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Research article

Association between basal metabolic rate and cardio-metabolic risk factors: Evidence from a Mendelian Randomization study

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ABSTRACT

Background: Cardio-metabolic risk factors play a crucial role in the development of cardiovascular and metabolic diseases. Basal metabolic rate (BMR) is a fundamental physiological parameter that affects energy expenditure and might contribute to variations in these risk factors. However, the exact relationship between BMR and cardio-metabolic risk factors has remained unclear.

Methods: We employed Mendelian Randomization (MR) analysis to explore the association between BMR (N: 534,045) and various cardio-metabolic risk factors, including body mass index (BMI, N: 681,275), fasting glucose (N: 200,622), high-density lipoprotein (HDL) cholesterol (N = 403,943), low-density lipoprotein (LDL) cholesterol (N = 431,167), total cholesterol (N: 344,278), and triglycerides (N: 441,016), C-reactive protein (N: 436,939), waist circumference (N: 232,101), systolic blood pressure (N: 810,865), diastolic blood pressure (N: 810,865),

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glycated haemoglobin (N: 389,889), and N-terminal prohormone brain natriuretic peptide (N: 21,758). We leveraged genetic variants strongly associated with BMR as instrumental variables to investigate potential causal relationships, with the primary analysis using the Inverse Variance Weighted (IVW) method.

Results: Our MR analysis revealed compelling evidence of a causal link between BMR and specific cardio-metabolic risk factors. Specifically, genetically determined higher BMR was associated with an increased BMI ($\beta = 0.7538$, 95% confidence interval [CI]: 0.6418 to 0.8659, $p < 0.001$), lower levels of HDL cholesterol ($\beta = -0.3293$, 95% CI: 0.4474 to −0.2111, $p < 0.001$), higher levels of triglycerides ($\beta = 0.1472$, 95% CI: 0.0370 to 0.2574, $p = 0.0088$), waist circumference ($\beta = 0.4416$, 95% CI: 0.2949 to 0.5883, $p < 0.001$), and glycated haemoglobin ($\beta = 0.1037$, 95% CI: 0.0080 to 0.1995, $p = 0.0377$). However, we did not observe any significant association between BMR and fasting glucose, LDL cholesterol, total cholesterol, C-reactive protein, systolic blood pressure, diastolic blood pressure, or N-terminal prohormone brain natriuretic peptide (all p-values>0.05).

Conclusion: This MR study provides valuable insights into the relationship between BMR and cardio-metabolic risk factors. Understanding the causal links between BMR and these factors could have important implications for the development of targeted interventions and therapies.

1. Introduction

Cardio-metabolic diseases [1–3], encompassing cardiovascular conditions and metabolic disorders, represent a global health challenge of immense magnitude. These conditions, including coronary heart disease [4], stroke [5], diabetes [6], and obesity [7], account for a substantial portion of the global disease burden and are major contributors to morbidity and mortality worldwide. Cardio-metabolic risk factors [8–10], such as body mass index (BMI) [11], fasting glucose [12], high density lipoprotein (HDL) cholesterol [13], low density lipoprotein (LDL) cholesterol [14], total cholesterol [15], and triglycerides [16,17], C-reactive protein [18], waist circumference [19], systolic blood pressure (SBP) [20], diastolic blood pressure (DBP) [21], glycated haemoglobin (HbA1c) [22], and N-terminal prohormone brain natriuretic peptide (NT-proBNP) [23], are well-established markers that play pivotal roles in the development and progression of these diseases. These factors are widely recognized as key indicators of cardio-metabolic risk, and numerous studies have consistently demonstrated their relevance in assessing overall cardiovascular health.

Basal metabolic rate (BMR) [24,25], on the other hand, represents a fundamental physiological parameter that characterizes the energy expenditure required for basic bodily functions at rest. It is influenced by various factors, including age, sex, genetics, and body composition. While BMR primarily serves as an indicator of the energy required to maintain vital bodily functions, emerging evidence suggests a broader role for BMR in influencing various diseases. Previous findings [26] have indicated a link between higher BMR and an elevated susceptibility to cancer, implying a noteworthy connection between increased BMR and the likelihood of developing cancer. Moreover, another study [27] has suggested that an elevated BMR could function as an indicator of specific cancer-related metabolic characteristics and might prove to be a valuable predictor of cancer risk irrespective of an individual's body weight status. Li et al.'s [28] research similarly highlights a substantial causal link between BMR and the risk of cardiovascular diseases, encompassing conditions such as aortic aneurysm, atrial fibrillation and flutter, heart failure, and myocardial infarction. However, the exact relationship between BMR and cardio-metabolic risk factors has remained unclear.

Understanding the potential interplay between BMR and cardio-metabolic risk factors is of significant interest, as it may offer novel insights into the mechanisms underlying the development and management of cardio-metabolic diseases. However, establishing causality in these relationships is a complex endeavor due to the intricate interconnections between multiple physiological factors. Mendelian Randomization (MR), a powerful methodological approach that utilizes genetic variants as instrumental variables, provides a promising avenue to investigate causal relationships between BMR and cardio-metabolic risk factors. By leveraging genetic variants associated with BMR, MR analysis can help elucidate whether variations in BMR directly influence cardio-metabolic risk factors or if these associations are merely correlative.

Thus, this study seeks to contribute to the growing body of knowledge in this field by employing MR to explore the association between BMR and a comprehensive array of cardio-metabolic risk factors. Through a rigorous analysis of large-scale genetic data, we aim to provide robust evidence regarding the causal links between BMR and specific risk factors. Such insights may have profound implications for the development of targeted interventions and strategies to mitigate cardio-metabolic risk and improve overall health outcomes.

2. Methods

2.1. Study design

In our MR study, we employed genetic variants as crucial tools to delve into the potential causal connections between BMR and various cardio-metabolic risk factors. The MR design rests upon three pivotal assumptions [29]: firstly, that genetic variants exert a direct influence on the exposure; secondly, that these genetic variants exhibit no associations with potential confounding factors; and lastly, that genetic variants exclusively affect outcomes through their impact on the mentioned exposures, as visually depicted in Fig. 1.

We obtained summary-level genetic data from six distinct genome-wide association studies (GWASs) [30–35], all involving individuals of European ancestry. Table 1 provides the characteristics of the studies included in this MR study.

2.2. Data sources

Summary-level BMR data was derived from a GWAS involving 534,045 individuals of European descent, conducted by Loh PR et al. [30]. This study identified an extensive pool of 11,973,469 single-nucleotide polymorphisms (SNPs). Similarly, BMI data was collected from a large-scale GWAS involving 681,275 individuals of European descent, resulting in a dataset encompassing 2,336,260 SNPs [31]. For fasting glucose, data were sourced from a substantial GWAS involving 200,622 individuals of European descent, producing a dataset that included information on 31,008,728 SNPs [32]. In the case of HDL cholesterol, a comprehensive GWAS involving 403,943 individuals of European descent was utilized, yielding a dataset comprising 12,321,875 SNPs [33]. For LDL cholesterol, data were sourced from a large-scale GWAS involving 431,167 individuals of European descent, resulting in a dataset encompassing 16,293,344 SNPs [34]. Total cholesterol data were obtained from a wide-ranging GWAS involving 344,278 individuals of European descent, which included information on 19,043,498 SNPs [35]. Summary-level data for triglycerides were extracted from a large-scale GWAS involving 441,016 individuals of European descent, encompassing a dataset of 12,321,875 SNPs [33]. Data on C-reactive protein were gathered from a large GWAS that included 436,939 individuals of European descent, providing details on 4,231,728 SNPs [36]. Waist circumference data originated from a comprehensive GWAS involving 232,101 individuals of European descent, encompassing information on 2,565,408 SNPs [37]. SBP information was collected from a broad GWAS that engaged 810,865 individuals of European descent, incorporating details on 236,549 SNPs [38]. Similarly, DBP data were obtained from the same large-scale GWAS involving 810,865 individuals of European descent, with information on 236,550 SNPs [38]. Data on HbA1c were sourced from a comprehensive GWAS that included 389,889 individuals of European descent, covering information on 10,783,722 SNPs [39]. Information on NT-proBNP was obtained from a widespread GWAS involving 21,758 individuals of European descent, comprising details on 9,461,972 SNPs [40].

2.3. Selection of instrumental variables

Selection of instrumental variables was guided by the aforementioned assumptions, with a specific focus on both the exposure variables—BMR—and the outcome variables, which encompassed BMI, fasting glucose, HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides, C-reactive protein, waist circumference, SBP, DBP, HbA1c and NT-proBNP. To avoid potential issues related to linkage disequilibrium [41,42], a stringent clumping procedure was implemented, utilizing a clump window set at $r^2 = 0.001$ and kb = 10,000. Additionally, a significance threshold of $p < 5*e^{-08}$ was applied to discern SNPs significantly associated with BMR. Furthermore, the chosen SNPs underwent comprehensive examination for potential connections with confounding factors, including

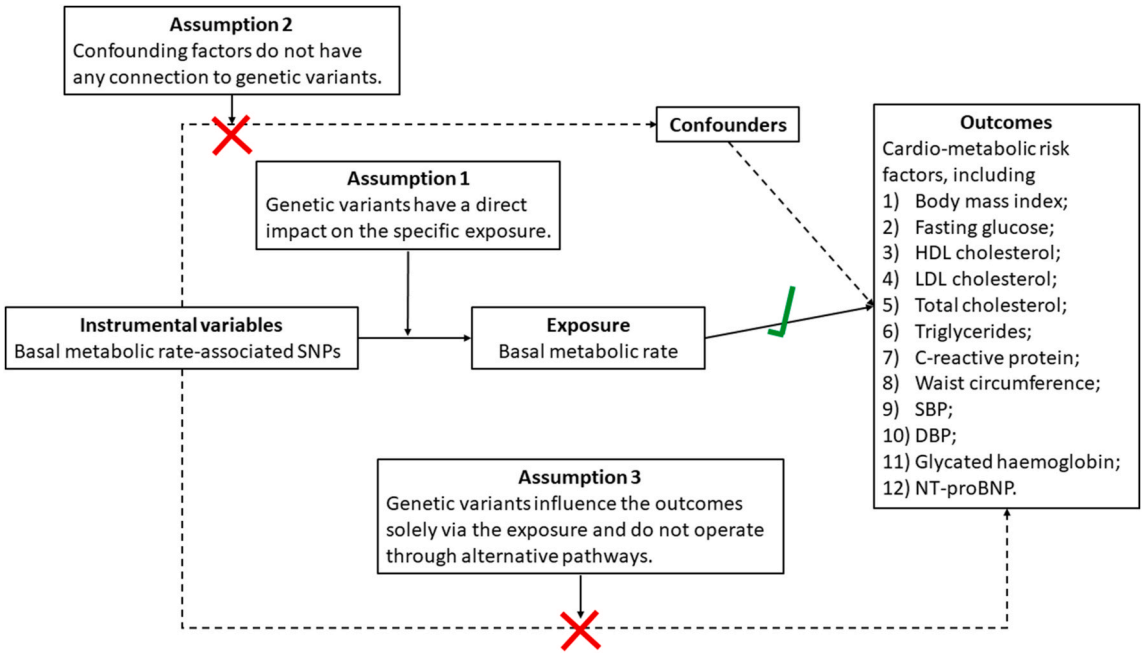

Fig. 1. Three pivotal assumptions for this Mendelian randomization study. HDL cholesterol: high density lipoprotein cholesterol; LDL cholesterol: low density lipoprotein cholesterol; SDP: systolic blood pressure; DBP: diastolic blood pressure; or NT-proBNP: N-terminal prohormone brain natriuretic peptide.

Table 1
Characteristics of the studies included in this Mendelian randomization study.

Authors	Types	Variables	Dataset ID	Year	Population	Sample size	Number of SNPs
Loh PR	Exposure	Basal metabolic rate	ebi-a-GCST90029025	2018	European	534,045	11,973,469
Yengo, L	Outcome	Body mass index	ieu-b-40	2018	European	681,275	2,336,260
Chen J	Outcome	Fasting glucose	ebi-a-GCST90002232	2021	European	200,622	31,008,728
Richardson, Tom	Outcome	HDL cholesterol	ieu-b-109	2020	European	403,943	12,321,875
Klimentidis YC	Outcome	LDL cholesterol	ebi-a-GCST90002412	2020	European	431,167	16,293,344
Sakaue S	Outcome	Total cholesterol	ebi-a-GCST90018974	2021	European	344,278	19,043,498
Richardson, Tom	Outcome	Triglycerides	ieu-b-111	2020	European	441,016	12,321,875
Barton AR	Outcome	C-reactive protein	ebi-a-GCST90025959	2021	European	436,939	4,231,728
Shungin D	Outcome	Waist circumference	ieu-a-61	2015	European	232,101	2,565,408
Surendran P	Outcome	Systolic blood pressure	ebi-a-GCST90000062	2020	European	810,865	236,549
Surendran P	Outcome	Diastolic blood pressure	ebi-a-GCST90000059	2020	European	810,865	236,550
Mbatchou J	Outcome	Glycated haemoglobin HbA1c	ebi-a-GCST90014006	2021	European	389,889	10,783,722
Folkersen L	Outcome	N-terminal prohormone brain natriuretic peptide	ebi-a-GCST90012082	2020	European	21,758	9,461,972

SNPs, single-nucleotide polymorphisms; HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol.

aspects such as age, gender, dietary patterns or other lifestyle factors, smoking habits, alcohol consumption, physical activity, autoimmune diseases, chronic kidney disease, medication usage, and any past history of cancer. This extensive assessment was carried out using an online website known as PhenoScanner: a database of human genotype–phenotype associations [43] (available at http://www.phenoscanner.medschl.cam.ac.uk/) and implemented with a strict threshold of $r^2 = 0.8$ and p-value $= 5*e^{-05}$. Any SNPs that displayed correlations with the aforementioned confounding factors were deliberately omitted from the study. To effectively address concerns regarding the potential for a weak instrument bias [44] resulting from a less stringent significance threshold, meticulous calculations of F statistics [45] were conducted. Any instrumental variables displaying an F-statistic value below 10 were identified as weak and consequently excluded from this MR study.

2.4. Statistical analysis

In the primary analysis, we applied the inverse variance weighted (IVW) [42] method to examine the relationships between genetically determined BMR and its impact on BMI, fasting glucose, HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides, C-reactive protein, waist circumference, SBP, DBP, HbA1c and NT-proBNP. To detect potential heterogeneity among the genetic instruments employed in the primary analysis, we employed Cochran's Q statistic [46].

Considering the possibility of biases affecting associations identified through the IVW method, either due to invalid instruments or pleiotropy, we implemented a series of steps to fortify the credibility of our findings. We initiated this process by utilizing the penalized IVW method, which fine-tunes the weights of SNPs potentially exhibiting pleiotropic effects. Additionally, we leveraged the simple median method, well-regarded for furnishing robust causal effect estimates, particularly when a minimum of 50% of genetic variants function as valid instrumental variables. Furthermore, we employed the weighted median method, holding the potential to deliver precise causal estimates, granted that at least 50% of the weight originates from valid instrumental variables. To further enhance the accuracy of our causal assessments and identify potential outliers, we introduced the MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) [47] method. In addition, the MR-Egger regression [48] method came into play for an evaluation of the average pleiotropic effects across all SNPs, facilitated through the intercept term. In a comprehensive evaluation of individual SNPs' impact on the collective outcomes, we undertook leave-one-out analyses [49]. This method allowed us to systematically exclude each SNP in succession, thereby providing insight into the influence of a single SNP on the overall findings.

The findings are reported in the form of beta (β) values accompanied by their corresponding 95% confidence intervals (CIs). All statistical analyses were carried out using the R statistical software (R version 4.2.2) with the following R packages: TwoSampleMR, MendelianRandomization, and MRPRESSO.

3. Results

3.1. The causal relationship between BMR and BMI, and fasting glucose

Fig. 2 illustrates the causal relationships between BMR and BMI, and fasting glucose. The IVW method detected a significant relationship between BMR and BMI, indicating that an increase in BMR leads to a substantial increase in BMI ($\beta = 0.7538$, 95% CI: 0.6418 to 0.8659, $p < 0.001$). Among the other four methods, except for MR Egger, none detected a significant relationship between BMR and BMI ($p = 0.1872$). All three other methods consistently identified a significant positive correlation between BMR and BMI ((all p-values<0.001). As for fasting glucose, regardless of the method employed, no significant relationship was found between BMR and fasting glucose (all p-values>0.05).

3.2. The causal relationship between BMR and HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides

Fig. 3 delineates the causal relationships between BMR and HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides. Regarding HDL cholesterol, all methods except MR-Egger identified a negative correlation between BMR and HDL cholesterol ($\beta = -0.3293$, 95% CI: 0.4474 to −0.2111, $p < 0.001$). In other words, an increase in BMR significantly leads to a decrease in HDL cholesterol concentration. For LDL cholesterol and total cholesterol, regardless of the method employed, no significant relationships were observed between BMR and these two indicators. This suggests that variations in BMR do not substantially affect LDL cholesterol and total cholesterol concentrations. On the other hand, we found that the IVW method detected a significant positive correlation between BMR and triglycerides ($\beta = 0.1472$, 95% CI: 0.0370 to 0.2574, $p = 0.0088$), implying that an increase in BMR results in a subsequent increase in triglyceride concentration.

3.3. The causal relationship between BMR and C-reactive protein, waist circumference, SBP and DBP

Fig. 4 illustrates the causal relationships between BMR and C-reactive protein, waist circumference, SBP, and DBP. As depicted in Fig. 4, a total of 15 SNPs were identified to be associated with C-reactive protein. Regardless of the methods employed, such as the analysis of IVW method, no significant relationship was found between BMR and C-reactive protein ($p > 0.05$). Furthermore, 49 SNPs were discovered to be correlated with waist circumference. The IVW method revealed a significant association between BMR and waist circumference ($\beta = 0.4416$, 95% CI: 0.2949 to 0.5883, $p < 0.001$), indicating that an increase in BMR is associated with a higher waist circumference. On the other hand, only 2 SNPs were found to be related to both SBP and DBP. Thus, the IVW method was exclusively used to examine the relationship between BMR and these two variables. The final results demonstrated no significant association between basal metabolic rate and both SBP and DBP ($p > 0.05$), suggesting that BMR has a limited impact on these blood pressure measures.

3.4. The causal relationship between BMR and HbA1c, and NT-proBNP

Fig. 5 illustrates the causal connections between BMR and HbA1c, as well as NT-proBNP. A total of 108 SNPs has been pinpointed in association with HbA1c. The outcomes from the IVW method confirm a noteworthy correlation between BMR and HbA1c, suggesting that an increase in BMR results in a considerable increase in HbA1c ($\beta = 0.1037$, 95% CI: 0.0080 to 0.1995, $p = 0.0337$). Moreover, 573 SNPs have been identified as being linked to NT-proBNP. Nevertheless, all methodologies, including MR Egger, Weighted Median,

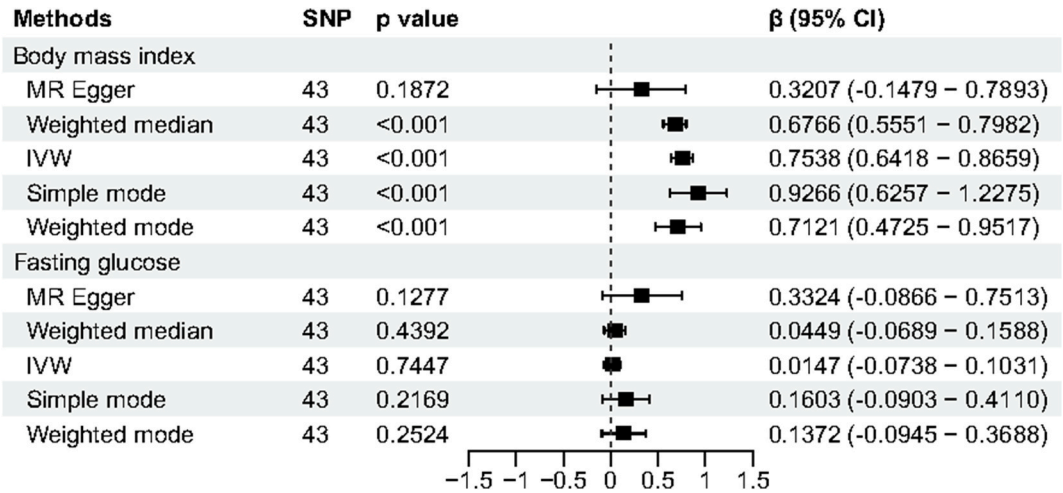

Fig. 2. The causal relationship between basal metabolic rate and body mass index, and fasting glucose.

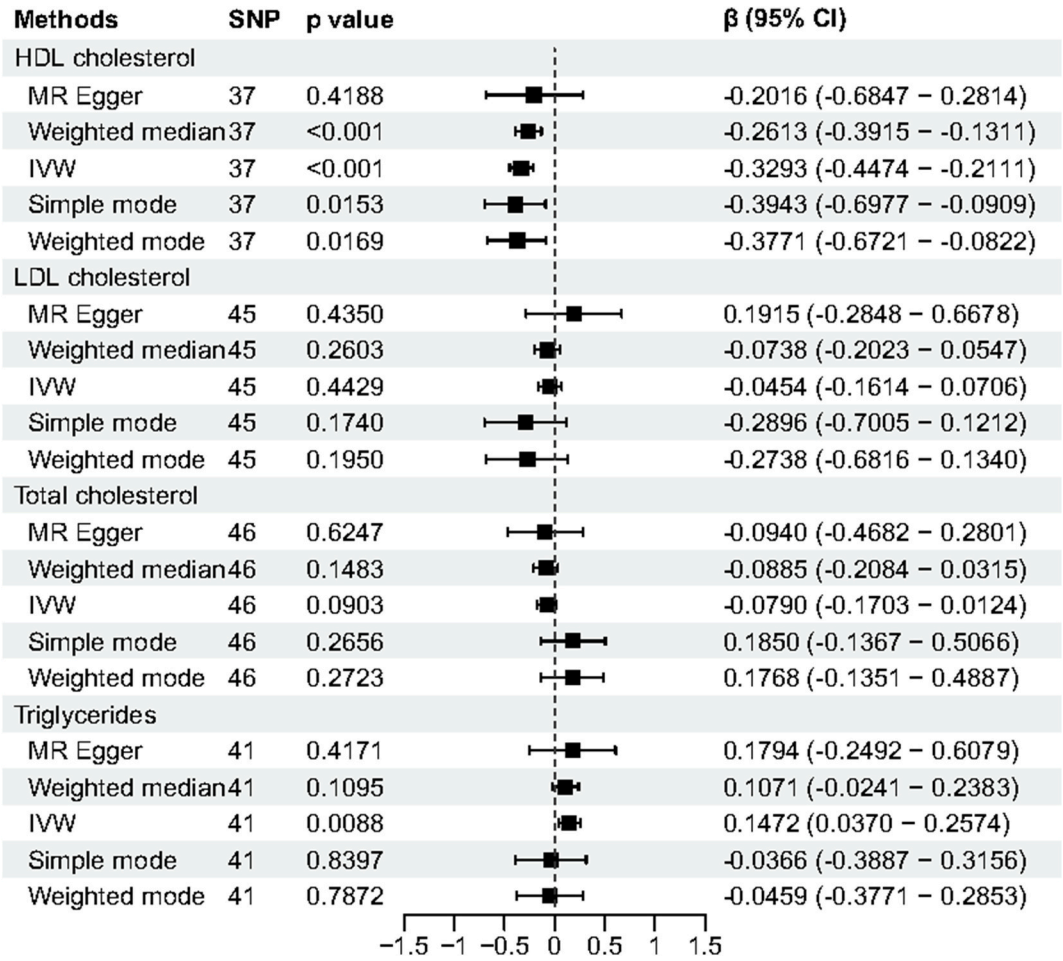

Fig. 3. The causal relationship between BMR and HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides. BMR: basal metabolic rate; HDL cholesterol: high density lipoprotein cholesterol; LDL cholesterol: low density lipoprotein cholesterol.

IVW, Simple Mode, and Weighted Mode, failed to disclose a substantial correlation between BMR and NT-proBNP ($p > 0.05$).

3.5. Heterogeneity assessment

Table 2 summarizes the heterogeneity assessment of BMR and various cardio-metabolic risk factors. As indicated in Table 2, regardless of the method employed, whether MR Egger or IVW, significant heterogeneity was detected in the association between BMR and BMI, fasting glucose, HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides, C-reactive protein, and HbA1c (all p-values<0.05). However, regardless of employing MR Egger or IVW methods, no significant associations were detected between BMR and waist circumference, SBP, DBP, or NT-proBNP.

3.6. Assessment of horizontal pleiotropy

Considering horizontal pleiotropy is a crucial consideration in MR study, as it can introduce bias and undermine the validity of causal inferences. To assess the presence of horizontal pleiotropy in our MR analysis investigating the association between BMR and various cardio-metabolic risk factors, we employed several methods and sensitivity analyses. We employed the MR-Egger regression analysis to formally test for the presence of horizontal pleiotropy. The MR-Egger intercept tests whether there is directional horizontal pleiotropy by assessing if the slope of the SNP-cardio-metabolic risk factor association is significantly different from zero. A significant MR-Egger intercept suggests the presence of horizontal pleiotropy. As described in Table 3, the MR-Egger intercept was not statistically significant (all p-values>0.05), suggesting no strong evidence of directional horizontal pleiotropy. Fig. 6a to f displays scatterplots that illustrate the relationships between BMR and several factors: BMI, fasting glucose levels, HDL cholesterol, LDL cholesterol, total cholesterol, and triglyceride levels, respectively. In Fig. 7a to f, similar scatterplots depict the associations between BMR and the following variables, respectively: C-reactive protein, waist circumference, SBP, DBP, HbA1c, and NT-proBNP. As seen in Fig. 6a to f and

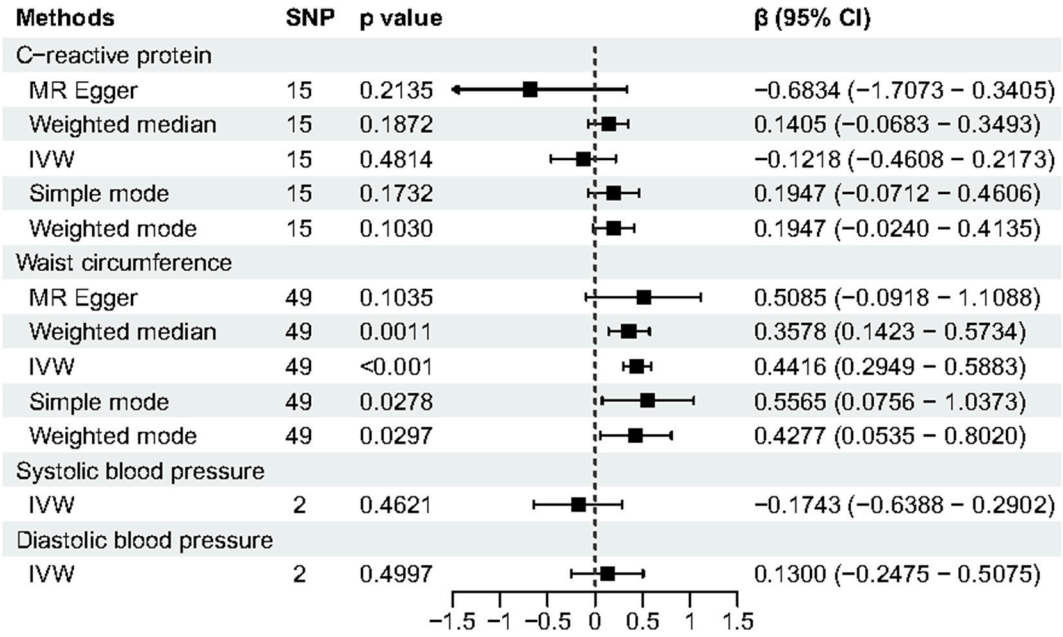

Fig. 4. The causal relationship between BMR and C-reactive protein, waist circumference, systolic blood pressure and diastolic blood pressure.

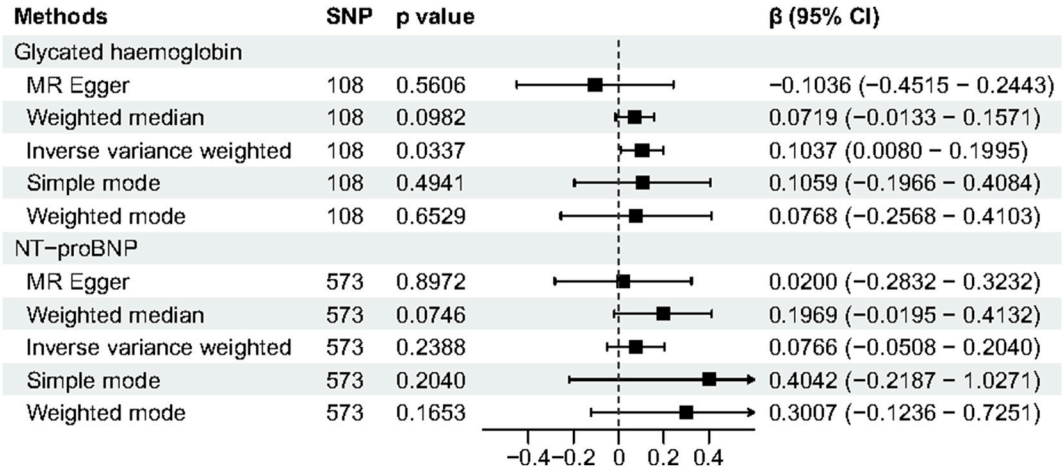

Fig. 5. The causal relationship between BMR and glycated haemoglobin, and N-terminal prohormone brain natriuretic peptide.

Fig. 7a to f, the MR-Egger intercept in each scatterplot is minimal, providing further support for the absence of horizontal pleiotropy.

4. Discussion

4.1. Key findings

Our MR analysis yielded compelling evidence of a causal relationship between BMR and selected cardio-metabolic risk factors. Specifically, genetically determined higher BMR was associated with an increased BMI ($\beta = 0.7538$, 95% CI: 0.6418 to 0.8659, $p < 0.001$), lower levels of HDL cholesterol ($\beta = -0.3293$, 95% CI: 0.4474 to −0.2111, $p < 0.001$), and higher levels of triglycerides ($\beta = 0.1472$, 95% CI: 0.0370 to 0.2574, $p = 0.0088$), waist circumference ($\beta = 0.4416$, 95% CI: 0.2949 to 0.5883, $p < 0.001$), and HbA1c (($\beta = 0.1037$, 95% CI: 0.0080 to 0.1995, $p = 0.0377$). These findings are particularly noteworthy, as they suggest that BMR may play a crucial role in shaping an individual's susceptibility to specific aspects of cardio-metabolic health. However, it is equally important to acknowledge the absence of a significant association between BMR and fasting glucose, LDL cholesterol, total cholesterol, C-reactive protein, SBP, DBP, or NT-proBNP.

Table 2
Heterogeneity assessment.

Exposure	Outcomes	Methods	Q statistics	P value
Basal metabolic rate	Body mass index	MR Egger	120.4649	<0.001
Basal metabolic rate	Body mass index	Inverse variance weighted	130.6581	<0.001
Basal metabolic rate	Fasting glucose	MR Egger	57.5940	0.044
Basal metabolic rate	Fasting glucose	Inverse variance weighted	60.8367	0.030
Basal metabolic rate	HDL cholesterol	MR Egger	75.0797	<0.001
Basal metabolic rate	HDL cholesterol	Inverse variance weighted	75.6924	<0.001
Basal metabolic rate	LDL cholesterol	MR Egger	102.5062	<0.001
Basal metabolic rate	LDL cholesterol	Inverse variance weighted	104.9148	<0.001
Basal metabolic rate	Total cholesterol	MR Egger	61.7641	0.040
Basal metabolic rate	Total cholesterol	Inverse variance weighted	61.7735	0.049
Basal metabolic rate	triglycerides |	MR Egger	76.4773	<0.001
Basal metabolic rate	triglycerides |	Inverse variance weighted	76.5227	<0.001
Basal metabolic rate	C-reactive protein	MR Egger	87.0972	<0.001
Basal metabolic rate	C-reactive protein	Inverse variance weighted	95.7726	<0.001
Basal metabolic rate	Waist circumference	MR Egger	37.8844	0.8261
Basal metabolic rate	Waist circumference	Inverse variance weighted	37.9351	0.8508
Basal metabolic rate	Systolic blood pressure	MR Egger	–	–
Basal metabolic rate	Systolic blood pressure	Inverse variance weighted	2.8435	0.0917
Basal metabolic rate	Diastolic blood pressure	MR Egger	–	–
Basal metabolic rate	Diastolic blood pressure	Inverse variance weighted	1.8733	0.1711
Basal metabolic rate	Glycated haemoglobin HbA1c	MR Egger	425.4428	<0.001
Basal metabolic rate	Glycated haemoglobin HbA1c	Inverse variance weighted	431.3678	<0.001
Basal metabolic rate	NT-proBNP	MR Egger	599.1084	0.2010
Basal metabolic rate	NT-proBNP	Inverse variance weighted	599.2789	0.2079

HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol; NT-proBNP: N-terminal prohormone brain natriuretic peptide.

Table 3
Assessment of horizontal pleiotropy.

Exposure	Outcomes	Egger intercept	P value
Basal metabolic rate	Body mass index	0.0040	0.0697
Basal metabolic rate	Fasting glucose	−0.0028	0.1364
Basal metabolic rate	HDL cholesterol	−0.0011	0.5964
Basal metabolic rate	LDL cholesterol	−0.0021	0.3204
Basal metabolic rate	Total cholesterol	0.0001	0.9354
Basal metabolic rate	triglycerides	−0.0003	0.8798
Basal metabolic rate	C-reactive protein	0.0056	0.2757
Basal metabolic rate	Waist circumference	−0.0006	0.8227
Basal metabolic rate	Systolic blood pressure	–	–
Basal metabolic rate	Diastolic blood pressure	–	–
Basal metabolic rate	Glycated haemoglobin HbA1c	0.0020	0.2271
Basal metabolic rate	NT-proBNP	0.0008	0.6870

HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol; NT-proBNP: N-terminal prohormone brain natriuretic peptide.

4.2. Association with increased BMI

Currently, there is a significant controversy regarding the relationship between basal metabolic rate and body mass index. In a study with 92 participants, Tataranni et al. [50]. examined the correlation between resting metabolic rate (RMR) and the increase in body weight within a non-diabetic population. The results revealed that a lower RMR was associated with an increase in body weight. Another study [51], involving 95 participants, also identified a link between lower energy expenditure and weight gain. Additionally, the study conducted by Anthanont et al. [52]. found that adults with low BMR did not gain more weight than those with high BMR. This suggests that dietary intake or exercise habits may offset the impact of BMR on weight changes. On the other hand, Findings from another previous study [53] conducted in the pre-pregnant population have indicated a correlation between elevated BMR and higher BMI, aligning with the results obtained in our MR study. Interestingly, Luke et al.'s study [54] recruited 744 lean adults and, after adjusting for potential confounding factors, found a correlation between higher resting energy expenditure and weight gain. Consistent with Luke et al.'s findings, the results of our study similarly identified a positive correlation between elevated BMR and weight gain. BMR represents the energy expenditure necessary for maintaining fundamental physiological functions at rest. Individuals with higher BMRs may have greater energy requirements, potentially reducing the likelihood of excess calorie storage as body fat. However, it is crucial to acknowledge that while a higher BMR can influence calorie expenditure, it constitutes just one facet of the intricate energy balance equation. One potential mechanism is that individuals with higher BMRs may compensate for energy expenditure by

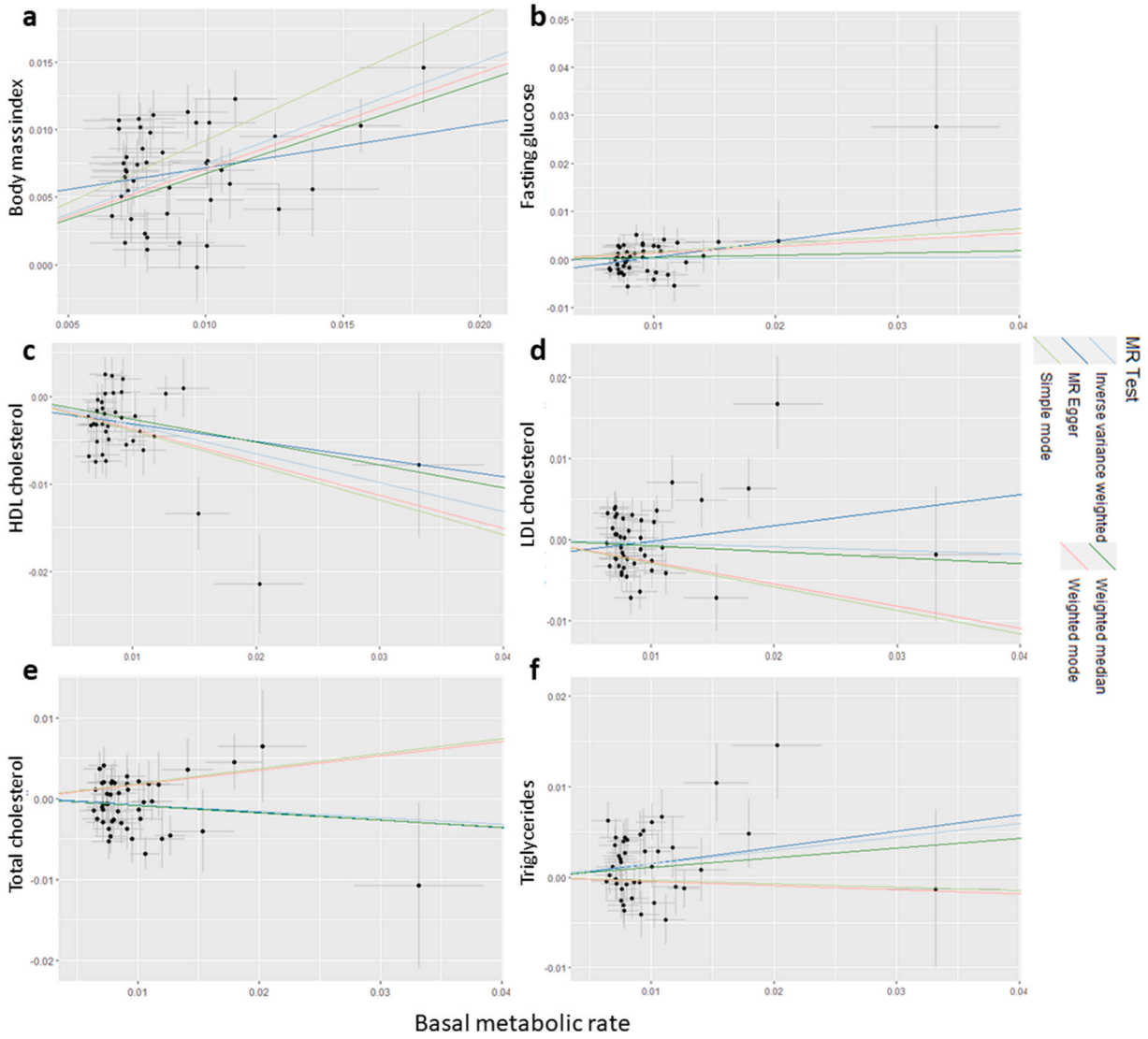

Fig. 6. Fig. 6 displays scatterplots depicting the relationships between basal metabolic rate and different cardio-metabolic risk factors. **a**, scatterplots of basal metabolic rate and body mass index; **b**, scatterplots of basal metabolic rate and fasting glucose; **c**, scatterplots of basal metabolic rate and HDL cholesterol; **d**, scatterplots of basal metabolic rate and LDL cholesterol; **e**, scatterplots of basal metabolic rate and total cholesterol; **f**, scatterplots of basal metabolic rate and triglycerides. HDL cholesterol: high density lipoprotein cholesterol; LDL cholesterol: low density lipoprotein cholesterol.

consuming larger quantities of food. If the additional energy intake surpasses their own energy expenditure, this could potentially lead to an increase in BMI. In addition, the relationship between BMR and BMI is further modulated by physical activity levels. Regular physical activity can augment BMR and aid in maintaining a healthy BMI. Conversely, a sedentary lifestyle may lead to a disconnect between BMR and BMI, where a higher BMR alone might not suffice to prevent excessive weight gain. According to Marra et al. [55], the increased energy expenditure seen in severely obese individuals, linked to a systemic, mild inflammatory process, could potentially shed light on the transition from obesity to metabolic syndrome.

4.3. Lower levels of HDL cholesterol

The inverse relationship between genetically higher BMR and lower levels of HDL cholesterol is intriguing. HDL cholesterol [56,57] is often referred to as "good" cholesterol due to its role in removing excess cholesterol from the bloodstream, and a lower HDL cholesterol level is associated with an increased risk of cardiovascular disease. The mechanism underlying this association is not immediately clear and warrants further investigation. It could involve altered lipid metabolism or other metabolic pathways influenced by BMR. Genetically higher BMR might influence lipid metabolism pathways, such as the production and clearance of HDL

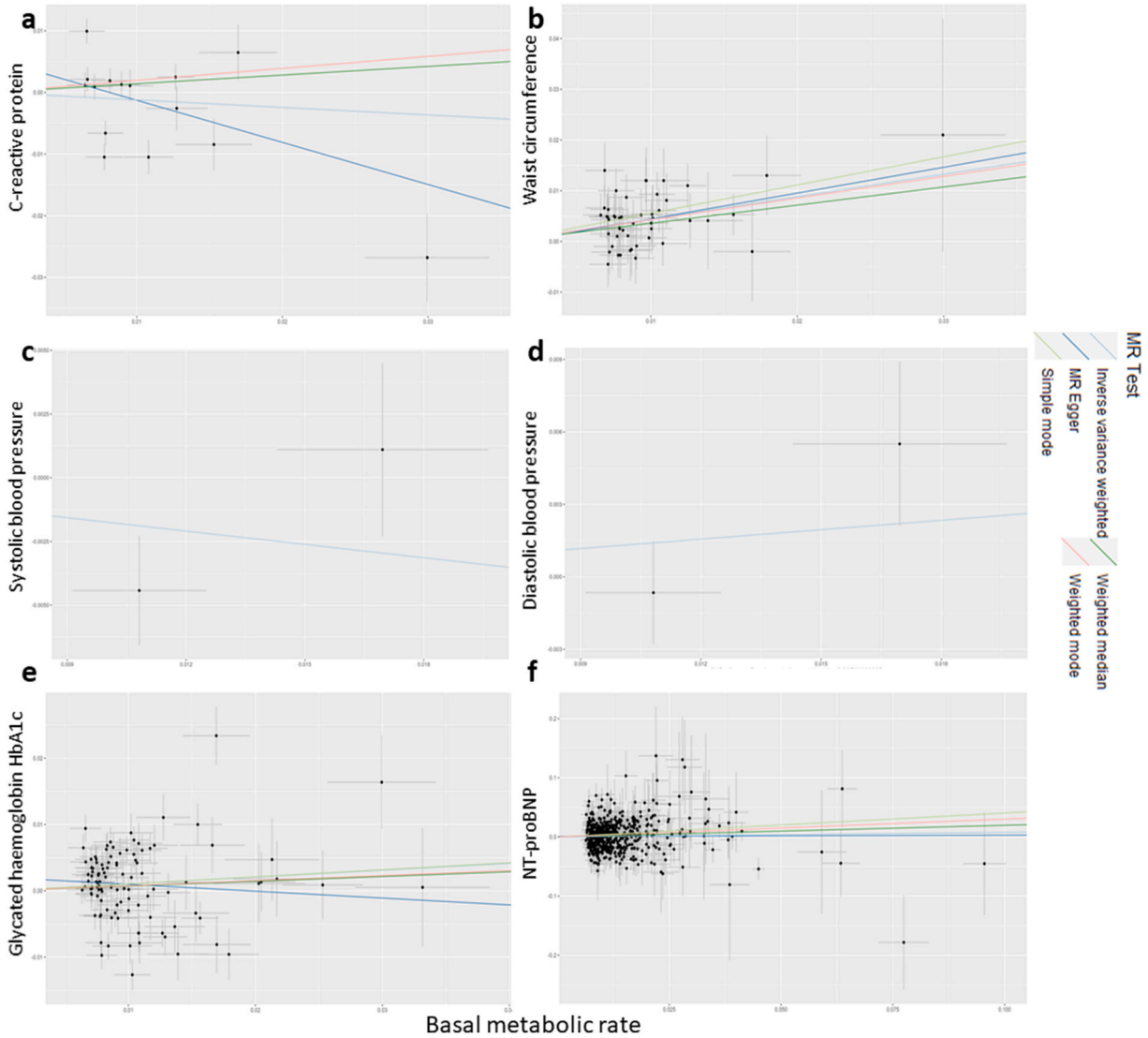

Fig. 7. Fig. 7 showcases scatterplots illustrating the connections between basal metabolic rate and various cardio-metabolic risk factors. **a**, scatterplots of basal metabolic rate and C-reactive protein; **b**, scatterplots of basal metabolic rate and waist circumference; **c**, scatterplots of basal metabolic rate and systolic blood pressure; **d**, scatterplots of basal metabolic rate and diastolic blood pressure; **e**, scatterplots of basal metabolic rate and glycated haemoglobin; **f**, scatterplots of basal metabolic rate and N-terminal prohormone brain natriuretic peptide.

cholesterol, potentially leading to lower HDL cholesterol levels. Investigating the specific genes and enzymes involved in these pathways may further explain the precise mechanisms. Furthermore, BMR is also influenced by various hormonal signals, including thyroid hormones [58,59], which also impact lipid metabolism. The interplay between these hormonal pathways and HDL cholesterol regulation may be a key determinant of the observed association. However, there is currently no research directly elucidating the potential mechanisms underlying the relationship between BMR and HDL cholesterol. This conclusion still requires further research for validation.

4.4. Higher levels of triglycerides

Higher levels of triglycerides, as observed in association with genetically higher BMR in our study, warrant careful consideration. Elevated triglyceride levels are a well-established risk factor for cardiovascular disease [60–62], making this finding of particular significance. It suggests that individuals with genetically determined higher BMR may possess a heightened propensity for triglyceride accumulation, potentially impacting their cardiovascular health. Several potential mechanisms could underlie the observed relationship between genetically higher BMR and increased triglyceride levels. Genetically elevated BMR may influence the metabolism of lipids in the body, potentially leading to increased triglyceride production or decreased clearance. Therefore, investigating specific

genes and enzymes involved in lipid metabolism could provide insights into these processes. In addition, higher BMR may result in increased energy expenditure, which, if not balanced by energy intake, could trigger the mobilization of stored triglycerides from adipose tissue as an energy source. This could lead to higher circulating triglyceride levels, especially in individuals with sustained elevated BMR. Finally, it's also possible that genetic factors related to both BMR and triglyceride levels interact with environmental factors, adding complexity to the relationship. Identifying gene-environment interactions may offer further insights for this association.

4.5. Higher levels of waist circumference and HbA1c

To the best of our knowledge, this study marks the first officially investigation into the link between BMR and waist circumference. In line with the BMI results, our findings indicate a correlation between a higher BMR and an increase in waist circumference. Given the lack of prior research exploring the connection between BMR and waist circumference, we hypothesize that potential mechanisms may parallel those observed in BMI studies. An increased BMR could potentially contribute to increased intake, and if energy intake exceeds expenditure, it may lead to an excess of stored energy, ultimately resulting in a significant increase in waist circumference. However, whether this process involves the participation of the sympathetic nervous system, parasympathetic nervous system, or disruptions in the endocrine system still requires further research for additional confirmation.

Previous studies have explored the relationship between BMR and HbA1c. Alawad et al.'s research [63] found that resting metabolic rate is significantly higher in obese diabetic patients compared to non-obese diabetic patients. Moreover, patients with elevated HbA1c levels exhibited higher resting metabolic rates than those with normal HbA1c levels, suggesting a positive correlation between resting metabolic rate and HbA1c. Similarly, another study's results [64] indicated that obese diabetic patients have a higher resting metabolic rate than non-obese diabetic patients, implying that resting metabolic rate can serve as a crucial indicator of disease severity. In line with prior research, the results of our study reveal an association between BMR and elevated HbA1c, further emphasizing the importance of assessing BMR. Increased concentrations of free fatty acids in diabetic patients lead to excessive gluconeogenesis, might contribute to increased energy expenditure in these individuals [63,65]. Based on the findings of our study, a plausible mechanism could be that diabetic patients with poorly controlled glucose exhibit significantly higher concentrations of free fatty acids compared to those with normal blood sugar control, consequently resulting in an increase in BMR.

4.6. No significant associations with fasting glucose, LDL cholesterol, total cholesterol, C-reactive protein, SBP, DBP, or NT-proBNP

The absence of significant associations between BMR and fasting glucose, LDL cholesterol, total cholesterol, C-reactive protein, SBP, DBP, or NT-proBNP is a noteworthy finding. This implies that BMR might not exert a predominant influence on the variability of these cardio-metabolic risk factors. Instead, it suggests that other contributing factors, including genetics, dietary choices, physical activity levels, and insulin resistance, are more likely to play substantial roles in shaping variations in fasting glucose, LDL cholesterol, or total cholesterol, C-reactive protein, SBP, DBP, or NT-proBNP.

4.7. Potential clinical implications

The findings from our MR Study, which investigated the association between BMR and cardio-metabolic risk factors, hold several clinical implications with potential relevance for healthcare practice and patient management. Firstly, recognizing the role of BMR in influencing cardio-metabolic risk factors can inform more personalized health interventions. Healthcare professionals can consider an individual's BMR when designing weight management and metabolic health strategies. Those with genetically higher BMRs may require tailored dietary and exercise recommendations to maintain a healthy body weight and lipid profile. Secondly, understanding the complex interplay between BMR and cardio-metabolic risk factors can enhance cardiovascular risk assessment. Incorporating BMR data alongside traditional risk factors like blood pressure and cholesterol levels may provide a more comprehensive view of an individual's risk profile, leading to more accurate risk stratification and personalized preventive measures. Thirdly, our findings underscore the need for further research into the mechanisms linking BMR to cardio-metabolic risk factors. Investigating these mechanisms may reveal novel targets for drug development, offering new therapeutic avenues for managing metabolic health and reducing cardiovascular risk.

5. Limitations

While our MR study provides valuable insights into the association between BMR and cardio-metabolic risk factors, it is essential to acknowledge several potential limitations in our study. Firstly, our MR study relies on the assumption that the genetic variants used as instrumental variables for BMR do not violate the core assumptions of MR, including no pleiotropy (i.e., genetic variants influence the outcome only through BMR) and no gene-environment interactions. Violations of these assumptions could introduce bias into our causal estimates. Secondly, this MR study primarily focuses on the relationships observed within the study population, and these associations may not be universally applicable to diverse populations with different genetic backgrounds and environmental exposures. Thirdly, although MR study helps control for observed confounders, unmeasured or unknown confounding variables may still exist. These unaccounted factors could potentially influence both BMR and cardio-metabolic risk factors, impacting the validity of our causal inferences.

In conclusion, our MR study provides evidence of a complex relationship between BMR and specific cardio-metabolic risk factors.

We find that genetically determined higher BMR is associated with an increased BMI, lower levels of HDL cholesterol, higher levels of triglycerides, waist circumference, and HbA1c, but no significant associations are observed with fasting glucose, LDL cholesterol, total cholesterol, C-reactive protein, SBP, DBP, or NT-proBNP. These findings highlight the multifaceted nature of metabolic health, suggesting that BMR plays varying roles in influencing different cardio-metabolic risk factors. However, the potential mechanisms underpinning these associations warrant further investigation.

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Ethics statement

We utilized genetic tools and summary statistics from previously published GWASs for this study. In each of these studies, all participants provided informed consent, and the research had received approval from the respective institutional review board. Ethical approval for our current study was deemed unnecessary since we did not utilize individual-level data.

Data availability

All the data used in this study are freely accessible on an online website (https://gwas.mrcieu.ac.uk/).

CRediT authorship contribution statement

Limeng Ning: Writing – review & editing, Writing – original draft, Supervision, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Changjing He:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Chunliu Lu:** Supervision, Software, Resources, Investigation, Data curation, Conceptualization. **Wanzhong Huang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Data curation, Conceptualization. **Ting Zeng:** Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Qiang Su:** Visualization, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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