Title: Assessment of *MTNR1B* type 2 diabetes genetic risk modification by shift work and morningness-eveningness preference in the UK Biobank

Short Title: *MTNR1B* type 2 diabetes genetic risk, shift work, and morningness-eveningness preference

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Diabetes Publish Ahead of Print, published online November 22, 2019

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Abstract

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 interactions of these risk factors on odds of type 2 diabetes (*n*=5,042 cases) and HbA1c levels (*n*=175,156). Current shift work, definite morning or evening preference, and *MTNR1B* rs10830963 risk-allele associate with type 2 diabetes and HbA1c 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 was seen on risk of type 2 diabetes, this interaction did not persist when analysis was expanded to include all participants regardless of employment status and when using accelerometer-derived sleep-midpoint as an objective measure of morningness-eveningness preference. Our findings suggest that the *MTNR1B* risk-allele carriers may not have greater vulnerability to shift work or morningness-eveningness preference.

Introduction

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 multi-ethnic 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% MAF 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 influence 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 non-carriers. A small trial 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 as compared to non-carriers, 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 vs. 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 night time 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 between *MTNR1B* risk-allele, night shift work and chronotype (self-report and accelerometer-derived), on prevalent type 2 diabetes and HbA1c levels, and *MTNR1B* x behavioral interactions on prevalent type 2 diabetes and HbA1c levels in a large population from the UK Biobank.

Methods

UK Biobank

Study participants for this analysis were from the UK Biobank, described in detail elsewhere (16). In brief, the UK Biobank is a prospective study of >500,000 people living in the United Kingdom. All people in the National Health Service registry who were aged 40–69 years and living less than 25 miles from a study center were invited to participate between 2006 and 2010. In total, 503,325 participants were recruited from over 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 body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared. Biological samples were also collected at baseline. Genotyping was performed by the UK Biobank on 488,377 participants using two similar arrays, UK BiLEVE and UKB 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, approximately 2.8 to 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 the raw accelerometer data.

Ascertainment of prevalent type 2 diabetes and HbA1c 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 International Classification of Diseases version-10 (ICD-10) and disease codes for type 2 diabetes mellitus (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*. to determine additional probable prevalent type 2 diabetes cases (20). 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 unlikely have diabetes based on self-report served as controls. HbA1c levels in red blood cells were determined using high-performance liquid chromatography using the Bio-Rad Variant II Turbo HbA1c analyzer and centrally conducted by the UK Biobank (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 9am to 5pm; 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 defined as "…a work schedule that involves working through the normal sleeping hours, for instance working through the hours from 12am to 6am." 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 set to 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 HbA1c analyses (*n* = 5,042 cases excluded). Furthermore, participants with missing or extreme HbA1c measures defined as those beyond 3 standard deviations 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 which 157,256 participants were

subsequently included in the HbA1c analysis. Missing BMI data (*n* =340) and sleep duration data (*n* =568) were imputed using sex-specific median values.

Associations between current shift work and morningness-eveningness preference and both prevalent type 2 diabetes and HbA1c 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, two to three times/week, four to six times/week, or daily), physical activity (continuous, metabolic equivalents [MET]), 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 between *MTNR1B* rs10830963 risk-allele and prevalent type 2 diabetes and HbA1c was estimated using logistic and linear regression models adjusted for age, sex, BMI, genotyping array and 10 principal components of ancestry.

Interactions between *MTNR1B* risk-allele and current shift work or morningness-eveningness preference on prevalent type 2 diabetes and HbA1c 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 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 actigraphy period, only self-reported employed participants 55 years of age or younger were included 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/grandparents/grandchildren/other). Statistical analyses were conducted with R (version 3.5.1; The R Foundation for Statistical Computing, Vienna, Austria) with a 2-sided significance threshold of $p < 0.05$.

Data and Resource Availability

The datasets 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, had a mean age of 53.5 years (sd =7.1 y), and a mean BMI of 27.2 kg/m^2 (sd =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 HbA1c analyses had a mean HbA1c of 5.3% (34.47 mmol/mol) [sd =2.5% (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 have 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 between current shift work and morningness-eveningness preference and outcomes type 2 diabetes and HbA1c. In age- and sex-adjusted logistic and linear regression models, we observed that current shift work was associated with higher odds of type 2 diabetes and higher HbA1c levels (**Table 2, Supplementary Table 1**). Compared to day workers, shift work without nights [OR (95% CI) =1.26 (1.15-1.39)], sometimes night shift work [OR (95% CI) =1.33 (1.17-1.5)], usual night shift work [OR (95% CI) =1.48 (1.18-1.86)], and always night shift work [OR (95% CI) =1.47 (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 to day workers, all categories of current shift work were associated with higher HbA1c levels, even upon adjustment for sleep duration or BMI and established risk factors (**Table 2, Supplementary Table 1**). Furthermore, we observed that morningness-

eveningness preference was associated with type 2 diabetes and HbA1c levels (**Table 2, Supplementary Table 1**). Compared to definite-morning preference, more morningness than eveningness preference [OR (95% CI) =0.86 (0.8-0.93)] was associated with lower odds of type 2 diabetes, whereas definite-evening preference [OR (95% CI) =1.30 (1.17-1.45)] was associated with higher odds of type 2 diabetes (**Table 2**). Similar associations were also evident for HbA1c (**Table 2**). Upon adjustment for BMI and other known risk factors, association estimates were attenuated but remained significant for definite-evening preference for type 2 diabetes and HbA1c (**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 (95% CI) =1.10 (1.05-1.15)] and 0.26 mmol/mol higher HbA1c per effect allele [Beta (95% CI) = 0.26 (0.23-0.28) mmol/mol]. No interaction was observed between *MTNR1B* risk-allele and current shift work on odds of type 2 diabetes (P_{int} =0.15) and HbA1c (P_{int} =0.25) and remained similar when further adjusted for morningness-eveningness preference (**Table 3, Supplementary Table 2**). As such, the effect of *MTNR1B* risk-allele were similar across categories of shift work on odds of type 2 diabetes [OR (95% CI) =1.10 [1.05-1.15] per effect allele] and HbA1c [Beta (95% CI) = 0.26 (0.23-0.28) mmol/mol per effect allele] (**Table 3**).

We observed an interaction between *MTNR1B* risk-allele and morningness-eveningness preference on odds of type 2 diabetes (P_{int} =0.04), which retained significance upon further adjustment for current shift work (P_{int} =0.04) (**Table 4, 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 (95% CI) =1.17 (1.07-1.28)], while no association was observed among definite-evening participants [OR (95% CI) =1.02 (0.88-1.18)] (**Table 4**). *MTNR1B* risk-allele effect, however, had comparable effects on HbA1c levels (P_{int} =0.87) across categories of morningness-eveningness preference [overall Beta (95% CI) =0.26 (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 between morningness-eveningness preference and type 2 diabetes and HbA1c levels remained similar, however no interaction was observed (P_{int} =0.10) (**Supplementary Table 4,5**). 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 between sleep midpoint and type 2 diabetes (**Supplementary Table 6**). Compared to the first quartile of sleep midpoint, both second [OR (95% CI) =0.64 (0.56-0.75)] and third [OR (95% CI) =0.72 (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 accounting for people residing in the household with the participant. We observed no interaction between *MTNR1B* risk-allele and sleep midpoint on odds of 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).

Discussion

In the present analysis, we show that among employed participants of European descent, current shift work, morningness-eveningness preference, and *MTNR1B* rs10830963 risk-allele associate with type 2 diabetes and HbA1c 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 HbA1c levels in non-diabetic workers in the UK Biobank. The relationships between shift work and adverse health is 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 between both definite-morning and definite-evening preference with higher odds of type 2 diabetes and levels of HbA1c 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 between *MTNR1B* and morningness-eveningness preference for odds of type 2 diabetes. Consistent with previous findings of *MTNR1B* SNP interaction early with wake-time from actigraphy data (12), we observed that the *MTNR1B* risk-allele association with type 2 diabetes is significant among participants self-reporting definite-morning preference, but not among those reporting more evening preference. This interaction 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, however, was not evident when analysis was expanded to include all participants of European ancestry regardless of employment status, and when using accelerometer-derived sleep-midpoint as a more precise objective measure of chronotype.

Despite mounting evidence indicating that night shift work, with likely concurrent chronic exposure to night-time eating, may exacerbate the associations between *MTNR1B* and type 2 diabetes (14), we did not observe an interaction between *MTNR1B* and current shift work on odds of 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). In light of our results, extrapolating findings to population-based recommendations is unclear at this point. 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 of light exposure, which is known to be a potent suppressor of melatonin secretion (35). It is possible that night-time 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-hour diet recall utilized in the UK Biobank, which assesses for dietary quantity and composition only. The current dataset 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 hours daily depending on the season, that identified that the *MTNR1B* G variant associated with 0.07 mmol/l lower 2-hour 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, 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 towards 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 HbA1c 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.

Acknowledgment

This project was conducted using the UK Biobank resource (project ID 6818). We would like to thank the participants of the UK Biobank for their participation. We would also like to thank the administrative support team at the UK Biobank for their responsiveness and support in all questions. MG is supported by the Spanish Government of Investigation, Development and Innovation (SAF2017-84135-R) including FEDER co-funding; Séneca Foundation (20795/PI/18) and NIDDK R01DK105072. MKR is supported by The University of Manchester Research Infrastructure Fund. MKR has acted as a consultant for GSK, Novo Nordisk, Roche and MSD, and also participated in advisory board meetings on their behalf. MKR has received lecture fees from MSD and grant support from Novo Nordisk, MSD and GSK. HSD and RS are supported by NIH R01DK107859. RS and FAJLS are supported by NIH R01DK102696 and R01DK105072. CV is supported by R01DK105072. FAJLS is further supported by R01DK099512, R01HL118601, and R01HL140574. RS is supported by MGH Research Scholar Fund. This study was supported in part by R01DK105072, R01HL118601 and the University of Manchester (Regional Innovation Funding). The funding sources had no influence on study design, data analyses, or interpretation of the findings.

Author Contributions

The study was designed by HSD, CV, JML, FAJLS, RS. HSD, CV, JML, MKR, MG, FAJLS, and RS participated in acquisition, analysis and/or interpretation of data. HSD, CV, and RS wrote the manuscript and all co-authors reviewed and edited the manuscript, before approving its submission. RS 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.

Conflict of Interest Disclosures

FAJLS has received speaker fees from Bayer Healthcare, Sentara Healthcare, Philips, Kellogg Company, Vanda Pharmaceuticals, and Pfizer Pharmaceuticals. MKR reports receiving research funding from Novo Nordisk, consultancy fees from Novo Nordisk and Roche Diabetes Care, and modest owning of shares in GlaxoSmithKline. All remaining authors declare no competing interests.

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Tables

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)
Sex, % male	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, hours	7.1 (0.9)	7.0 (1.0)	6.9 (1.0)	6.9 (1.1)	6.8 (1.2)
Townsend 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), 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.

Table 2. Associations between current shift work (*n* =189,488) and morningness-eveningness preference (*n* =169,926) with adjusted odds of type 2 diabetes and adjusted mean difference in HbA1c (in mmol/mol) across shift work and morningness-eveningness preference categories in employed UK Biobank participants of European descent.

	Type 2 diabetes			HbA1c (mmol/mol)		
	Type 2 diabetes cases /controls	**Sex- and age-adjusted OR [95% CI]**	**BMI, and add' -adjusted OR [95% CI]**	***N***	**Sex- and age-adjusted Beta [95% CI]**	**BMI, and add' -adjusted Beta [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 [0.28-0.4]**	**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--0.09]**	-0.02 [-0.07-0.03]
More evening than morning	1,268 /48,593	0.96 [0.89-1.04]	1.02 [0.93-1.13]	46,267	-0.04 [-0.09-0.01]	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]**

Legend: Prevalent type 2 diabetes associations are sex- and age- adjusted odds ratios [95% confidence interval], 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, metabolic equivalents [MET]), hypertension (yes/no), hypertension medication use (yes/no), hypercholesterolemia (yes/no), and lipid-lowering medication intake (yes/no)]. HbA1c associations are restricted to participants with no prevalent type 2 diabetes. HbA1c associations are sex- and age- adjusted betas [95% confidence interval] 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. Bold P <0.05.

Table 3. Adjusted odds ratios (OR) or adjusted betas and 95% confidence intervals (CI) of type 2 diabetes and HbA1c (in mmol/mol) with each additional copy of the *MTNR1B* G risk-allele across categories of current work schedule (*n* =189,488).

	Type 2 diabetes			HbA1c (mmol/mol)		
	Type 2 diabetes cases /controls	OR [95% CI]	P_{int}	*N*	Beta [95% CI]	P_{int}
Overall	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 [-0.04-0.45]	
Always night shift work	156 /4,186	1.28 [0.99-1.65]		3,979	0.19 [0.02-0.37]	

Legend: Association results are adjusted odds ratios [95% confidence interval] of type 2 diabetes per each additional copy of the *MTNR1B* G risk-allele or adjusted betas [95% confidence interval] describing differences in HbA1c 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.

Table 4. Adjusted odds ratios (OR) or adjusted betas and 95% confidence intervals (CI) of type 2 diabetes and HbA1c (in mmol/mol) with each additional copy of the *MTNR1B* G risk-allele across categories of morningness-eveningness preference (*n* =169,926).

	Type 2 diabetes			HbA1c (mmol/mol)		
	Type 2 diabetes cases /controls	OR [95% CI]	P_{int}	*N*	Beta [95% CI]	P_{int}
Overall	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]	

Legend: Association results are adjusted odds ratios [95% confidence interval] of type 2 diabetes per each additional copy of the *MTNR1B* G risk-allele or adjusted betas [95% confidence interval] describing differences in HbA1c 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 between quartiles of accelerometer-derived sleep midpoint (*n* =38,701) with adjusted odds of type 2 diabetes in employed UK Biobank participants of European descent.

	Type 2 diabetes cases /controls	Sex- and age-adjusted OR [95% CI]	Sex- and age- and household status- adjusted OR [95% CI]
Sleep midpoint (Q1)	168 /9,508	*reference*	*reference*
Sleep midpoint (Q2)	104 /9,571	**0.64 [0.55-0.75]**	**0.65 [0.56-0.77]**
Sleep midpoint (Q3)	120 /9,555	**0.72 [0.61-0.86]**	**0.75 [0.63-0.89]**
Sleep midpoint (Q4)	163 /9,512	0.95 [0.77-1.17]	0.96 [0.78-1.19]

Legend: Prevalent type 2 diabetes associations are sex- and age- adjusted odds ratios [95% confidence interval] and bold *P* <0.05. In sensitivity analysis, associations were further adjusted for people residing in the household with the participant (household status).

Supplementary Tables

Supplementary Table 1. Association analyses between current shift work (*n* =189,488) and morningness-eveningness preference (*n* =169,926) with unadjusted/adjusted odds of type 2 diabetes and mean difference in HbA1c (in mmol/mol) across shift work and morningness-eveningness preference categories in employed UK Biobank participants of European descent.

	Type 2 diabetes			HbA1c (mmol/mol)		
	Type 2 diabetes cases /controls	Unadjusted OR [95% CI]	Sleep duration adjusted OR [95% CI]	*N*	Unadjusted Beta [95% CI]	Sleep duration adjusted Beta [95% CI]
Shift work						
Day workers	4,047 /154,792	*reference*	*reference*	146,993	*reference*	*reference*
Shift work without nights	475 /14,863	**1.22 [1.11-1.35]**	**1.26 [1.14-1.39]**	14,110	**0.29 [0.22-0.35]**	**0.33 [0.27-0.39]**
Sometimes night shift work	284 /8,434	**1.29 [1.14-1.46]**	**1.32 [1.17-1.49]**	8,005	**0.25 [0.17-0.33]**	**0.46 [0.38-0.54]**
Usual night shift work	80 /2,171	**1.41 [1.13-1.77]**	**1.47 [1.17-1.85]**	2,069	0.16 [0-0.32]	**0.43 [0.27-0.58]**
Always night shift work	156 /4,186	**1.43 [1.21-1.68]**	**1.45 [1.23-1.71]**	3,979	**0.54 [0.43-0.66]**	**0.72 [0.60-0.83]**
Morningness-eveningness preference						
Definite-morning	1,272 /42,097	*reference*	*reference*	39,976	*reference*	*reference*
More morning than evening	1,482 /60,064	**0.82 [0.76-0.88]**	**0.86 [0.8-0.93]**	57,127	**-0.25 [-0.3--0.2]**	**-0.12 [-0.17--0.08]**
More evening than morning	1,268 /48,593	**0.86 [0.8-0.93]**	0.96 [0.89-1.04]	46,267	**-0.28 [-0.32--0.23]**	-0.03 [-0.08-0.01]
Definite-evening	497 /14,653	**1.12 [1.01-1.25]**	**1.30 [1.17-1.44]**	13,886	**-0.17 [-0.24--0.1]**	**0.11 [0.04-0.18]**

Legend: Prevalent type 2 diabetes associations are unadjusted and then sex-, age-, and sleep-duration adjusted odds ratios [95% confidence interval]. HbA1c associations are restricted to participants with no prevalent type 2 diabetes. HbA1c associations are unadjusted and then sex-, age-, and sleep-duration adjusted betas [95% confidence interval] in mmol/mol. Bold *P* <0.05.

Supplementary Table 2. Adjusted odds ratios (OR) or adjusted betas and 95% confidence intervals (CI) of type 2 diabetes and HbA1c (in mmol/mol) with each additional copy of the *MTNR1B* G risk-allele across categories of current work schedule with further adjustment for morningngess-eveningness preference (*n* =169,926).

	Type 2 diabetes			HbA1c (mmol/mol)		
	Type 2 diabetes cases /controls	OR [95% CI]	P_{int}	*N*	Beta [95% CI]	P_{int}
Overall	4,519 /165,407	1.10 [1.05-1.15]	0.10	157,256	0.26 [0.23-0.29]	0.34
Day workers	3,634 /139,090	1.09 [1.03-1.15]		132,249	0.25 [0.22-0.28]	
Shift work without nights	430 /13,389	1.25 [1.07-1.45]		12,720	0.32 [0.22-0.42]	
Sometimes night shift work	247 /7,450	0.94 [0.76-1.16]		7,074	0.35 [0.22-0.48]	
Usual night shift work	70 /1,889	0.84 [0.56-1.27]		1,799	0.21 [-0.05-0.46]	
Always night shift work	138 /3,589	1.24 [0.94-1.63]		3,414	0.18 [-0.01-0.37]	

Legend: Association results are adjusted odds ratios [95% confidence interval] of type 2 diabetes per each additional copy of the *MTNR1B* G risk-allele or adjusted betas [95% confidence interval] describing differences in HbA1c 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, 10 principal components of ancestry, and morningness-eveningness preference. 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.

Supplementary Table 3. Adjusted odds ratios (OR) or adjusted betas and 95% confidence intervals (CI) of type 2 diabetes and HbA1c (in mmol/mol) with each additional copy of the *MTNR1B* G risk-allele across categories of morningness-eveningness preference with further adjustment for current work schedule (*n* =169,926).

	Type 2 diabetes			HbA1c (mmol/mol)		
	Type 2 diabetes cases /controls	OR [95% CI]	P_{int}	*N*	Beta [95% CI]	P_{int}
Overall	4,519/165,407	1.10 [1.04-1.15]	0.044	157,256	0.26 [0.23-0.29]	0.86
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	1.01 [0.87-1.18]		13,886	0.36 [0.27-0.46]	

Legend: Association results are adjusted odds ratios [95% confidence interval] of type 2 diabetes per each additional copy of the *MTNR1B* G risk-allele or adjusted betas [95% confidence interval] describing differences in HbA1c 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, 10 principal components of ancestry, and current work schedule. 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.

Supplementary Table 4. Sensitivity analyses of morningness-eveningness preference association with adjusted odds of type 2 diabetes (*n* =298,953) and adjusted mean difference in HbA1c (in mmol/mol; *n* =272,220) in UK Biobank participants of European descent regardless of employment status.

	Type 2 diabetes		HbA1c (mmol/mol)	
	Type 2 diabetes cases /controls	Sex- and age-adjusted OR [95% CI]	*N*	Sex- and age-adjusted Beta [95% CI]
Morningness-eveningness preference				
Definite-morning	3,490 /75,909	*reference*	72,013	*reference*
More morning than evening	4,006 /104,746	**0.86 [0.82-0.90]**	99,552	**-0.12 [-0.15--0.08]**
More evening than morning	3,455 /81,559	1.01 [0.96-1.06]	77,517	-0.03 [-0.06-0.01]
Definite-evening	1,373 /24,415	**1.40 [1.31-1.49]**	23,138	**0.17 [0.12-0.22]**

Legend: Prevalent type 2 diabetes associations are sex-, and age- adjusted odds ratios [95% confidence interval]. HbA1c associations are restricted to participants with no prevalent type 2 diabetes. HbA1c associations are sex- and age-, adjusted betas [95% confidence interval] in mmol/mol. Bold *P* <0.05.

Supplementary Table 5. Sensitivity analyses of morningness-eveningness preference association with adjusted odds of type 2 diabetes (*n* =298,953) and adjusted mean difference in HbA1c (in mmol/mol; *n* =272,220) with each additional copy of the *MTNR1B* G in UK Biobank participants of European descent regardless of employment status.

	Type 2 diabetes			HbA1c (mmol/mol)		
	Type 2 diabetes cases /controls	OR [95% CI]	P_{int}	*N*	Beta [95% CI]	P_{int}
Overall	12,324 /286,629	1.10 [1.07-1.14]	0.17	272,220	0.24 [0.22-0.26]	0.83
Definite morning	3,490 /75,909	1.14 [1.08-1.2]		72,013	0.26 [0.22-0.30]	
More morning than evening	4,006 /104,746	1.11 [1.05-1.16]		99,552	0.22 [0.18-0.25]	
More evening than morning	3,455 /81,559	1.07 [1.02-1.13]		77,517	0.23 [0.19-0.27]	
Definite evening	1,373 /24,415	1.09 [0.99-1.19]		23,138	0.27 [0.20-0.35]	

Legend: Association results are adjusted odds ratios [95% confidence interval] of type 2 diabetes per each additional copy of the *MTNR1B* G risk-allele or adjusted betas [95% confidence interval] describing differences in HbA1c 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.

Supplementary Table 6. Characteristics of subset of UK Biobank participants of European descent with up to 7-day actigraphy information.

	Employed Participants	All Participants
N	38,701	82,923
Age, years	56.4	62.5
Sex, % male	41.90	43.9
BMI, kg/m^2	26.5	26.7
Type 2 diabetes, *n* cases (%)	555 (1.4)	2,165 (2.6)
Sleep midpoint, clock time	26.91	26.99
Townsend Index*	-1.64	-1.80
People in Household, *n* (%)		
Husband, Wife or Partner	29,166 (75.4)	63,354 (76.4)
Son and/or Daughter	21,163 (54.7)	29,413 (35.5)
Mother and/or Father	149 (0.4)	287 (0.3)
Grandchild	809 (2.1)	1,285 (1.5)
Other	7 (0.02)	10 (0.01)

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.

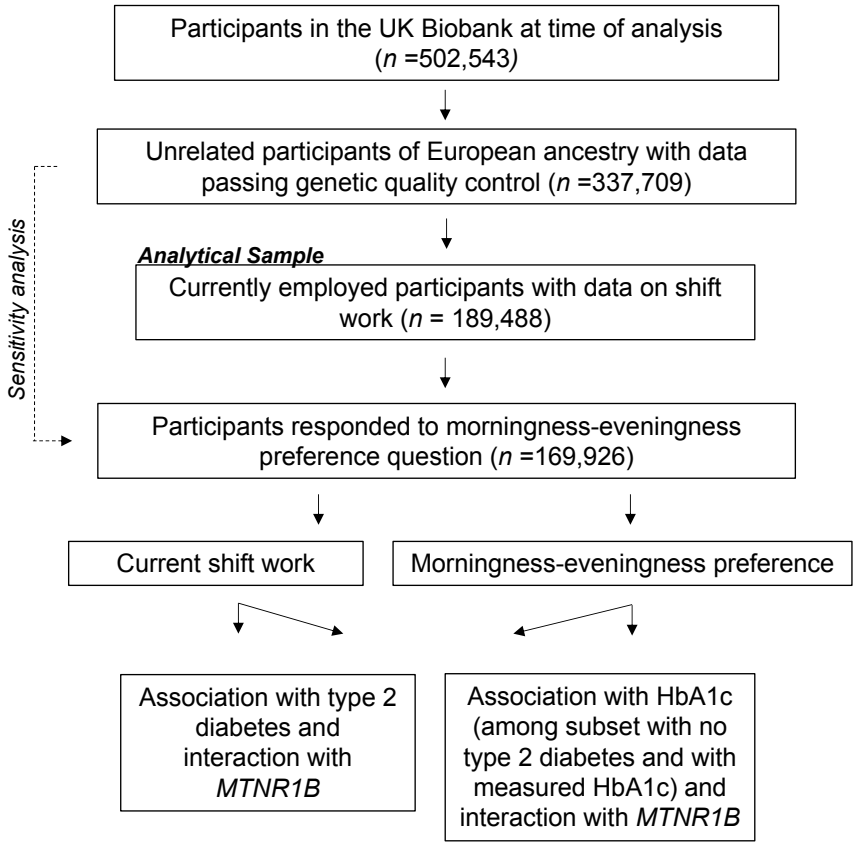
Supplementary Table 7. Associations between quartiles of accelerometer-derived sleep midpoint (*n* =82,923) with adjusted odds of type 2 diabetes in UK Biobank participants of European descent regardless of employment status.

	Type 2 diabetes cases /controls	Sex- and age-adjusted OR [95% CI]	Sex- and age- and household status- adjusted OR [95% CI]
Sleep midpoint (Q1)	590 / 20,141	*reference*	*reference*
Sleep midpoint (Q2)	474 / 20,258	**0.79 [0.72-0.88]**	**0.80 [0.73-0.89]**
Sleep midpoint (Q3)	481 / 20,249	**0.79 [0.71-0.87]**	**0.80 [0.72-0.88]**
Sleep midpoint (Q4)	620 / 20,110	0.99 [0.88-1.11]	1.00 [0.89-1.12]

Legend: Prevalent type 2 diabetes associations are sex- and age- adjusted odds ratios [95% confidence interval] and bold *P* <0.05. In sensitivity analysis, associations were further adjusted for people residing in the household with the participant (household status).

Supplementary Figures

Supplementary Figure 1. Analysis workflow.



Supplementary Figure 2. Adjusted odds ratios (OR) of type 2 diabetes with each additional copy of the *MTNR1B* G risk-allele in the overall sample and across categories of morningness-eveningness preference in employed UK Biobank participants of European descent (*n* =169,926).