No association between a common type 2 diabetes risk gene variant in the melatonin receptor gene (MTNR1B) and mortality among type 2 diabetes patients

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Abstract
The minor G risk allele in the common melatonin receptor gene (MTNR1B, rs10830963) has been associated with an increased risk of myocardial infarction among patients with type 2 diabetes (T2D). Furthermore, activating the melatonin receptor 1B through melatonin has been shown to promote cell proliferation, which could be hypothesized to increase cancer risk. Cardiovascular disease (CVD) and cancer are common causes of death among patients with T2D. Using data from 14,736 patients with T2D who participated in the UK Biobank investigation, we hypothesized an additive effect of the G risk allele on all-cause mortality, CVD mortality, and cancer mortality. As shown by Cox regression adjusted for confounders such as age, glucose-lowering medication, and socioeconomic status, no significant trend between the number of G risk alleles and mortality outcomes was found during the follow-up period of 11.1 years. Our negative findings do not speak against the role of this gene variant in the development of T2D, as repeatedly shown by previous large-scale studies. Instead, they may suggest that rs10830963 is less relevant for mortality risk in patients with T2D.

KEYWORDS
cancer, cardiovascular disease, melatonin receptor, mortality, type 2 diabetes

1 | INTRODUCTION

The melatonin receptor gene (MTNR1B) encodes melatonin receptor 1B (also known as MT2), a high-affinity receptor for melatonin, the primary hormone secreted by the pineal gland.1 Melatonin receptor 1B is found primarily in the retina of the eye and brain.1 A common single nucleotide polymorphism (SNP) in the MTNR1B gene, rs10830963 (chromosome 11, intron variant), has been tied to a greater risk of type 2 diabetes (T2D). Specifically, with each additional G risk allele (rs10830963), the odds of developing T2D increase about 10% among carriers.2–4 Furthermore, carriers of the G risk allele have higher fasting blood glucose concentrations5 and exhibit a less pronounced insulin response to glucose challenges.2 One possible mechanism relates to an altered glucose-stimulated insulin release by the pancreatic islets. Once melatonin binds to melatonin receptor 1B expressed by pancreatic β-cells, carriers of the G risk allele release less insulin in response to glucose than non-carriers.6,7 A
recent study suggests that rs10830963 may also play a role in T2D comorbidities. Specifically, the risk of myocardial infarction increased by 19% with each additional G risk allele. Cardiovascular disease (CVD), including myocardial infarction, is a major cause of death among people with T2D. A previous study demonstrated that the melatonin receptor 1A (also known as MT1) curbs the proliferation of brain tumor cells. In contrast, melatonin receptor 1B promotes the proliferation of brain tumor cells. These findings could suggest that these two melatonin receptors play opposite roles in cell proliferation. Given that cells of G risk allele carriers expressing melatonin receptor 1B respond stronger to melatonin than those of non-carriers, carriers of the G risk allele may be more prone to neoplasm and have a greater risk to develop cancer. Noteworthy, cancer is one of the most common causes of death among patients with T2D.

In summary, past research has established a role of rs10830963 in the development of T2D. However, it is unclear whether patients with T2D may exhibit a greater mortality risk than non-carriers with T2D. Thus, in the present study, using 11.1 years of follow-up data from 14736 patients with T2D, we examined whether the number of G risk alleles was associated with all-cause mortality, CVD mortality, and cancer mortality.

2 | MATERIALS AND METHODS

2.1 | Study population

The present analysis was based on data from the UK Biobank investigation, https://www.ukbiobank.ac.uk/. Initially, 337 452 unrelated individuals of White British ancestry passing genomic quality control were available. A validated algorithm based on self-reported disease, medication, and T2D diagnosis in medical history or HbA1c ≥ than 6.5% (measured by Bio-Rad VARIANT II TURBO HbA1c analyzer, Bio-Rad, Hercules, California) was used as criteria to identify participants with probable T2D in the present study. At the time of the baseline investigation (extended to two years after the baseline investigation), 42.8% of the included participants had an actual T2D diagnosis (ICD-10 E11). Following further exclusions due to missing baseline information on confounders or presence of potential type 1 diabetes or likely gestational diabetes (Figure 1), 14736 participants having probable T2D were eligible for the present analysis. The UK Biobank received ethics approval from the National Health Service Research Ethics Service (reference 11/NW/0382), and participants gave informed consent.

2.2 | Genotyping

As described elsewhere, the MTNRIB rs10830963 genotype (chromosome 11, intron variant) was directly genotyped by the Affymetrix UK Biobank Lung Exome Evaluation Axiom array (Thermo Fisher Scientific, Santa Clara, California) or the Applied Biosystems UK Biobank Axiom Array (Thermo Scientific). Quality control and imputation using the Haplotype Reference Consortium, UK10K, and 1000 Genomes phase 3 reference panels were conducted centrally. Testing for Hardy-Weinberg equilibrium revealed that the single nucleotide polymorphism did not deviate from the expected genotype proportion. The minor allele frequency of the rs10830963 G risk allele was 29.4%.

2.3 | Mortality

Mortality information was obtained from the National Health Service for England and Wales and the NHS Central Register in Scotland. The primary outcome was all-cause mortality. Death due to external causes (eg, accident) was not considered an event of interest when examining the association of the gene variant with all-cause mortality. We additionally examined the association of the G risk allele with mortality due to CVD and cancer. The ICD-10 codes to define cancer and CVD events are shown in Table 1 and were selected based on the literature. Stroke represents a cerebrovascular disease. Thus, stroke was included as an event in all-cause mortality but not CVD mortality.

2.4 | Potential confounders

The following potential confounders were included in the analysis, as they may be related to mortality: participants' age, sex, body mass index (BMI), Townsend index reflecting socioeconomic status, systolic blood pressure (automated reading; if not available, we used manual reading), prescription of antihypertensive drugs (derived from the UK Biobank baseline verbal interview), prescription of statins (UK Biobank baseline verbal interview), prescription of glucose-lowering drugs (UK Biobank baseline verbal interview), prescription of antidepressants (UK Biobank baseline verbal interview), smoking status, alcohol intake frequency, habitual daily sleep duration, physical activity level, HbA1c, and serum LDL. We additionally included the three following variables as confounders in the adjusted analyses:
N=502,543
In the present UK Biobank dataset

n=165,091
Excluded based on genetic data:
Without available genetic data on rs 10830963 (n=15,216);
Not British descent (n=57,142);
Not Caucasian by genetic ethnic grouping (n=21,328);
Principal components relatedness (n=71,405).

n=337,452
Participants with available genetic data

n=320,798
Excluded participants without T2D.

n=16,654
Participants with probable T2D

n=1,863
Excluded because of missing data:
Body mass index (n=121);
Systolic blood pressure (n=35);
Smoking statues (n=111);
Alcohol intake frequency (n=13);
Townsend index (n=21);
HbA1c (n=626);
LDL(n=793);
Sleep duration(n=143).

n=14,791

n=55
Excluded because participant died from external causes (e.g. accident).

n=14,736
Final cohort

FIGURE 1 Exclusions
1. Baseline history of diseases other than cancer, CVD, and T2D that, according to the World Health Organization, belonged to the top ten mortality risk factors among adults in 2019 (ICD-10: I22-I24, I60, I61, I63, I64, J44, A15, J12-J18, J20-J22, J40-J42, G30, G31, A00-A09, N00-N19, N25-N27). We had no a priori hypothesis that the baseline history of diseases other than cancer, CVD, and T2D can lie along the causal pathway between the rs10830963 and mortality. Thus, the confounder was included in all adjusted Cox regression analyses.

2. Baseline history of cancer (corresponding ICD-10 codes can be found in Table 1). This confounder was used in the adjusted Cox regression investigating the association of the rs10830963 with CVD mortality. We did not include the baseline history of cancer in the cancer mortality analysis, as this confounder may lie along the causal pathway between the rs10830963 and cancer mortality.

3. Baseline history of CVD (corresponding ICD-10 codes can be found in Table 1). This baseline confounder was used in the adjusted Cox regression investigating the association of rs10830963 with cancer mortality. Since this confounder may lie along the causal pathway between the rs10830963 and CVD-related death, we did not consider it when investigating the association of this gene variant with CVD mortality.

Baseline history was defined either as a diagnosis at any time point before the baseline investigation or a diagnosis within two years after the baseline investigation. Finally, we adjusted our analysis for the region of the test center and the principal genetic components of ancestry (first ten columns).

2.5 | Statistical analysis

Analyses were performed with SPSS 24.0 (Inc.). Group comparisons of baseline characteristics relied on one-way analysis of variance or chi-square testing. Previous studies have shown a linear trend between the number of $G$ risk alleles, T2D, and myocardial infarction. $^{2-4,8}$ Thus, an additive genetic model was assumed (ie, the more $G$ risk alleles, the higher the mortality risk). To examine the association of the $G$ risk allele with mortality among patients with T2D, we used Cox proportional hazard regression analysis. In the unadjusted Cox analysis, we only controlled for the principal genetic components of ancestry (first ten columns). In the fully adjusted Cox analysis, the following confounders were included: age, sex, BMI, Townsend index, systolic blood pressure, smoking status, alcohol intake, sleep duration, physical activity, HbA1c, serum LDL, self-reported medication, baseline disease history (see 2.4, for definitions), location of the test center, and the principal genetic components of ancestry (first ten columns). The time at risk was calculated from the date of the baseline investigation to the date of death or the date where mortality information was obtained from the National Health Service for England and Wales and the NHS Central Register in Scotland (date of retrieval: 2020–12–18). Proportional hazard assumptions were confirmed using Kaplan-Meier survival curves. We also performed a sensitivity analysis by censoring up to 2019–12–31 (we consider this date as the start of the COVID-19 pandemic) to minimize the possible bias caused by the pandemic. Overall, a two-sided P-value of less than 0.05 was regarded as statistically significant.

3 | RESULTS

Table 2 summarizes population characteristics, stratified by rs10830963. 49.8% carried two copies of the $C$ allele, 41.6% were heterozygous carriers (ie, $CG$ or $GC$), and 8.6% had two copies of the $G$ risk allele. During the mean follow-up period of 11.1 years, a total of 2455 deaths (16.7% of the initial cohort) were observed, of which 499 were attributable to CVD and 991 to cancer (Figure 2).

As summarized in Figure S1a-c, several factors were associated with all-cause and disease-specific mortality among patients with T2D. For example, patients reporting high levels of regular physical activity exhibited a 26.1% lower hazard ratio (HR) for all-cause mortality and a
| Characteristic(s)                      | Total  | CC    | CG/GC | GG    | p-value |
|---------------------------------------|--------|-------|-------|-------|---------|
| Type 2 diabetes patients, n           | 14 736 | 7342  | 6129  | 1265  | –       |
| Death from all cause, n (%)           | 2455 (16.7) | 1210 (16.5) | 1027 (16.8) | 218 (17.2) | .775d |
| Death from CVD, n (%)                 | 499 (3.4) | 249 (3.4) | 211 (3.4) | 39 (3.1) | .812d |
| Death from cancer, n (%)              | 991 (6.7) | 500 (6.8) | 406 (6.6) | 85 (6.7) | .912d |
| Time at risk, years                   | 11.1 (2.3) | 11.2 (2.3) | 11.1 (2.3) | 11.1 (2.4) | –       |
| Age, years                            | 60.6 (6.6) | 60.6 (6.5) | 60.5 (6.6) | 60.5 (6.7) | .808b |
| Sex, n (%)                            |        |       |       |       |         |
| Women                                 | 5267 (35.7) | 2611 (35.6) | 2224 (36.3) | 432 (34.2) | .318d |
| Men                                   | 9469 (64.3) | 4731 (64.4) | 3905 (63.7) | 833 (65.8) |         |
| BMI, kg/m²                            | 31.9 (5.8) | 31.9 (5.8) | 31.9 (5.7) | 31.8 (5.6) | .257b |
| Region of the test center, n (%)      |        |       |       |       |         |
| England                               | 12 940 (87.8) | 6437 (87.7) | 5397 (88.1) | 1106 (87.4) | .085d |
| Scotland                              | 709 (4.8) | 341 (4.6) | 290 (4.7) | 78 (6.2) |         |
| Wales                                 | 1087 (7.4) | 564 (7.7) | 442 (7.2) | 81 (6.4) |         |
| Townsend indexA                        | −0.83 (3.26) | −0.84 (3.27) | −0.82 (3.27) | −0.88 (3.21) | .795b |
| Systolic blood pressure, mmHg         | 145 (19) | 145 (19) | 145 (18) | 145 (19) | .392b |
| Therapeutic regimen of T2D at baseline|         |       |       |       |         |
| On no antidiabetic prescription       | 5761 (39.1) | 2796 (38.1) | 2449 (40.0) | 516 (40.8) | .095d |
| Received only one oral antidiabetic drug | 4344 (29.5) | 2179 (29.7) | 1790 (29.2) | 375 (29.6) |         |
| At least on two oral antidiabetics or insulin therapy | 4631 (31.4) | 2367 (32.2) | 1890 (30.8) | 374 (29.6) |         |
| Other prescriptions, n (%)            |        |       |       |       |         |
| Antihypertensive drugs                | 2695 (18.3) | 1381 (18.8) | 1093 (17.8) | 221 (17.5) | .253d |
| Statins                               | 591 (4.0) | 324 (4.4) | 215 (3.5) | 52 (4.1) | .028d |
| Antidepressants                       | 573(3.9) | 285 (3.9) | 245 (4.0) | 43 (3.4) | .605d |
| Smoking, n (%)                        |        |       |       |       |         |
| Current                               | 1655 (11.2) | 829 (11.3) | 686 (11.2) | 140 (11.1) | .019d |
| Former                                | 6960 (47.2) | 3,562 (48.5) | 2824 (46.1) | 574 (45.4) |         |
| Never                                 | 6121 (41.5) | 2951 (40.2) | 2,619 (42.7) | 551 (43.6) |         |
| Alcohol intake frequency, n (%)       |        |       |       |       |         |
| Occasional/sometimes/usually          | 12 940 (87.8) | 6456 (87.9) | 5376 (87.7) | 1,108 (87.6) | .899b |
| Never                                 | 1,796 (12.2) | 886 (12.1) | 753 (12.3) | 157 (12.4) |         |
| Sleep duration, h/d, n (%)            |        |       |       |       |         |
| <7                                    | 3934 (26.7) | 1932 (26.3) | 1653 (27.0) | 349 (27.6) | .298d |
| 7–9                                   | 10 154 (68.9) | 5082 (69.2) | 4198 (68.5) | 874 (69.1) |         |
| >9                                    | 648 (4.4) | 328 (4.5) | 278 (4.5) | 42 (3.3) |         |
| HbA1c, mmol/mol                       | 53.05 (14.61) | 53.12 (14.22) | 52.97 (15.21) | 53.01 (13.81) | .824b |
| HbA1c, %                              | 7.00 (1.34) | 7.01 (1.30) | 7.00 (1.39) | 7.00 (1.26) | .824b |
| Serum LDL, mmol/l                     | 2.80 (0.84) | 2.79 (0.83) | 2.81 (0.86) | 2.80 (0.82) | .685b |
| Physical activity levelB, n (%)       |        |       |       |       |         |
| Low                                   | 5180 (35.2) | 2578 (35.1) | 2156 (35.2) | 446 (35.3) | .062d |
| Moderate                              | 5361 (36.4) | 2744 (37.4) | 2177 (35.5) | 440 (34.8) |         |
| High                                  | 4195 (28.5) | 2020 (27.5) | 1796 (29.3) | 379 (30.0) |         |

(Continues)
33.7% lower HR for CVD mortality, compared to the patient group with low physical activity levels. We also found that the therapeutic regimen of T2D at baseline was associated with mortality. Specifically, patients using at least two oral antidiabetics or being on insulin therapy, often prescribed to those with poor glycemic control, had a two oral antidiabetics or being on insulin therapy, often prescribed to those with poor glycemic control, had a two oral antidiabetics or being on insulin therapy, often prescribed to those with poor glycemic control, had a two oral antidiabetics or being on insulin therapy, often prescribed to those with poor glycemic control, had a two oral antidiabetics or being on insulin therapy, often prescribed to those with poor glycemic control, had a 1.26-fold higher HR for all-cause mortality and a 1.62-fold higher HR for CVD mortality than untreated patients. Finally, self-reported long (more than 9 h per day) but not short (less than 7 h per day) sleep duration was associated with a 1.31-fold higher HR for all-cause mortality than normal sleep duration.

When investigating the association of the rs10830963 with mortality, neither the unadjusted nor the adjusted Cox regression analysis revealed a linear trend between the number of G risk alleles and mortality (Figure S1a-c). Specifically, no significant association between the number of G risk alleles and all-cause mortality was observed (HR [95% CI]; unadjusted HR per G risk allele: 1.027 [0.966, 1.092], \(p = .397\); fully adjusted HR per G risk allele: 1.040 [0.978, 1.106], \(p = .206\)). Similarly, the HR for dying from CVD was not associated with the number of G risk alleles (unadjusted HR per G risk allele: 0.986 [0.859, 1.131], \(p = .84\); fully adjusted HR per G risk allele: 0.994 [0.866, 1.141], \(p = .931\)). Finally, the number of G alleles did not significantly predict cancer mortality (unadjusted HR per G risk allele: 0.990 [0.898, 1.091], \(p = .832\); fully adjusted HR per G risk allele: 0.999 [0.906, 1.101], \(p = .979\)) did not differ between carriers and non-carriers of the G risk allele.

In the sensitivity analysis censoring up to December 31, 2019 (ie, the start of the COVID-19 pandemic; mean observational period of ~10.3 years; a total of 2099 deaths), all associations of the rs10830963 with mortality outcomes remained non-significant (all-cause mortality: unadjusted HR per G risk allele, 1.043 [0.976, 1.114], \(p = .213\); adjusted HR per G risk allele, 1.053 [0.985, 1.125], \(p = .127\); CVD mortality: unadjusted HR per G risk allele, 0.998 [0.863, 1.153], \(p = .976\); adjusted HR per G risk allele, 1.001[0.865, 1.158], \(p = .990\); and cancer mortality: unadjusted HR per G risk allele, 1.005 [0.907, 1.113], \(p = .922\); adjusted HR per G risk allele, 1.014 [0.916, 1.124]), \(p = .784\).

### DISCUSSION

To our best knowledge, the present study represents the first investigation into the possible association between the common T2D risk gene variant in the MTNR1B (rs10830963) and mortality among patients with T2D. Notably, factors known to modulate the progression of T2D, such as physical activity and sleep duration, were associated with mortality risk. For example, moderate-to-high levels of regular physical activity, which are often recommended as a behavioral strategy in the therapy of T2D, were associated with lower mortality risk during the observational period (ie, 11.1 years). We also found that long sleep duration, defined as more than 9 h of sleep per day, was associated with greater all-cause mortality among patients with T2D. Long sleep duration and frequent napping have both been associated with indicators of poor T2D control. However, whether long sleep duration contributes to T2D disease progression and death risk among patients with T2D remains unclear.

In contrast to these behavioral factors, no significant association was found between the number of G risk alleles in the MTNR1B and all-cause mortality, CVD mortality, and cancer mortality. Our negative findings do not speak against the role of this gene variant in the development of T2D, as repeatedly shown by previous large-scale studies. Instead, they may suggest that rs10830963 is
The strengths of this study include the prospective study design, careful control of confounders, the findings were confirmed in a sensitivity analysis, and comparisons with other mortality risk-modifying factors (eg, physical inactivity and sleep duration). However, several limitations apply. Our findings must be confirmed in studies with longer follow-up and other ethnicities. We further assumed that all confounders measured at baseline were time-invariant throughout the follow-up.

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CONFLICT OF INTEREST
Christian Benedict has served as a scientific consultant for Repha GmbH, Langenhagen, Germany. No other disclosures were reported.

AUTHOR CONTRIBUTIONS
Pei Xue, Xiao Tan, and Christian Benedict conceived the idea and led the study design. Pei Xue, Jiafei Wu, Xiao Tan, and Christian Benedict involved in the data analysis and wrote the manuscript. Xiangdong Tang gave critical suggestions and contributed to the editing of the manuscript.

DATA AVAILABILITY STATEMENT
Data may be obtained from a third party and are not publicly available. Data were derived from the UK Biobank investigation. Thus, data may be obtained from the UK Biobank upon request.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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