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Associations between chronotype, morbidity and mortality in the UK Biobank cohort

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Abstract

Later chronotype (i.e. evening preference) and later timing of sleep have been associated with greater morbidity, including higher rates of metabolic dysfunction and cardiovascular disease. However, no one has examined whether chronotype is associated with mortality risk to date. Our objective was to test the hypothesis that being an evening type is associated with increased mortality in a large cohort study, the UK Biobank. Our analysis included 433,268 adults aged 38-73 at the time of enrolment and an average 6.5-year follow-up. The primary exposure was chronotype, as assessed through a single self-reported question defining participants as definite morning types, moderate morning types, moderate evening types, or definite evening types. The primary outcomes were all-cause mortality and mortality due to cardiovascular disease (CVD). Prevalent disease was also compared among the chronotype groups. Analyses were adjusted for age, sex, ethnicity, smoking, body mass index, sleep duration, socioeconomic status and comorbidities. Greater eveningness, particularly being a definite evening type, was significantly associated with a higher prevalence of all comorbidities. Comparing definite evening type to definite morning type, the associations were strongest for psychological disorders (OR 1.94, 95% CI 1.86 to 2.02, $p < .001$), followed by diabetes (OR 1.30, 95% CI 1.24 to 1.36, $p < .001$), neurological disorders (OR 1.25, 95% CI 1.20 to 1.30, $p < .001$), gastrointestinal/abdominal disorders (OR 1.23, 95% CI 1.19 to 1.27, $p < .001$), and respiratory disorders (OR 1.22, 95% CI 1.18 to 1.26, $p < .001$). The total number of deaths was 10,534, out of which 2,127 were due to CVD. Greater eveningness, based on chronotype as an ordinal variable, was associated with a small increased risk of all-cause mortality (HR 1.02, 95% CI 1.004 to 1.05, $p = .017$) and CVD mortality (HR 1.04, 95% CI 1.00 to 1.09, $p = .06$). Compared to definite morning types, definite evening types had significantly increased risk of all-cause mortality (HR 1.10, 95% CI 1.02 to 1.18, $p = .012$). This first report of increased mortality in evening types is consistent with previous reports of increased levels of cardiometabolic risk factors in this group. Mortality risk in evening types may be due to behavioural, psychological, and physiological risk factors, many of which may be attributable to chronic misalignment between internal physiological timing and externally

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Declaration of Interest statement

The authors report no conflicts of interest.

imposed timing of work and social activities. These findings suggest the need for researching possible interventions aimed at either modifying circadian rhythms in individuals or at allowing evening types greater working hour flexibility.

Introduction

Identifying novel, potentially modifiable, life style factors associated with increased morbidity and mortality can lead to innovative strategies for improving health. We investigated a measure of chronotype, which is an estimate of the general part of the day (ranging between morning and evening) that a person prefers for their daily activities. Later chronotype (i.e. evening preference) and later timing of sleep (which is associated with later chronotype) have been associated with morbidity, including higher rates of metabolic dysfunction and cardiovascular disease (Reutrakul and Knutson, 2015, Merikanto et al., 2013, Yu et al., 2015, Koopman et al., 2017) and psychiatric symptoms (Jankowski, 2016, Melo et al., 2017, Putilov, 2017). In the UK Biobank Study, a large prospective cohort study, a preference for evening was also associated with more cardiovascular risk factors, such as higher rates of smoking and overweight/obesity (Patterson et al., 2017).

Current evidence therefore implicates later chronotype (i.e. being a self-described “evening person”) in the risk of a variety of diseases. The objective of this study was to test the hypothesis that a later chronotype is associated with increased risk of all-cause mortality as well as mortality due to cardiovascular disease (CVD) in a large study of adults in the UK.

Methods

Study Design and Participants

We used data from the UK Biobank, a large, prospective, population-based cohort study that was designed to investigate risk factors for major disease of middle and older age (Sudlow et al., 2015). The UK Biobank enrolled 502,642 people aged 37-73 years (53% women) from across the UK. Identical assessment procedures were used across field sites. The recruitment strategy aimed to be as inclusive as possible, with every individual within the inclusion age range who were registered with the National Health Service and living up to about 25 miles from one of the assessment centres invited to participate (Allen et al., 2012). The baseline assessment was conducted between March 2006 and October 2010. For the analyses presented here, the mean follow-up time was 6.5 years.

Our primary exposure variable was chronotype, which in the UK Biobank questionnaire was assessed through a single question that asked, “Do you consider yourself to be” with the four options (in addition to “Do not know”): “definitely a morning person” (definite morning types), “more a morning than evening person” (moderate morning types), “more an evening than a morning person” (moderate evening types), and “definitely an evening person” (definite evening types). This question is very similar to the last question of the Morningness-Eveningness Questionnaire (MEQ) (Horne and Ostberg, 1976), which asks, “One hears about ‘morning’ and ‘evening’ types of people. Which ONE of these types do you consider yourself to be?” and had the response options “Definitely a ‘morning’ type,

Rather more a ‘morning’ than an ‘evening’ type, Rather more an ‘evening’ type than a ‘morning’ type, Definitely an ‘evening’ type”.

Primary outcomes included all-cause mortality and mortality due to cardiovascular disease (CVD). Mortality information was obtained from the National Health Service for England and Wales and by the NHS Central Register in Scotland. All details from the death certificate were provided to UK Biobank. Primary cause of death was codified according to ICD10 by trained UK Biobank personnel. We identified the ICD10 codes I00-I99 as CVD-related.

Comorbidities were based on self-report. Specifically, participants were asked to report any illnesses they had and if the participant was uncertain of the type of illness he/she had, they described it to the interviewer (a trained nurse) who attempted to code it. If the illness could not be coded during the interview, the interviewer entered a free-text description, which was subsequently reviewed by a physician and, where possible, matched to codes. Using these codes, cases of self-reported cardiovascular disease, diabetes, other endocrine disorders, neurological disorders, renal disorders respiratory disorders, musculoskeletal disorders, gastrointestinal/abdominal disorders and psychological disorders were identified (see Supplemental Table 1).

Covariates in the model were selected based on the potential to confound associations between chronotype and mortality. These covariates included age, sex, ethnicity, smoking status, body mass index (BMI), socioeconomic status (SES), sleep duration and comorbidities. Age at baseline assessment was calculated in years based on date of birth. Three age bins were defined based on previous analyses of UK Biobank data (Ganna and Ingelsson, 2015): 37-52 years, 53-62 years and 63-73 years. Sex (male/female) and ethnicity were self-identified. Since a large majority of the sample (94%) self-identified as “white”, we dichotomised ethnicity into “white” and “non-white”. Smoking status was obtained by self-report with the following categories: “Never”, “Previous smoker”, “Current smoker”, and “prefer not to answer”. Standing height was measured using a Seca 240cm height measure while participants stood barefoot with posture verified by trained staff. Weight was measured using a Tanita BC418MA body composition analyser and BMI was calculated as weight (kg) divided by height squared (m²). SES was based on the Townsend deprivation index (Townsend et al., 1988), which was calculated immediately prior to participants joining UK Biobank and was based on the preceding national census output areas. Each participant was assigned a score based on their postcode.

Finally, sleep duration came from the touchscreen interview based on the question, “About how many hours sleep do you get in every 24 hours (please include naps)?” and responses were provided as integers.

Statistical Analyses

Analyses were restricted to those participants who provided a response to the question about chronotype (n=444,281) and further excluded those who were missing any of the covariate data resulting in a final sample size of 433,268 participants. The chronotype groups were compared in unadjusted analyses using analyses of variance (ANOVA) for continuous

variables (e.g. age, BMI, sleep duration, SES) or *chi* squared tests for categorical variables (e.g. sex, ethnicity, smoking, comorbidities). Mean chronotype score was also compared between groups using t tests (for dichotomous variables) or ANOVA (for variables with >2 groups). The prevalence of the comorbidities between the chronotype groups were also compared after adjusting for age and sex using logistic regression models. Cox proportional hazards model were used to estimate the risk of mortality according to chronotype. We modelled chronotype as an ordinal variable and, to allow for non-linear associations, we also created dummy variables with definite morning type as the referent. Cox proportional hazards models were estimated adjusting for age (as continuous variable), sex, ethnicity, smoking status, body mass index (BMI), socioeconomic status (SES), diagnosed comorbidities, and sleep duration. We also created interaction terms between chronotype (ordinal variable) and both sex and the 3 age groups to test for differences in associations between mortality and chronotype. When interaction terms were significant, we conducted stratified analyses. Finally, a significant number of participants (n=50,061) selected the answer “Do not know” to the chronotype question. Other investigators reporting UK Biobank data (Jones et al., 2016) have chosen to classify this group as a fifth, intermediate response. So, to verify our findings, we have repeated the analysis of chronotype and mortality risk using a 5-level chronotype variable: 2 definite Morning Type, 1 moderate morning types, 0 Do not know, -1 moderate evening types, -2 definite evening types. The probability $p < .05$ (two-sided) was set as the accepted level of statistical significance. All statistical analyses were performed using Stata, v14 (Statacorp, College Station, TX).

Results

Our final sample included 433,268 participants. Ages ranged from 38-73 years (mean 56.5, SD 8.1) and 55.7% was women. Approximately 27% identified as definite morning types, 35% as moderate morning types, 28% as moderate evening types, and 9% as definite evening types. Table 1 describes the full sample as well as each chronotype group. Those who identified as definite morning types were on average older, included a higher proportion of women and non-smokers, and lower proportions of white ethnicity than definite evening types.

The prevalence of the various disorders differed significantly among the Chronotype groups (Table 1). Table 2 presents the odds ratios associated with having each comorbidity based on chronotype after adjusting for age and sex. When chronotype is modeled as an ordinal variable, it is significantly associated with all the comorbidities. Each incremental increase in eveningness from definite morning to definite evening type was associated with increased odds of having each comorbidity. When chronotype was treated as categories, those who were definite evening types were significantly more likely to have each comorbidity compared to those who were definite morning types. The association was strongest for psychological disorders (OR 1.94), followed by diabetes (OR 1.30), neurological disorders (OR 1.25), gastrointestinal/abdominal disorders (OR 1.23) and respiratory disorders (OR 1.22). Mean chronotype scores also varied by demographic and comorbidity groups in a similar pattern, with higher mean scores (greater eveningness) in younger age groups, men, whites, current smokers, in those without CVD, and in those with diabetes, neurological

disorders, respiratory disorders, gastrointestinal disorders or psychological disorders (Supplemental Table 2).

There were 10,534 deaths from all causes during the follow-up period and, of these, 2,127 were due to CVD. Table 3 presents the hazard ratios for mortality associated with chronotype as an ordinal variable as well as the HR for the covariates. Chronotype as an ordinal variable was associated with all-cause mortality (1.02 per level, $p=.017$) and CVD mortality (1.04 per level, $p=.06$), such that increasing eveningness was associated with greater mortality. When chronotypes were considered as categories, being a definite evening type was associated with a 10% increased risk of all-cause mortality (OR 1.10, 95% CI 1.02, 1.18, $p=.012$) compared to definite morning types. Neither of the two intermediate groups was associated with increased risk of all-cause mortality. None of the chronotype categories was significantly associated with increased risk of CVD mortality compared to definite morning types. Results from analyses where the answer “do not know” was interpreted as an intermediate chronotype were very similar to the findings above (Supplemental Table 3). Greater morningness was associated with lower risk of all-cause mortality (HR 0.98, 95% CI 0.97, 0.996, $p=.012$) and CVD mortality (HR 0.97, 95% CI 0.94, 0.998, $p=.037$).

No significant interactions by sex were observed (both $p>.30$), indicating that the association between chronotype and all-cause or CVD mortality did not differ between men and women. There was, however, a significant interaction between chronotype and age for all-cause mortality ($p=.02$), but not CVD mortality ($p=.45$). Analyses of all-cause mortality were then stratified by the 3 age groups, and the number of deaths was 1,229 in the 37–52-year-old group, 3,821 in the 53–62-year-old group, and 5,484 in the 63–73-year-old group. The association between chronotype and all-cause mortality was significant in the 63–73-year age group (HR 1.04, 95% CI 1.01, 1.07, $p=.006$), but not in the 37–52-year old group (HR 1.00, 95% CI 0.94, 1.06, $p=.94$) or the 53–62-year-old group (HR 1.01, 95% CI 0.98, 1.04, $p=.55$).

Discussion

Increased eveningness, particularly definite evening type, was associated with increased prevalence of a wide variety of diseases or disorders, including diabetes, psychological, neurological, respiratory and gastrointestinal/abdominal disorders. Further, increased eveningness, was significantly associated with increased risk of all-cause mortality over 6.5 years. Chronotype as an ordinal variable was also associated with increased risk CVD mortality, but did not reach statistical significance. The effect size was small (2% increased risk with each level of chronotype); however, this effect size is similar to the effect we observed for BMI, endocrine disorders (excluding diabetes), renal disorders, musculoskeletal disorders and gastrointestinal/abdominal disorders. Further, mortality is a significant clinical outcome and any increase in age-adjusted risk of death warrants attention. There was no evidence for a difference in these associations between men and women. We did observe differences between age groups in that the association between later chronotype and increased risk of all-cause was significant and strongest in the oldest age group.

The unique strengths of this study include its large sample size and the prospective study design. No previous prospective population-based studies have included a measure of chronotype and mortality. An important potential weakness is the single question used to assess chronotype. A significant number of participants (50,061) selected the answer “Do not know”, however, as shown in Supplemental Table 3, including them did not appreciably change our findings. Circadian biologists mainly use two validated instruments used to assess either circadian preference, the Morningness-Eveningness Questionnaire (MEQ) (Horne and Ostberg, 1976), or circadian timing of behaviour, the Munich Chronotype Questionnaire (Roenneberg et al., 2003). Both instruments require several questions to estimate circadian preference or chronotype, while the UK Biobank participants rated their chronotype through the answer to a single question. However, this question is practically identical to the final question of the MEQ, which has been found to have the highest correlation ($\rho=.89$) to the total MEQ score (Adan and Almirall, 1991), which suggests that misclassification may have been minimal. Further, the brevity of the question makes it more acceptable for use in clinic or public health settings. Second, the comparison of chronotype and prevalent disease does not indicate causal direction. Finally, the UK Biobank cohort is generally healthier than the general UK population (Fry et al., 2017), and the degree to which these findings are generalisable to the entire population, or to other countries, is not known.

Our findings both agree with and crucially add to previously reported associations between evening types and increased morbidity and associated risk factors (Merikanto et al., 2013, Yu et al., 2015, Koopman et al., 2017). Eveningness has been associated with less healthy diets, including greater proportion of fat intake (Kanerva et al., 2012, Sato-Mito et al., 2011), which could increase risk of cardiometabolic diseases. Other studies have found that people with later chronotypes had a higher prevalence of type 2 diabetes (Yu et al., 2015, Merikanto et al., 2013) and hypertension (Merikanto et al., 2013), which is consistent with our finding that later chronotypes were more likely to have CVD and diabetes. Greater eveningness has also been associated with depression and mood disorders, particularly in those 50 years or older (Kim et al., 2010). Behaviourally, evening types have a greater tendency towards impulsivity and novelty seeking and lower harm avoidance (Adan et al., 2010, Caci et al., 2004). Evening types have also reported greater consumption of legal psychoactive substances (nicotine, alcohol, and caffeine) (Adan, 1994) as well as illegal drugs (Prat and Adan, 2011), which could reflect either biological differences or sheer opportunity offered by being awake and active late at night. These findings are consistent with our observed association between chronotype and psychological disorders, which includes mood disorders and substance abuse. One population-based study in Finland reported that evening chronotypes were more likely to have respiratory disorders, such as asthma (Merikanto et al., 2014), and we made similar observations in the UK cohort. We also found that evening types have a greater prevalence of neurological and gastrointestinal/abdominal disorders, which has not been reported previously. In sum, several physical and mental health measures could underlie the association between eveningness, morbidity and mortality risk.

To date, no prospective population-based studies have examined associations between chronotype and mortality. A prospective study of approximately 11,000 Finnish twins examined chronotype, shift work in the incidence as well as mortality due to prostate cancer

(Dickerman et al., 2016). That study found that those who identified as “somewhat evening” types had a significantly increased risk of developing prostate cancer compared to definite morning types (HR 1.3; 95 % CI 1.1, 1.6). The study reported no significant association between chronotype and prostate cancer mortality; however, they only observed 110 such deaths, and may have been underpowered.

The health of evening types could be compromised by misalignment between their endogenous biological clocks and the timing of social activities (e.g. work or meals), termed circadian misalignment. Experimentally induced circadian misalignment has resulted in impairments in glucose metabolism (Scheer et al., 2009, Buxton et al., 2012, Leproult et al., 2014), profound disruption of rhythmic gene expression programmes (Archer et al., 2014), and impairments in mood (Boivin et al., 1997). Evening types also commonly experience greater “social jetlag” (Wittmann et al., 2006), which is caused by going to bed and waking up later on non-work days compared to work days. Greater social jetlag has been associated with being overweight (BMI ≥ 25 kg/m²) (Roenneberg et al., 2012) and adverse cardiometabolic profiles (Rutters et al., 2014, Parsons et al., 2015). Shorter sleep durations are more common in evening types (Roenneberg et al., 2007) and shorter sleep is associated with increased morbidity and mortality (Knutson, 2010, Yin et al., 2017). However, the difference in self-reported sleep duration between the chronotype groups in our study was minimal (and controlled for) and thus, differences in sleep duration are not likely to explain our observations. Finally, increased morbidity among evening types may also be due to greater exposure to artificial light at night that acutely suppresses melatonin. Lower levels of melatonin have been associated with greater insulin resistance (Reutrakul et al., 2017), increased risk of diabetes (McMullan et al., 2013), and breast and prostate cancer (Kloog et al., 2009, Kloog et al., 2010).

The heritable component of chronotype has been calculated to be between 21 and 52% (von Schantz et al., 2015). Our data do not reveal to what extent the association between eveningness and higher morbidity and mortality reflects genetic and environmental components. However, key environmental determinants of chronotype are potentially modifiable by interventions aimed at advancing circadian phase, such as administration of light in the morning and of melatonin in the evening. Another strategy to improve health of evening types would be to adjust work schedules to suit individual chronotype. It is also worth noting that daylight savings time (DST)/summer time places a further burden on individuals who are already struggling with the dictates of social norms on when to start the working day, and the switch to DST, which is perceived as more uncomfortable by evening types than by morning types (Nascimento de Alencar et al., 2017, Kantermann et al., 2007), also coincided with greater incidence of cardiovascular events (Jiddou et al., 2013).

Thus, our findings suggest a need for more research on the physiological consequences of being an evening type to explain the increased risk of mortality. Understanding the link between chronotype and mortality could lead to the development of additional behavioural strategies to mitigate risk associated with being an evening type. Strategies could include therapies that target the circadian system and tailoring schedules to suit individual chronotype whenever possible (Roenneberg and Merrow, 2016). These novel therapies have

the potential to critically improve not only well-being and health, but even life expectancy of evening types.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of individuals by chronotype.

	Full Sample	Definite Morning Type	Moderate Morning Type	Moderate Evening Type	Definite Evening Type
N	433,268	117,224 (27.1%)	153,895 (35.5%)	123,282 (28.5%)	38,867 (9.0%)
Age (years; mean, SD) *	56.5 (8.1)	57.4 (7.8)	56.8 (8.0)	55.8 (8.3)	55.1 (8.3)
37-52 years (%)	32.3%	27.9%	30.8%	36.1%	39.6%
53-62 years (%)	39.6%	40.8%	40.6%	38.0%	37.6%
63-73 years (%)	28.1%	31.2%	28.7%	25.9%	22.8%
Female (%) *	55.7%	56.5%	56.2%	55.2%	53.3%
White ethnicity (%) *	94.6%	93.1%	95.6%	95.0%	93.7%
Smoking Status (%) *	89.4%	91.1%	91.9%	87.1%	81.3%
Never	54.4%	57.0%	57.0%	51.3%	45.6%
Previous	34.7%	33.8%	34.6%	35.6%	35.4%
Current	10.6%	8.8%	8.1%	12.9%	18.6%
No answer	0.3%	0.42%	0.28%	0.29%	0.29%
Body Mass Index (kg/m ² ; mean, SD) *	27.4 (4.8)	27.6 (4.8)	27.2 (4.6)	27.5 (4.8)	27.9 (5.2)
Sleep Duration (hours; mean, SD) *	7.2 (1.1)	7.1 (1.1)	7.2 (1.0)	7.2 (1.1)	7.1 (1.2)
Prevalent Comorbidities:					
CVD *	36.2%	38.4%	35.5%	35.2%	36.1%
Diabetes *	5.0%	5.4%	4.4%	4.9%	6.2%
Neurological *	9.4%	9.0%	9.1%	9.6%	10.8%
Endocrine *	6.3%	6.4%	6.2%	6.3%	6.7%
Renal *	4.6%	4.7%	4.6%	4.4%	4.6%
Respiratory *	16.2%	16.1%	15.2%	16.5%	18.9%
Musculoskeletal *	21.5%	22.1%	20.9%	21.5%	22.3%
Gastrointestinal/abdominal *	14.6%	14.3%	14.1%	15.1%	16.0%
Psychological *	7.4%	6.1%	6.5%	8.6%	11.2%

*
p<.001 per ANOVA or *Chi-square* tests

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Table 2

Associations between chronotype and prevalent comorbidities adjusting for age and sex. Chronotype was examined as both an pseudo-continuous 4-level variable and as categorical variables with Definite Morning Type as Referent.

	4-level Chronotype (1= definite morning type to 4= definite evening type)	Categorical Variables			
		Definite Morning Type	Moderate Morning Types	Moderate Evening Types	Definite Evening Type
Prevalent Comorbidity	OR per level (95% CI)		OR (95% CI)	OR (95% CI)	OR (95% CI)
CVD	1.01 (1.004, 1.02) <i>p</i> =.002	Ref	0.91 (0.90, 0.93) <i>p</i> <.001	0.97 (0.95, 0.99) <i>p</i> =.001	1.07 (1.04, 1.10) <i>p</i> <.001
Diabetes	1.06 (1.05, 1.08) <i>p</i> <.001	Ref	0.82 (0.80, 0.85) <i>p</i> <.001	0.98 (0.94, 1.01) <i>p</i> =.20	1.30 (1.24, 1.36) <i>p</i> <.001
Neurological	1.06 (1.05, 1.08) <i>p</i> <.001	Ref	1.02 (1.00, 1.04) <i>p</i> =.20	1.08 (1.05, 1.11) <i>p</i> <.001	1.25 (1.20, 1.30) <i>p</i> <.001
Endocrine	1.04 (1.03, 1.06) <i>p</i> <.001	Ref	0.98 (0.95, 1.02) <i>p</i> =.34	1.04 (1.01, 1.08) <i>p</i> =.015	1.17 (1.12, 1.23) <i>p</i> <.001
Renal	1.02 (1.004, 1.04) <i>p</i> =.015	Ref	1.01 (0.97, 1.05) <i>p</i> =.65	1.01 (0.97, 1.05) <i>p</i> =.58	1.10 (1.04, 1.16) <i>p</i> =.001
Respiratory	1.05 (1.04, 1.06) <i>p</i> <.001	Ref	0.94 (0.92, 0.96) <i>p</i> <.001	1.03 (1.01, 1.05) <i>p</i> =.007	1.22 (1.18, 1.26) <i>p</i> <.001
Musculoskeletal	1.04 (1.03, 1.05) <i>p</i> <.001	Ref	0.96 (0.94, 0.98) <i>p</i> <.001	1.05 (1.03, 1.07) <i>p</i> <.001	1.14 (1.11, 1.18) <i>p</i> <.001
Gastrointestinal/abdominal	1.07 (1.06, 1.08) <i>p</i> <.001	Ref	1.00 (0.98, 1.02) <i>p</i> =1.0	1.12 (1.09, 1.14) <i>p</i> <.001	1.23 (1.19, 1.27) <i>p</i> <.001
Psychological	1.25 (1.23, 1.26) <i>p</i> <.001	Ref	1.07 (1.04, 1.11) <i>p</i> <.001	1.44 (1.40, 1.49) <i>p</i> <.001	1.94 (1.86, 2.02) <i>p</i> <.001

Table 3

Hazard ratios for all-cause mortality by chronotype as ordinal variable.

	All-Cause Mortality	CVD Mortality
	Hazard Ratio (95% CI) ^a	Hazard Ratio (95% CI) ^a
Number of Deaths ^a	10,534	2,127
Chronotype (4-level variable)	1.02 (1.004 to 1.05) <i>p</i> =.017	1.04 (1.00 to 1.09) <i>p</i> =.06
Age (per 10 years)	2.31 (2.24 to 2.39) <i>p</i> <.001	2.41 (2.24 to 2.59) <i>p</i> <.001
Sex	1.59 (1.53, 1.65) <i>p</i> <.001	2.72 (2.46 to 3.00) <i>p</i> <.001
BMI (per 5 kg/m ²)	1.01 (0.99 to 1.04) <i>p</i> =.18	1.19 (1.13 to 1.24) <i>p</i> <.001
Smoking Status		
Never	1.0 (referent)	1.0 (referent)
Previous	1.33 (1.27 to 1.39) <i>p</i> <.001	1.26 (1.14 to 1.39) <i>p</i> <.001
Current	2.6 (2.4 to 2.7) <i>p</i> <.001	2.96 (2.63 to 3.34) <i>p</i> <.001
No answer	1.74 (1.35 to 2.24) <i>p</i> <.001	1.80 (1.06 to 3.05) <i>p</i> =.03
Sleep duration (h)	1.04 (1.02 to 1.05) <i>p</i> <.001	1.03 (1.00 to 1.07) <i>p</i> =.072
Prevalent Comorbidities:		
CVD	1.30 (1.25 to 1.35) <i>p</i> <.001	2.04 (1.85 to 2.26) <i>p</i> <.001
Diabetes	1.73 (1.63 to 1.84) <i>p</i> <.001	2.12 (1.89 to 2.38) <i>p</i> <.001
Neurological	1.17 (1.10 to 1.25) <i>p</i> <.001	1.23 (1.08 to 1.41) <i>p</i> =.003
Endocrine	(0.94 to 1.10) <i>p</i> =.76	.98 (.81 to 1.18) <i>p</i> =.83
Renal	(0.95 to 1.11) <i>p</i> =.45	1.11 (.95 to 1.30) <i>p</i> =.17
Respiratory	1.30 (1.23 to 1.36) <i>p</i> <.001	1.30 (1.17 to 1.44) <i>p</i> <.001
Musculoskeletal	(0.97 to 1.06) <i>p</i> =.68	1.05 (.95 to 1.15) <i>p</i> =.37
Gastrointestinal/abdominal	1.05 (1.001 to 1.11) <i>p</i> =.045	0.93 (0.82 to 1.04) <i>p</i> =.20
Psychological	1.27 (1.19 to 1.36) <i>p</i> <.001	1.27 (1.10 to 1.47) <i>p</i> =.001
White ethnicity	1.47 (1.32 to 1.65) <i>p</i> <.001	1.25 (1.003 to 1.55) <i>p</i> =.047
Socioeconomic deprivation (Townsend Index)	1.06 (1.05 to 1.06) <i>p</i> <.001	1.07 (1.06 to 1.08) <i>p</i> <.001
Pseudo r ²	.03	.06

^aNo missing data