Assessment of *MTNR1B* Type 2 Diabetes Genetic Risk Modification by Shift Work and Morningness-Eveningness Preference in the UK Biobank

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Night shift work, behavioral rhythms, and the common *MTNR1B* risk single nucleotide polymorphism (SNP), rs10830963, associate with type 2 diabetes; however, whether they exert joint effects to exacerbate type 2 diabetes risk is unknown. Among employed participants of European ancestry in the UK Biobank (N = 189,488), we aimed to test the cross-sectional independent associations and joint interaction effects of these risk factors on odds of type 2 diabetes (n = 5,042 cases) and HbA_{1c} levels (n = 175,156). Current shift work, definite morning or evening preference, and *MTNR1B* rs10830963 risk allele associated with type 2 diabetes and HbA_{1c} levels. The effect of rs10830963 was not modified by shift work schedules. While marginal evidence of interaction between self-reported morningness-eveningness preference and rs10830963 on risk of type 2 diabetes was seen, this interaction did not persist when analysis was expanded to include all participants regardless of employment status and when accelerometer-derived sleep midpoint was used as an objective measure of morningness-eveningness preference. Our findings suggest that *MTNR1B* risk allele carriers who carry out shift work or have more extreme morningness-eveningness preference may not have enhanced risk of type 2 diabetes.

MTNR1B encodes the high-affinity melatonin receptor 1B, and the common risk single nucleotide polymorphism (SNP), rs10830963 G, has consistently been associated with fasting glucose, measures of reduced insulin secretion in response to glucose, and increased risk of type 2 diabetes in multiethnic populations (1–6). Melatonin, which is naturally secreted by the pineal gland during the biological night in humans, causes impairment of glucose tolerance in vivo (7) and inhibits baseline and glucose-stimulated insulin secretion in vitro (7). The gain-of-function common genetic variant (>30% minor allele frequency in people of European, Asian, or Native American ancestry) results in increased expression of the melatonin receptor 1B in pancreatic islets and has been shown to potentiate the inhibitory effect of melatonin on insulin release, leading to reduced insulin secretion, increased fasting glucose, and type 2 diabetes risk (7–10).

The influences of melatonin signaling, *MTNR1B* genetic variation, and their combined impact on glucose metabolism at different times of day have begun to be explored in experimental studies, raising the hypothesis that prolonged concurrence of elevated melatonin and food intake in *MTNR1B* risk allele carriers may contribute to their increased diabetes risk relative to noncarriers. A small trial

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in 17 women observed that exogenous melatonin more adversely affected glucose tolerance in *MTNR1B* risk allele carriers, particularly in the morning (11). Data from highly controlled in-laboratory protocols indicated that endogenous melatonin production may be prolonged later into the morning in *MTNR1B* risk allele carriers compared with noncarriers and suggested that the *MTNR1B* risk allele may influence type 2 diabetes risk among morning types who are likely to eat breakfast while melatonin levels are still high (12). A recent randomized crossover study of 40 overweight or obese women found that *MTNR1B* risk allele further impairs glucose tolerance in response to late night versus early dinners (i.e., in the presence of elevated endogenous melatonin concentrations) (13). This observation may reflect the adverse impact of food intake coincident with high melatonin levels.

Circadian misalignment between the endogenous circadian cycle and behavioral cycles also adversely impacts glucose metabolism (14). Shift work, an example of circadian misalignment that involves a drastic change in daily behavioral cycles, has also been shown to consistently increase risk of type 2 diabetes (15). Given that the *MTNR1B* common risk SNP links daily melatonin rhythms and food intake to type 2 diabetes, we tested the possibility that misalignment between behavioral and internal circadian rhythms may exacerbate the type 2 diabetes genetic risk conferred by the genetic variant. Specifically, we hypothesized that the type 2 diabetes risk conferred by the *MTNR1B* risk allele is exacerbated by *1*) night shift work as a likely consequence of chronic exposure to nighttime eating and *2*) morning chronotype as a likely result of breakfast intake concurrent with extended melatonin production later into the morning. Thus, the aim of the current investigation was to test the independent associations of *MTNR1B* risk allele, night shift work, and chronotype (self-report and accelerometer derived) on prevalent type 2 diabetes and HbA_{1c} levels and interaction effects of *MTNR1B* by behavior on prevalent type 2 diabetes and HbA_{1c} levels in a large population from the UK Biobank.

RESEARCH DESIGN AND METHODS

UK Biobank

Study participants for this analysis were from the UK Biobank, previously described in detail (16). In brief, the UK Biobank is a prospective study of >500,000 people living in the U.K. All people in the National Health Service registry who were aged 40–69 years and living <25 miles from a study center were invited to participate between 2006 and 2010. In total, 503,325 participants were recruited from >9.2 million mailed invitations. Baseline data were collected at assessment centers by questionnaires as previously described (15). Height and weight were also measured, and BMI was calculated as weight in kilograms divided by the square of height in meters. Biological samples were also collected at baseline. Genotyping was performed by the UK Biobank for 488,377 participants using two similar arrays, UK BiLEVE and UK Biobank Axiom. Genotyping and quality control have been previously described in detail (15,16). Arrays included markers of known associations with, or possible roles in, phenotypic variation and disease risk, including the *MTNR1B* risk allele SNP, rs10830963.

A subset of 103,711 participants from the UK Biobank wore actigraphy devices (Axivity AX3) for up to 7 days ~2.8–9.7 years after their study baseline visits. Details on quality control and data processing have been described previously (17,18). Sleep midpoint, an objective measure of chronotype (19), was derived by processing of the raw accelerometer data.

Ascertainment of Prevalent Type 2 Diabetes and HbA_{1c} Levels

Prevalent cases of type 2 diabetes were defined based on hospital admission data and self-report. Hospital in-patient diagnoses were coded according to the ICD-10, and disease codes for type 2 diabetes (E11) prior to date of baseline assessment were used to denote type 2 diabetes cases. We also followed the algorithms described by Eastwood et al. (20) to determine additional probable prevalent type 2 diabetes cases. These cases were determined from self-report through a verbal interview by a trained nurse at the UK Biobank assessment center on past and current medical conditions and medication use. Participants with no disease codes for any other diabetes and who were determined to be unlikely have diabetes based on self-report served as control subjects. HbA_{1c} levels in red blood cells were centrally determined by the UK Biobank using high-performance liquid chromatography using the Bio-Rad VARIANT II TURBO HbA_{1c} analyzer (21).

Assessment of Shift Work and Morningness-Eveningness Preference

At assessment centers, participants self-reported current work schedule and morningness-eveningness preference. Employed participants were then asked to report whether their current main job involved shift work (i.e., a schedule that falls outside of the normal daytime working hours of 9:00 A.M.–5:00 P.M.; by definition, such schedules involved afternoon, evening, or night shifts or rotating through these kinds of night shifts). If yes, participants were further asked whether their main job involved night shifts, which were defined as work schedules that involve working through the normal sleeping hours, e.g., working through the hours from 12:00 A.M. to 6:00 A.M. Response options were "never/rarely," "sometimes," "usually," or "always" and included "prefer not to answer" and "do not know." 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" based on responses to these questions. Participants further self-reported morningness-eveningness preference in response to the question, "Do you

consider yourself to be?" Response options were as follows: "definite-morning person," "more morning than evening," "more evening than morning," and "definite-evening person" and also included "prefer not to answer" and "do not know." Participants who responded "do not know" or "prefer not to answer" were characterized as missing. This assessment question was taken from the Morningness-Eveningness Questionnaire (22) and is an accepted measure of chronotype, as it explains the highest fraction of variance in preferences in sleep-wake timing (19).

Statistical Analyses

The current analysis was restricted to employed or self-employed participants at baseline (57.0% of UK Biobank) with genetic and covariate information and to unrelated participants of European descent (67.2% of UK Biobank) to limit confounding effects by race. Our final analytic sample consisted of 189,488 participants. Participants determined to have type 2 diabetes at baseline were excluded from HbA_{1c} analyses (n = 5,042 cases excluded). Furthermore, participants with missing or extreme HbA_{1c} measures defined as those beyond 3 SDs from the mean were further excluded (n = 9,290 excluded). Among the 189,488 participants, a total of 169,926 responded to the morningness-eveningness preference question, of whom 157,256 participants were subsequently included in the HbA_{1c} analysis. Missing BMI data (n = 340) and sleep duration data (n = 568) were imputed using sex-specific median values.

Associations of current shift work and morningness-eveningness preference on both prevalent type 2 diabetes and HbA_{1c} were estimated using crude and adjusted logistic and linear regression models adjusted for age (continuous) and sex (male/female), further adjusted for sleep duration (continuous), and then further adjusted for BMI (continuous) and other previously established covariates (15) including family history of type 2 diabetes (yes/no), Townsend deprivation index (continuous [23]), alcohol consumption (never, once/week, 2–3 times/week, 4–6 times/week, or daily), physical activity (continuous, METs), hypertension (yes/no), hypertension medication use (yes/no), hypercholesterolemia (yes/no), and lipid-lowering medication intake (yes/no). The Townsend deprivation index is a measure of the level of social deprivation in which the participant lives and is based on unemployment, non–car ownership, non–home ownership, and household overcrowding calculated prior to joining the UK Biobank based on previous national census data (24). Day workers or definite morning preference participants served as the reference group. Association of *MTNR1B* rs10830963 risk allele on prevalent type 2 diabetes and HbA_{1c} was estimated using logistic and linear regression models adjusted for age, sex, BMI, genotyping array, and 10 principal components of ancestry.

Interaction effects of *MTNR1B* risk allele and current shift work or morningness-eveningness preference on prevalent type 2 diabetes and HbA_{1c} were tested using a log likelihood ratio test to compare models with and without cross-product interaction terms including main effect terms in logistic or linear regression models adjusted for the aforementioned covariates. Subsequently, stratified *MTNR1B* association analyses by current shift work or morningness-eveningness preference categories were conducted. In sensitivity analyses, we further adjusted for current shift work or morningness-eveningness preference in our interaction analyses and lastly expanded our analytical sample to include all unrelated participants of European descent regardless of employment status (n = 298,953) in all morningness-eveningness preference analyses. Lastly, we tested for *MTNR1B* interaction effect with accelerometer-derived sleep midpoint as an objective measure of chronotype to verify findings from the self-reported morningness-eveningness preference analyses. These analyses were limited to type 2 diabetes as an outcome. To account for the ~10-year time period between baseline assessment when employment status was reported and the accelerometer period, we included only self-reported employed participants 55 years of age or younger at baseline in the primary analysis (n = 38,701). Accelerometer analyses were later repeated to include all unrelated participants of European descent regardless of employment status (n = 82,923). In sensitivity analysis, we further adjusted for household status: people residing in the household with the participant (husband, wife, or partner; sons or daughters; brothers or sisters; mother or father; and grandparents/grandchildren/other). Statistical analyses were conducted with R (version 3.5.1; The R Foundation for Statistical Computing, Vienna, Austria) with a two-sided significance threshold of $P < 0.05$.

Data and Resource Availability

The data sets generated during and/or analyzed during the current study are available from the UK Biobank. Data may be accessed by contacting the UK Biobank, but restrictions may apply to the availability of these data. No applicable resources were generated or analyzed during the current study.

RESULTS

From a total sample of 189,488 participants, 51% were female, mean (SD) age was 53.5 (7.1) years, and mean BMI was 27.2 (4.7) kg/m^2 (Table 1). We observed 5,042 prevalent cases of type 2 diabetes. The subset of 175,156 participants included in the HbA_{1c} analyses had a mean HbA_{1c} of 5.3% (2.5%) [34.47 (3.69) mmol/mol)]. A total of 30,649 (16.2%) current workers reported being involved in some shift work, with 15,311 (8.1%) reporting any night shift work. Among 169,926 participants who reported morningness-eveningness preference, a total of 43,369 (25.5%) reported being a definite morning person and 15,150 (8.9%) reported being a definite evening person. The minor allele frequency of the rs10830963 G risk allele was 27.5%.

We first tested associations of current shift work and morningness-eveningness preference on outcomes type 2 diabetes and HbA_{1c}. In age- and sex-adjusted logistic and linear regression models, we observed that current shift work was associated with higher odds of type

Table 1—Characteristics of employed UK Biobank participants of European descent by current shift work (n = 189,488)

	Current work schedule				
	Day workers	Shift work without nights	Sometimes night shift work	Usual night shift work	Always night shift work
N	158,839	15,338	8,718	2,251	4,342
Age, years	53.6 (7.1)	53.3 (7.0)	52.0 (6.8)	51.7 (6.7)	52.2 (6.8)
Male sex, *n* (%)	75,307 (47.4)	7,392 (48.2)	5,508 (63.2)	1,469 (65.3)	2,773 (63.9)
BMI, kg/m^2	27.1 (4.6)	27.8 (4.9)	28.2 (4.8)	28.2 (4.8)	28.6 (4.8)
Sleep duration, h	7.1 (0.9)	7.0 (1.0)	6.9 (1.0)	6.9 (1.1)	6.8 (1.2)
Townsend deprivation index*	−1.72 (2.79)	−0.97 (3.09)	−1.00 (3.10)	−0.93 (3.12)	−0.84 (3.09)

Data are mean (SD) unless otherwise indicated. *Positive values of the index will indicate areas with high material deprivation, whereas negative values will indicate relative affluence.

2 diabetes and higher HbA_{1c} levels (Table 2 and Supplementary Table 1). Compared with day workers, shift work without nights (odds ratio [OR] 1.26 [95% CI 1.15–1.39]), sometimes night shift work (OR 1.33 [95% CI 1.17–1.5]), usual night shift work (OR 1.48 [95% CI 1.18–1.86]), and always night shift work (OR 1.47 [95% CI 1.24–1.73]) were associated with higher odds of type 2 diabetes, but none retained significance upon adjustment for BMI and other established risk factors (Table 2). Compared with day workers, all categories of current shift work were associated with higher HbA_{1c} levels, even upon adjustment for sleep duration or BMI and established risk factors (Table 2 and Supplementary Table 1). Furthermore, we observed that morningness-eveningness preference was associated with type 2 diabetes and HbA_{1c} levels (Table 2 and Supplementary Table 1). Compared with definite morning preference, more morningness than eveningness preference (OR 0.86 [95% CI 0.8–0.93]) was associated with lower odds of type 2 diabetes, whereas definite evening preference (OR 1.30 [95% CI 1.17–1.45]) was associated with higher odds of type 2 diabetes (Table 2). Similar associations were also evident for HbA_{1c} (Table 2). Upon adjustment for BMI and other known risk factors, association estimates were attenuated but remained significant for definite evening preference on type 2 diabetes and HbA_{1c} (Table 2).

We then tested whether the *MTNR1B* genetic risk may be exacerbated by current shift work or morningness-eveningness preference. We first observed that each additional G risk allele (rs10830963) was associated with 10% higher odds of type 2 diabetes per effect allele (OR 1.10 [95% CI 1.05–1.15]) and 0.26 mmol/mol higher HbA_{1c} per effect allele (β 0.26 [95% CI 0.23–0.28] [mmol/mol]). No interaction effects were observed between *MTNR1B* risk allele and current shift work on type 2 diabetes ($P_{\text{interaction}}$ [P_{int}] = 0.15) and HbA_{1c} (P_{int} = 0.25), with results remaining similar after further adjustment for morningness-eveningness preference (Table 3 and Supplementary Table 2). As such, the effect of *MTNR1B* risk allele was similar across categories of shift work on odds of type 2 diabetes (OR 1.10 [95% CI 1.05–1.15] [per effect allele]) and on HbA_{1c} (β 0.26 [95% CI 0.23–0.28] [mmol/mol per effect allele]) (Table 3).

We observed an interaction effect of *MTNR1B* risk allele and morningness-eveningness preference on type 2 diabetes (P_{int} = 0.04), which retained significance upon further adjustment for current shift work (P_{int} = 0.04) (Table 4 and Supplementary Table 3). In analyses stratified by morningness-eveningness preference, the effect of *MTNR1B* risk allele on odds of type 2 diabetes was stronger among definite morning participants (OR 1.17 [95% CI 1.07–1.28]), while no association was observed among definite evening participants (OR 1.02 [95% CI 0.88–1.18]) (Table 4). *MTNR1B* risk allele, however, had comparable effects on HbA_{1c} levels (P_{int} = 0.87) across categories of morningness-eveningness preference (β 0.26 [95% CI 0.23–0.29] [mmol/mol per effect allele]).

In sensitivity analyses expanded to include all unrelated participants of European descent regardless of employment status (n = 298,953), association of morningness-eveningness preference on type 2 diabetes and HbA_{1c} levels remained similar; however, no interaction effect was observed with *MTNR1B* (P_{int} = 0.10) (Supplementary Tables 4 and 5). Using a more precise objective measurement of chronotype in a subset of 38,701 employed participants of European descent with 7-day accelerometer-derived sleep midpoint data, we observed similar U-shaped associations of sleep midpoint on type 2 diabetes (Supplementary Table 6). Compared with the first quartile of sleep midpoint, both second (OR 0.64 [95% CI 0.56–0.75]) and third (OR 0.72 [95% CI 0.61–0.86]) quartiles of sleep midpoint were associated with lower odds of type 2 diabetes (Table 5), which remained similar when analyses were expanded to include all 82,923 unrelated participants of European descent regardless of employment status (Supplementary Table 7) and when people residing in the household with the participant were accounted for. We observed no interaction effects between *MTNR1B* risk allele and sleep midpoint on type 2 diabetes among employed participants (P_{int} = 0.21) and all unrelated participants of European descent regardless of employment status (P_{int} = 0.11).

Table 2—Associations of current shift work (n = 189,488) and morningness-eveningness preference (n = 169,926) on adjusted odds of type 2 diabetes and adjusted mean difference in HbA_{1c}

	Type 2 diabetes			HbA_{1c} (mmol/mol)		
	Type 2 diabetes case/control subjects, *n/n*	Sex- and age-adjusted OR (95% CI)	Multivariable-adjusted OR (95% CI)	*N*	Sex- and age- adjusted β (95% CI)	Multivariable-adjusted β (95% CI)
Shift work						
Day workers	4,047/154,792	Reference	Reference	146,993	Reference	Reference
Shift work without nights	475/14,863	**1.26 (1.15–1.39)**	0.99 (0.88–1.12)	14,110	**0.34 (0.28–0.40)**	**0.14 (0.08–0.20)**
Sometimes night shift work	284/8,434	**1.33 (1.17–1.50)**	1.01 (0.87–1.17)	8,005	**0.48 (0.40–0.56)**	**0.24 (0.16–0.32)**
Usual night shift work	80/2,171	**1.48 (1.18–1.86)**	1.12 (0.84–1.49)	2,069	**0.44 (0.29–0.60)**	**0.20 (0.05–0.35)**
Always night shift work	156/4,186	**1.47 (1.24–1.73)**	1.01 (0.82–1.24)	3,979	**0.75 (0.64–0.86)**	**0.38 (0.27–0.49)**
Morningness-eveningness preference						
Definite morning	1,272/42,097	Reference	Reference	39,976	Reference	Reference
More morning than evening	1,482/60,064	**0.86 (0.80–0.93)**	0.93 (0.85–1.03)	57,127	**−0.13 (−0.18 to 0.09)**	−0.02 (−0.07 to 0.03)
More evening than morning	1,268/48,593	0.96 (0.89–1.04)	1.02 (0.93–1.13)	46,267	−0.04 (−0.09 to 0.01)	0.04 (0–0.09)
Definite evening	497/14,653	**1.30 (1.17–1.45)**	**1.29 (1.13–1.47)**	13,886	**0.12 (0.05–0.19)**	**0.14 (0.07–0.21)**

Associations are across shift work and morningness-eveningness preference categories in employed UK Biobank participants of European descent. Prevalent type 2 diabetes associations are sex- and age-adjusted ORs (95% CI), then further adjusted for BMI (continuous) and other previously established covariates (family history of type 2 diabetes [yes/no], Townsend deprivation index [continuous], alcohol consumption [never, once/week, two to three times/week, four to six times/week, or daily], physical activity [continuous, METs], hypertension [yes/no], hypertension medication use [yes/no], hypercholesterolemia [yes/no], and lipid-lowering medication intake [yes/no]). HbA_{1c} associations are restricted to participants with no prevalent type 2 diabetes. HbA_{1c} associations are sex- and age-adjusted βs (95% CI) in mmol/mol, then further adjusted for BMI and other previously established covariates. In all analyses, day workers or definite morning participants serve as reference group. Boldface type indicates $P < 0.05$.

Table 3—Adjusted ORs of type 2 diabetes and adjusted βs of HbA_{1c} with each additional copy of the *MTNR1B* G risk allele across categories of current work schedule

	Type 2 diabetes			HbA_{1c} (mmol/mol)		
	Type 2 diabetes case/control subjects, *n/n*	OR (95% CI)	P_{int}	*N*	β (95% CI)	P_{int}
Overall (*n* = 189,488)	5,042/184,446	1.10 (1.05–1.15)	0.15	175,156	0.26 (0.23–0.28)	0.25
Day workers	4,047/154,792	1.09 (1.03–1.14)		146,993	0.25 (0.22–0.28)	
Shift work without nights	475/14,863	1.24 (1.07–1.43)		14,110	0.32 (0.22–0.41)	
Sometimes night shift work	284/8,434	0.99 (0.82–1.20)		8,005	0.36 (0.24–0.48)	
Usual night shift work	80/2,171	0.85 (0.58–1.25)		2,069	0.20 (−0.04 to 0.45)	
Always night shift work	156/4,186	1.28 (0.99–1.65)		3,979	0.19 (0.02–0.37)	

Association results are adjusted ORs (95% CI) of type 2 diabetes per each additional copy of the *MTNR1B* G risk allele or adjusted βs (95% CI) describing differences in HbA_{1c} in mmol/mol per each additional copy of the *MTNR1B* G risk allele across categories of current work schedule. Association analyses are adjusted for age, sex, BMI, genotyping array, and 10 principal components of ancestry. P_{int} is log likelihood ratio test comparing models with and without cross-product interaction terms (*MTNR1B* and current work schedule) including main effect terms in logistic or linear regression models adjusted for the aforementioned covariates.

DISCUSSION

In the present analysis, we showed that among employed participants of European descent, current shift work, morningness-eveningness preference, and *MTNR1B* rs10830963 risk allele associated with type 2 diabetes and HbA_{1c} levels in the UK Biobank. *MTNR1B* type 2 diabetes–associated risk did not appear to be modified by shift work schedules or morningness-eveningness preference.

Shift work schedules have been observed to associate with modest increases in the risk for type 2 diabetes (15,25,26), coronary heart disease (27), and cancer (28), and our present findings further support and extend our previously reported relationship with type 2 diabetes (15) to HbA_{1c} levels in workers without diabetes in the UK Biobank. The relationships between shift work and adverse health are hypothesized to result from chronic misalignments between the endogenous biological rhythms and behavioral rhythms such as daily sleep/wake and fasting/feeding cycles (14,29–31).

In addition, while earlier studies have primarily focused on adverse health problems associated with eveningness preference (32), our observed relationship of both definite morning and definite evening preference on higher odds of type 2 diabetes and levels of HbA_{1c} relative to moderate morningness or eveningness preferences suggests that extreme preference may be related to adverse health problems. These U-shaped association findings for type 2 diabetes were also supported by accelerometer-derived sleep midpoint as an objective measure of chronotype. Associations, however, remained significant only for definite evening preference after accounting for BMI and other risk factors, supporting higher cardiometabolic disease risk among this subgroup.

Our *MTNR1B* risk allele associations are similar in magnitude to two recent reports of genome-wide association studies for type 2 diabetes (5,6), suggesting ∼10% higher odds of type 2 diabetes with each additional G risk allele. Furthermore, among employed participants only, we observed a suggestive interaction effect between *MTNR1B* and morningness-eveningness preference on type 2 diabetes. Consistent with previous findings of *MTNR1B* SNP interaction effect with early wake time from actigraphy data (12), we observed that the *MTNR1B* risk allele association on type 2 diabetes is significant among participants self-reporting definite morning preference but not among those reporting more evening preference. This interaction effect

Table 4—Adjusted ORs of type 2 diabetes and adjusted βs of HbA_{1c} with each additional copy of the *MTNR1B* G risk allele across categories of morningness-eveningness preference

	Type 2 diabetes			HbA_{1c} (mmol/mol)		
	Type 2 diabetes case/control subjects, *n/n*	OR (95% CI)	P_{int}	*N*	β (95% CI)	P_{int}
Overall (*n* = 169,926)	4,519/165,407	1.10 (1.04–1.15)	0.044	157,256	0.26 (0.23–0.29)	0.87
Definite morning	1,272/42,097	1.17 (1.07–1.28)		39,976	0.30 (0.25–0.36)	
More morning than evening	1,482/60,064	1.09 (1.00–1.18)		57,127	0.23 (0.19–0.28)	
More evening than morning	1,268/48,593	1.06 (0.97–1.16)		46,267	0.23 (0.18–0.28)	
Definite evening	497/14,653	1.02 (0.88–1.18)		13,886	0.36 (0.27–0.45)	

Association results are adjusted ORs (95% CI) of type 2 diabetes per each additional copy of the *MTNR1B* G risk allele or adjusted βs (95% CI) describing differences in HbA_{1c} in mmol/mol per each additional copy of the *MTNR1B* G risk allele across categories of morningness-eveningness preference. Association analyses are adjusted for age, sex, BMI, genotyping array, and 10 principal components of ancestry. P_{int} is log likelihood ratio test comparing models with and without cross-product interaction terms (*MTNR1B* and morningness-eveningness preference) including main effect terms in logistic or linear regression models adjusted for the aforementioned covariates.

Table 5—Associations of quartiles of accelerometer-derived sleep midpoint (n = 38,701) on adjusted odds of type 2 diabetes in employed UK Biobank participants of European descent

Sleep midpoint	Type 2 diabetes case/control subjects, *n/n*	Sex- and age-adjusted OR (95% CI)	Sex-, age-, and household status–adjusted OR (95% CI)
Quartile 1	168/9,508	Reference	Reference
Quartile 2	104/9,571	**0.64 (0.55–0.75)**	**0.65 (0.56–0.77)**
Quartile 3	120/9,555	**0.72 (0.61–0.86)**	**0.75 (0.63–0.89)**
Quartile 4	163/9,512	0.95 (0.77–1.17)	0.96 (0.78–1.19)

Prevalent type 2 diabetes associations are sex- and age-adjusted ORs (95% CI). Boldface type indicates $P < 0.05$. In sensitivity analysis, associations were further adjusted for people residing in the household with the participant (household status).

supports our earlier hypothesis that, given the *MTNR1B* risk allele extends duration of endogenous melatonin production later in the morning, eating breakfast early, when melatonin levels are high, may magnify the type 2 diabetes risk conferred by the risk allele (12). In further support of these findings, morning circadian misalignment conferred by short sleep duration, rather than *MTNR1B*, has also been observed to elevate type 2 diabetes risk when coinciding with early morning food intake (33). In agreement with results of similar investigations in the UK Biobank (34), the interaction effect, however, was not evident when analysis was expanded to include all participants of European descent regardless of employment status and when accelerometer-derived sleep midpoint was used as a more precise objective measure of chronotype.

Despite mounting evidence indicating that night shift work, with likely concurrent chronic exposure to nighttime eating, may exacerbate the associations of *MTNR1B* on type 2 diabetes (14), we did not observe an interaction effect between *MTNR1B* and current shift work on type 2 diabetes. Our hypothesis is derived from experimental studies indicating that enhanced melatonin signaling, either from endogenous or exogenous melatonin, dysregulates glucose metabolism particularly among *MTNR1B* risk allele carriers (11,13). Our results suggest that additional studies in shift workers are needed before population-based recommendations can be made. Worth noting is that our assumption of the concurrence of food intake and endogenous circulating melatonin might not hold true in the night shift work population investigated herein. Furthermore, we have no information about light exposure, which is known to be a potent suppressor of melatonin secretion (35). It is possible that nighttime light exposure in various work environments may suppress endogenous melatonin secretion, which may limit the concurrency between systemic melatonin levels and food intake.

Findings reported here should also be interpreted in light of various other limitations. Lack of information on time-specific eating episodes is a limitation of the traditional 24-h diet recall utilized in the UK Biobank, which assesses for dietary quantity and composition only. The current data set also lacks data on melatonin measures and light exposure, which may be a relevant interacting factor in light of preliminary findings from a northern Sweden cohort, where daylight duration varies from 4.5 to 22 h daily depending on the season, that identified that the *MTNR1B* G variant associated with 0.07 mmol/L lower 2-h glucose concentrations only in participants examined during the dark season (36). In addition, as a result of limited data, we were unable to account for irregular shifts during the accelerometer period, which may have influenced our sleep midpoint estimates. Furthermore, despite our large sample size, our analysis in the UK Biobank population is limited to adults aged 40–69 years, of which only 57% are currently employed. Our findings may also be affected by misclassification of shift worker exposure as a result of sicker employees transitioning from night to day shift schedules with the onset of type 2 diabetes, thus biasing our results toward the null. Lastly, considering the cross-sectional nature of the current analysis, we are unable to infer direct causality for any of our findings. Therefore, it is plausible that the detected associations could be explained by reverse causality (type 2 diabetes onset affecting morningness-eveningness preference or influencing job options). Thus, follow-up longitudinal investigations with detailed assessment of food intake, light exposure, and melatonin levels are necessary to unravel true effects.

Type 2 diabetes, recently estimated to affect 422 million people worldwide, remains a major public health challenge imposing substantial health, societal, and economic burdens (37). Our analyses point at two modifiable lifestyle risk factors, night shift work and definite morningness-eveningness preference, that associate with type 2 diabetes prevalence and HbA_{1c} levels and may variably affect disease risk based on genetics. Furthermore, our findings on shift work, morningness-eveningness preference, and *MTNR1B* may help in developing interventions and guide initiatives aimed at attenuating the further rise of type 2 diabetes prevalence.

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Author Contributions. The study was designed by H.S.D., C.V., J.M.L., F.A.J.L.S., and R.S. H.S.D., C.V., J.M.L., M.K.R., M.G., F.A.J.L.S., and R.S. participated in acquisition, analysis, and/or interpretation of data. H.S.D., C.V., and R.S. wrote the manuscript, and all coauthors reviewed and edited the manuscript before approving its submission. R.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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