Association of heart rate and diabetes among 0.5 million adults in the China Kadoorie Biobank: results from observational and Mendelian randomization analyses

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Abstract

Background and Aims: Observational studies have associated resting heart rate with incident diabetes. Whether the associations are causal remains unclear. We aimed to examine the shape and strength of the associations and assessed the causal relevance of such associations in Chinese adults.

Methods and Results: The China Kadoorie Biobank enrolled 512,891 adults in China. Cox proportional hazard regression models was conducted to estimate hazard ratios (HRs) for the associations of resting heart rate with type 2 diabetes and total diabetes. Among 92,724 participants, 36 single-nucleotide polymorphisms (SNPs) related to resting heart rate were used to construct genetic risk score. We used Mendelian randomization analysis to make the causal inferences. During a median follow-up of 9 years, 7,872 incident type 2 diabetes and 13,349 incident total diabetes were documented. After regression dilution bias adjustment, each 10 bpm higher heart rate was associated with about a 26% higher risk of type 2 diabetes (HR, 1.26 [95% CI, 1.23, 1.29]) and 23% higher risk of total diabetes (HR, 1.23 [95% CI, 1.20, 1.26]). Instrumental variable analyses showed participants at top quintile compared with those at bottom quintile had 30% higher risk for type 2 diabetes (HR, 1.30 [95% CI, 1.17, 1.43]), and 10% higher risk for total diabetes (HR, 1.10 [95% CI, 1.02, 1.20]).

Conclusions: This study provides evidence that resting heart rate is an important risk factor for diabetes risk. The results suggest that novel treatment approaches targeting reduction of high heart rate for incidence of diabetes may be worth further investigation.

Keywords: Heart rate; Diabetes; Mendelian randomization**;** Causal association.

Introduction

Diabetes becomes a severe health problem worldwide. It has been projected that diabetic population will increase to 438 million by 2030.[1] A national representative survey among Chinese adults in 2017 showed that the estimated prevalence of prediabetes and diabetes were 35.2% and 12.8%, respectively.[2] Given the heavy burden of diabetes in China, identification of causal factors for incident diabetes and understanding the aetiology are essential for preventing this epidemic in China.

Observational studies in European populations have reported that higher resting heart rate, which was identified as an indicator of autonomic nervous system regulation is an independent risk factor for diabetes.[3,4] Recently, the Health Professionals Follow-up Study and a meta-analysis were consistently identified positive associations between resting heart rate and type 2 diabetes risk (17 % increased risk per 10 bpm).[5] Likewise, a high resting heart rate was an independent risk factor for an increased risk of type 2 diabetes[6], a higher risk of impaired fasting glucose (IFG) and diabetes in two Chinese prospective cohorts,[7] suggesting that heart rate could be used to identify individuals at high risk of developing diabetes. However, conventional studies examining the relationship between resting heart rate and diabetes have been unable to fully avoid the reverse causality and confounders. Hence, the causal relevance of these observations is not fully understood.

Mendelian randomization (MR) approach that overcomes such limitations aforementioned has been widely accepted to examine potential causal inferences about exposure and disease.[8-13] This method is regarded as a natural randomized controlled trial, as the random segregation of genetic instruments that occurs during conception allows confounders to equally distribute among the population. Thus, results from MR are less likely to be influenced by reverse

causality and confounding.[9,14] Recently, a genome-wide association study (GWAS) identified 64 loci for heart rate.[15] Therefore, these genetic variants can be used to proxy for resting heart rate to make inferences about the potential causal relationship between resting heart rate and diabetes risk.

The aims of the present study among Chinese adults were (i) to explore the shape and strength of the relationships between resting heart rate and incident diabetes risk; and (ii) to perform MR analyses to test the hypothesis that a higher heart rate is a potential risk factor for incident diabetes using data from the China Kadoorie Biobank (CKB).

Methods

Study population

Detailed information on the study design and data collection in CKB has been reported previously.[16,17] We recruited 512,891 Chinese participants aged 30-79 years from the general population in 5 urban and 5 rural areas during 2004-2008. Information on the baseline demographic and socioeconomic status, alcohol intake, smoking status, food intake, physical activity, self-reported general health status and family history were collected by trained investigators using laptop-based questionnaires during the face-to-face interview in local assessment centres. In addition, data on weight, waist circumference, hip circumference, height, and blood pressure were undertaken using standard protocols. Relevant local, national, and international ethics committees collected the written informed consent from all participants.

Measurement of resting heart rate

After participants had been in the seated position for at least 5 minutes, a UA-779 digital sphygmomanometer (A&D Instruments; Abingdon, UK)[18] were used to measure resting heart rate and blood pressure. Calibrated by trained fieldworkers before using, sphygmomanometers were used to measure the right brachial blood pressure and heart beats at the level of the heart twice. The mean heart rate and blood pressure was calculated based on these two readings. In addition, about 3 years after baseline, a random selected subgroup of 19,788 participants were repeatedly measured heart rate using the same procedures as in the baseline survey; thus, in this study, we used the repeat measurement for correction of regression dilution. Age- and sex-specific regression dilution ratios were calculated by using Rosner's regression method (**eTable 1**).[19]

Follow-up for incident diabetes

The primary outcomes examined in the present study were type 2 diabetes and total diabetes. Incident total diabetes diagnoses (10th international classification of diseases [ICD-10]: E10-E14) and type 2 diabetes (ICD-10: E11) were identified through linkage to local disease, death registries and health insurance system. In order to confirm survival and minimize follow-up loss, active follow-up is conducted annually and local resident records are checked.

Single-nucleotide polymorphisms selection, genotyping and calculation of genetic risk score

Using a genome-wide scan in the CKB, a total of 100,640 randomly selected participants were genotyped. Previous GWAS for resting heart rate among European has identified 64 loci (**eTable 2**).[15] To avoid ancestry mismatch, we replicated these loci in our cohort. Considering multiple testing, a Bonferroni correction significance threshold was set as 0.0008 (0.05 / 64). Of which, 36 loci were significantly associated with resting heart rate in Chinese adults, thus

a genetic risk score (GRS) based on these 36 loci were calculated and used as an instrumental variable for heart rate. We summed the number of risk allele for resting heart rate, and effect size for each Single-nucleotide polymorphisms (SNP) observed in European GWAS,[15] was used to create a weighted GRS for each individual (**eTable 3)**. The total variance explained by the 36 selected SNPs for resting heart rate was 1.5%. χ^2 and Haploview were used to assess the Hardy-Weinberg equilibrium and linkage disequilibrium between SNPs, respectively. No SNPs were in linkage disequilibrium with each other, and all SNPs were in Hardy–Weinberg equilibrium.

Statistical methods

Participants were excluded because of missing information on resting heart rate, extreme values of heart rate (<30 bpm or ≥200 bpm), lost to follow-up in the age range 40-79 years, and a history of diabetes, stroke or transient ischaemic attack.

Observational analyses

Cox proportional hazards models were used to evaluate adjusted hazard ratios (HRs) for the relationships between resting heart rate and diabetes risk. Analyses were adjusted for age, sex, education, region, marital status, income, metabolic equivalent tasks (METs), smoking and alcohol intake. Adjustment for the following variables was also conducted: frequency of fruit, vegetable and meat intake, body mass index (BMI), waist-hip ratio (WHR), systolic blood pressure (SBP) and self-reported general health status. The log HRs for each 10 bpm higher resting heart rate were calculated by fitting heart rate as a continuous variable in each age group (40-49, 50-59, 60-79 years). We used age-specific and sex-specific regression dilution ratios to correct age-specific and sex-specific HRs per 10 bpm higher heart rate. The overall HRs were then calculated by taking the inverse variance weighted average.

According to baseline heart rate, we divided all participants into five quintiles groups in categorical analyses. Lowest heart rate group was served as reference group, HRs of each group were estimated, and plotted against mean heart rate in each of heart rate groups; the 95% CIs were calculated with the log risk variance by using floating absolute risks.[20]

Effect modification and sensitivity analyses

Effect modification analyses were restricted to type 2 diabetes. The assessment was made for effect modification by: age (40-49, 50-59, and 60-79 years), sex, urban/rural, smoking, drinking, physical activity, and BMI. In addition, we further assessed the heterogeneity of associations between the ten regions. Our sensitivity analyses assessed the effect of excluding the first three years of follow-up, excluding participants taking blood pressure-lowering medication at baseline, and excluding participants without genetic genotyping.

Mendelian randomization analysis

A total of 92,724 participants were included in the MR analysis. We used linear regression to assess the per allele effects of GRS on heart rate and used F-statistics to calculate the strength of relationships of GRS and heart rate and F-statistics >10 were considered strong. The two stage least squares regression method was used to examine the causal associations of differences in genetically-predicted heart rate with risk of diabetes (**eFigure 1**)[21]. Firstly, resting heart rate was regressed on the GRS, and the predicted fitted values were saved. Then, diabetes was regressed on the predicted fitted values obtained from the first stage. Adjustments were made for age, sex, region, and BMI in both stages. Participants were grouped into approximate quintiles according to their genetically-predicted heart rate. HRs for diabetes and their corresponding 95% CIs were plotted at the mean genetically-predicted heart

rate within each quintile. To test for evidence of pleiotropy, we performed MR-Egger regression test, which has been used to test and correct for directional (unbalanced) pleiotropy.[22] All analyses were conducted using STATA software (version 14).

Results

Baseline characteristics of participants

Of 512,891 participants from 10 diverse areas in the CKB prospective study, the mean age at baseline was 51.5 years (SD 10.6) and 210,259 (41.0) were men, and 226,186 (44.1) resided in urban areas. Mean resting heart rate was 78.8 bpm (SD 11.8) (**Table 1**). During a median follow-up of 9 years, 488 participants were lost to follow-up in the age range 40-79 years and therefore excluded. Among the 475,242 adults with no prior history of stroke, transient ischemic attack, or diabetes at baseline, individuals with higher heart rate were more likely to be female, younger, and living in rural areas, and have unhealthy lifestyle and poor health than those with lower heart rate. Likewise, higher heart rate was also associated with higher waist circumference, hip circumference, BMI, and blood pressure (**eTable 4)**.

Mean resting heart rate decreased linearly with age in male. Mean resting heart rate also decreased with age until about 50 years, but keep unchanged thereafter in female (**Figure 1**). At resurvey, about 3 years after the baseline survey, the overall regression dilution ratio for heart rate was 0.55, but it was slightly lower in men than women, and in younger than in older individuals (**eTable 1**).

During a median follow-up of 9 years (IQR 8-10), 7,872 incident type 2 diabetes events and 13,349 total diabetes occurred. For each decade of age, higher heart rate was linearly associated with higher risk of type 2 diabetes throughout the heart rate range examined (P for

trend < 0.001). There is no evidence of a threshold down to at least 60 bpm. The HRs were almost twice as steep at ages 40-49 years than 60-79 years (**Figure 2**).

Observational association

Higher resting heart rate was linearly associated with higher risks of type 2 diabetes and total diabetes throughout the heart rate range examined, with no evidence of a threshold up to at least 100 bpm (**Figure 3 & eTable 5**). The associations of resting heart rate with type 2 diabetes were independent of BMI, WHR, and SBP (**eFigure 2**). Overall, each 10 bpm higher heart rate was associated with about a 26% higher risk of type 2 diabetes (HR 1.26 [95% CI 1.23-1.29]) and 23% higher risk of total diabetes (HR, 1.23 [95% CI, 1.20, 1.26]). Individuals in the top quintile of heart rate had 61% higher risk of developing type 2 diabetes (HR, 1.61; 95% CI, 1.54, 1.67) compared with those in the bottom quintile. For diabetes, the adjusted HRs for the top vs bottom quintile of heart rate were 1.55 (HR, 1.55 [95% CI, 1.50, 1.60]). These results were unaltered by further adjustment for BMI, WHR and baseline SBP (**eTable 5**).

Subgroup analyses showed that risks for type 2 diabetes were similar in groups according to area (rural/urban), ever smoker (yes/no), physical activity (<12.29, 12.29~25.31, >25.31), and obesity status (normal, overweight, obesity). However, the HRs for type 2 diabetes were not significant among ever drinkers (**Figure 4**). In sensitivity analyses, the associations were similar in 10 diverse areas (**eTable 7**), and were not materially altered by excluding the first 3 years of follow-up (to assess for reverse causality), excluding participants taking blood pressure-lowering medication at baseline, and excluding participants without genetic data (**eTable 8**).

Instrumental analyses

A genetic risk score (GRS) based on 36 SNPs associated with resting heart rate was calculated as an instrumental variable for heart rate. **eTable 2** & **eTable 3** also compare the effect sizes of the 36 SNPs on heart rate in the CKB with those in the European GWAS, and show good concordance for genetically predicted differences in heart rate in both Western and Chinese populations. In the CKB, the GRS for heart rate was associated with the heart rate (F=1387.45) (**Figure 5**), but the GRS was not associated with major confounders such as age, sex, income, smoking, alcohol intake, physical activity, WHR, and SBP, except for BMI (**eTable 6**).

Figures 3 compares the HRs for risk differences in directly measured and genetically-instrumented differences in heart rate for type 2 diabetes and total diabetes. Genotype-predicted mean resting heart rate had a continuously positive linear relationship with risk type 2 diabetes and total diabetes. Instrumental variable analyses using individual participant data generally showed less extreme effect sizes (top vs bottom quintile) compared with observational analyses for type 2 diabetes (HR, 1.30 [95% CI, 1.17, 1.43]), and total diabetes (HR, 1.10 [95% CI, 1.02, 1.20]). The risks increased progressively in a dose-response manner with genetically determined heart rate. The MR-Egger analyses did not show evidence of unbalanced horizontal pleiotropy for the genetic scores (P=0.26).

Discussion

This is a large-scale assessment of the causal relationships between heart rate and incident diabetes using a genetic instrument in Chinese adults. The risk of diabetes increased progressively in a dose-response manner with more extreme differences in heart rate. The

present study provides strong evidence for an important role of heart rate for development of diabetes.

The findings in the present observational analyses are consistent with previous findings in Western populations, where average resting heart rate was associated with increased risks of diabetes,[3,4] and higher incidence of a wide range of diseases individuals with T2D.[23] Likewise, the Shanghai Women's Health Study reported that a high resting heart rate is an independent risk factor for incident type 2 diabetes in Chinese women.[6] Furthermore, the Kailuan cohort in China including 57,719 men and 15,638 women also found that faster resting heart rate might increase the risk of developing IFG and diabetes, implying that resting heart rate could identify individuals at higher risk of developing diabetes.[7] However, the potential causal associations remains uncertain.

Identifying causal factors that predict diabetes risk is important for precision prevention of diabetes in high-risk populations. Interestingly, the Look AHEAD study demonstrated that lifestyle intervention may improve heart rate recovery from exercise in diabetic adults,[24] suggesting that heart rate may play an important role in diabetes. However, Dongfeng-Tongji cohort involving 16,201 Chinese participants showed a positive association, but not a causal association of resting heart rate with incident diabetes[25], which might be partly explained by the relatively small sample size in the MR analyses and the small contribution of GRS to the variation of heart rate risk.[25] Findings from the present large scale MR analysis provide novel evidence that genetically elevated heart rate is associated with diabetes. Our results are broadly consistent with findings from previous genetic studies in European populations[26], where resting heart rate has significant estimated causal effect on risk of type 2 diabetes and weaker causal estimates from diabetes to heart rate. Similarly, shared heritability estimates

among resting heart rate and diabetes or diabetes related risk factors such as blood pressure, body mass index, active smoking behavior suggested that heart rate and diabetes also shared genetic basis.[15] Furthermore, results from the UK Biobank demonstrated a significant genetic correlation between heart rate and type 2 diabetes.[26] A total of 7 shared genes were identified and suggested the involvement of energy and glucose metabolism, telomere dysfunction, and vascular endothelial aging in such shared etiologies.[26]

Several potential mechanisms may help explain the observed associations. First, a resting heart rate has been regarded as a surrogate marker for autonomic activity.[27,28] It has been proposed that sympathetic activation may lead to higher diabetes risk.[5,7] For example, sympathetic overactivity causes vasoconstriction, inhibits the insulin secretion from the pancreas and impairs glucose uptake in skeletal muscle,[29] resulting in both acute and chronic insulin resistance.[30,31] Second, sympathetic activation may promote the development of obesity by downregulating the thermogenic response mediated by β-adrenergic receptors[32], and has also been reported to be associated with reduced insulin sensitivity, high blood pressure, and subclinical inflammation,[33] which are well- established risk factors for diabetes.

Our findings are of public health significance and provides clues that lowering heart rate may be a novel therapeutic approach to prevention of diabetes. Our findings were supported by several intervention studies.[24,34,35] For example, the Diabetes Control and Complications Trial (DCCT) in 1,441 individuals with type 1 diabetes showed that intensive treatment was associated with lower resting heart rate, suggesting that the lower heart rate with intensive therapy may be associated with improvement of type 1 diabetes.[34] Interestingly, a meta-analysis showed that attenuated heart rate recovery is associated with a higher diabetes risk in a dose-dependent manner.[35] It was supported by a graded exercise treadmill test in healthy

Korean men where a delayed heart rate recovery after exercise may predict development of type 2 diabetes.[36] Therefore, lifestyle intervention, which was demonstrated in clinical trial to improve heart rate recovery in diabetic adults,[24] is worth recommending as part of diabetes management in clinical routines.[35]

The strengths of the present study include the use of standardized protocols of data collection by well-trained technicians and a large number of diabetes cases. Further, all participants were recruited at random from the general population, thus the potential for selection bias is minimal. Importantly, we considered three assumptions to ensure the validity of our analyses. Firstly, the genetic risk score is associated with resting heart rate (F statistic=1155.92). Secondly, the genetic risk score is not associated with main confounding factors; thus satisfying an important assumption for such a valid MR approach. Thirdly, the genetic risk score has no pleiotropic effect on the outcomes, which is also an important assumption in MR analysis. Directional horizontal pleiotropy may lead to biased causality from MR.[37] Importantly, the absence of evidence for pleiotropy from the intercept on MR-Egger confirmed the absence of evidence for directional pleiotropy.

Limitations

However, the results should be interpreted with caution. Firstly, although the MR approach is theoretically well established, we acknowledge that there are still many limitations in practice, such as weak instrument and genetic pleiotropy. Second, collected information on diets was limited, most of the risk factors were not static, but dynamic instead, although the associations were not altered after further adjustment for fruit, vegetable and meat intakes. Resting heart rate and diabetes relationship is also particularly susceptible to several unmeasured confounding factors. For example, detailed treatment information, thyroid function[38], and

coffee intake[39] have been associated with diabetes risk, which might also affect resting heart rate. Third, we acknowledge that the SNPs for heart rate used in this study and the effect size used in calculating the genetic risk score are from European population. Therefore, our results might be biased due to ancestry mismatch. Fourth, to minimize ancestry mismatch, we selected SNPs based on their associations with resting heart rate in our database, which might result in overestimated associations with resting heart rate, and overestimated associations with the outcome.[22] Fifth, self-reported diabetes at baseline was substantially higher in the top vs. bottom quintiles of heart rate (3.6% vs. 9.1%), indicating that population with higher heart rate was substantially unhealthier. Therefore, it is not surprising to observe increased rates of incident diabetes; and even a weak genetic correlate would still result in a significant association. Sixth, the mean resting heart rate in our cohort was similar to results from a series of national surveys in China[40], but slightly higher than most European studies[15], mainly due to race difference. Therefore, the extrapolation of our results needs to be considered. Finally, although we identified the conventional and genetic evidence of resting heart rate and diabetes risk, whether it is the elevated resting heart rate that causes the increased diabetes risk, or the factors increasing heart rate (e.g. sympathetic activation) causes the increased risk regardless of their effect on heart rate remains to be elucidated. Future research targeting the exact mechanism of the association is merited.

Conclusions

In summary, this large-scale analysis provides reliable evidence the higher heart rate was linearly and positively associated with higher risk of diabetes. The associations were confirmed by genetic analyses. Thus, the highly consistent results of observational and genetic analyses support further research into heart rate management to prevent diabetes in adults.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee, University of Oxford (Oxford, United Kingdom).

Consent for publication

Not applicable.

Availability of data and materials

The access policy and procedures are available at www.ckbiobank.org.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WW and TH designed the research. WW and TH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. WW, JW, and TH wrote the paper and performed the data analysis. All authors contributed to the statistical analysis, critically reviewed the manuscript during the writing process, and approved the final version to be published. WW and TH are the guarantors for the study.

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Figure Legends

Figure 1. Mean resting heart rate at baseline, by age and sex

Means standardized for region. Analyses were conducted in 475,242 participants.

Figure 2. Age-specific incidence of type 2 diabetes versus resting heart rate

HRs are adjusted for age at risk (5-year groups), sex, area, education, smoking, alcohol consumption, body-mass index, waist: hip ratio and systolic blood pressure. (A) The area of each square is inversely proportional to the variance of the category-specific log risk. (B) The area of each square is inversely proportional to the variance of the log HR. The results were corrected for regression-dilution bias for age- and sex-specific groups. Corresponding 95% CIs are plotted as lines. P-for-trend tests were conducted for linear trend (all P-values < 0.001). Analyses were done in 475,242 participants. HR=hazard ratio.

Figure 3. Incidence of diabetes versus directly measured or genetically determined resting heart rate

The left panel for type 2 diabetes or diabetes presents observational associations of resting heart rate, adjusted for age, sex, region, education, income, marital status, smoking, alcohol status, physical activity, and frequency of fruit intake, vegetable intake, and meat intake. Individuals with prior diabetes, stroke, and transient ischemic attack are excluded from all analyses. The right panel presents causal associations of genetically-predicated resting heart rate, adjusted for age, sex, and region. For each category, the area of each square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% CI. The HR is shown above each square and numbers of events below. (A) and (B): associations of directly measured and genetically determined resting heart rate with risk of type 2 diabetes, respectively; (C) and (D): associations of directly measured and genetically determined resting heart rate with risk of total diabetes, respectively.

Figure 4. Subgroup analyses for HR (95% CI) for risk of type 2 diabetes per 10 bpm higher resting heart rate.

Cox regression was used to estimate the adjusted HR (95%CI) for the risk of type 2 diabetes per 10 bpm higher resting heart rate. Individuals with prior diabetes, stroke, and transient ischemic attack are excluded from all analyses. Analyses were done in 475,242 participants. The results were corrected for regression-dilution bias for age- and sex-specific groups.

Figure 5. Distribution of genetic risk score and genetic association with resting heart rate.

Table 1. Characteristics of the study population

	CKB whole cohort	Genotyped subsets
No. of participants	512,891	100,640
Demographic factors		
Age, y	51.5±10.6	53.70±11.0
Male, No. (%)	210,259(41.0)	43,014(42.7)
Female, No. (%)	302,632(59.0)	57,626 (57,3)
Urban region, No. (%)	226,186(44.1)	43,970(43.7)
Socioeconomic factors, No. (%)		
Household income >20,000 yuan/year	219,046(42.7)	39,159(38.9)
Middle school education and above	252,454(49.2)	47,184(46.9)
Lifestyle factors		
Physical activity, MET-h/d	21.1±13.8	19.9±13.8
Regular drinker, No. (%)	76,152(14.8)	15,489(15.4)
Regular smoker, No. (%)	135,555(26.4)	27,681(27.5)
Meat intake (everyday), No. (%)	150,037(29.3)	30,107(29.9)
Vegetable intake (everyday), No. (%)	486,073(94.8)	95,190(94.6)
Fruit intake (everyday), No. (%)	96,586(18.8)	19,255(19.1)
Self-reported conditions at baseline, No. (%)		
Diabetes	30,300(5.9)	6,766(6.7)
Cancer	2,577(0.5)	421(0.4)
Hypertension	59,703(11.6)	13,435(13.4)
Poor health	53,105(10.4)	11,622(11.6)
Physical measurements, mean (SD)		
BMI, kg/m^2	23.6±3.4	23.7±3.5
Waist : hip ratio, %	0.88±0.07	0.88±0.07
SBP, mmHg	131.1±21.3	133.6±22.7
Resting heart rate, bpm	78.8±11.8	79.0±11.9

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SBP, systolic blood pressure; MET-h/d, metabolic equivalents of task per hours per day.
Data are presented as mean ± SD for continuous variables and No. (%) for categorical variables, respectively.