime reports used in this study are likely to be more prone to error, as they cover a whole lifetime of employment. It is noteworthy that the potential exposure misclassification resulting from such errors would bias toward to the null and thus result in an underestimation of the association between shift work and type 2 diabetes. Fourth, our investigation uniquely linked genetic and observational data in a large population with detailed lifetime employment history. Finally, the detailed shift work history collected in the UK Biobank provides novel and unique insights into what are likely to be the most critical aspects of work schedules in relation to health and thereby provides invaluable guidance for future studies and the design of prevention strategies.

We also acknowledge some weaknesses of our study. First, we could not assess links between shift work and incident type 2 diabetes for which supplementary primary care data are necessary. Second, a general weakness of observational datasets is a risk of bias due to residual confounding; yet, we minimized confounding through high-resolution covariate adjustment considering an extensive list of continuous rather than categorical variables whenever possible. Risk factors that we did not account for were dietary composition and meal timing. Only a subset of participants answered a validated 24-h diet recall, which included questions on the consumption of ~200 commonly consumed items (46). When we restricted our analyses to this subsample (N = 109,696) and additionally accounted for caloric, carbohydrate, fat, and protein intake in our analyses, results did not change, suggesting that, at least in this subgroup of currently employed individuals, dietary intake did not additionally confound the association between shift work and type 2 diabetes odds. Information on food timing was not available in the UK Biobank and might be of critical importance in glucose control and metabolic health, especially in shift workers (5,47). Third, the cross-sectional nature of our study represents a weakness because it prevents any assessment of causality. However, the current results are consistent with controlled experimental studies showing that misalignment between the circadian system and the sleep/wake and fasting cycles, as is typical in shift workers, causes relative impairment of glucose tolerance and insulin sensitivity (35–37,39,42), even in chronic shift workers (40,41). Finally, UK Biobank participation rates were low at ~5%, which might have introduced selection bias. This is supported by the lower prevalence of type 2 diabetes in the overall UK Biobank sample (4.1%) compared with the general U.K. population of the same age-group (48). Low response rate is also of concern in relation to shift work studies, as work hours might hinder daytime recruitment at assessment centers.

Overall, our results add to the current body of literature in that they suggest that reducing night shift work frequency might represent another avenue to improve metabolic health during working life and beyond. A more detailed assessment of shift schedules should thus be incorporated in occupational health and preventive medicine settings as well as in ongoing and novel studies of modifiable risk factors of health and disease.

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