Basal metabolic rate and risk of multiple sclerosis: a Mendelian randomization study

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Research Article

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Abstract

Objective

To determine the relationship between basal metabolic rate (BMR) and multiple sclerosis (MS) susceptibility, we used genome-wide association study (GWAS) summary statistics data from the International Multiple Sclerosis Genetics Consortium on a total of 115,803 participants of European descent, including 47,429 MS patients and 68,374 controls.

Methods

We selected 378 independent genetic variants strongly associated with BMR in a GWAS involving 454,874 participants as instrumental variables to examine a potential causal relationship between BMR and MS.

Results

A genetically predicted higher BMR was associated with a greater risk of MS (odds ratio [OR]: 1.283 per one standard deviation increase in BMR, 95% confidence interval [CI]: 1.108–1.486, *P* = 0.001). Moreover, we used the lasso method to eliminate heterogeneity (Q statistic = 384.58, *P* = 0.370). There was no pleiotropy in our study and no bias was found in the sensitivity analysis using the leave-one-out test.

Conclusions

We provide novel evidence that a higher BMR is an independent causal risk factor in the development of MS. Further work is warranted to elucidate the potential mechanisms.

Introduction

Multiple sclerosis (MS) is a challenging and devastating autoimmune disease of the central nervous system, with both genetic and environmental factors implicated in its etiology. Genome-wide association studies (GWAS) revealed that 233 independently associated variants mediate disease risk, accounting for 48% of variance in MS risk between individuals. Heredity affects its progression to disability.(International Multiple Sclerosis Genetics 2019; International Multiple Sclerosis Genetics, Wellcome Trust Case Control, Sawcer, Hellenthal, Pirinen, Spencer, Patsopoulos et al. 2011; Patsopoulos, De Jager 2020) Its environmental risk factors include obesity, low vitamin D levels, cigarette smoking, and lack of exercise.(Olsson, Barcellos, Alfredsson 2017; Reich, Lucchinetti, Calabresi 2018; Wesnes, Myhr, Riise, Cortese, Pugliatti, Bostrom, Landtblom et al. 2018) Whether these risk factors act by the same mechanism, or whether there are other susceptible factors remains unclear.

Basal metabolic rate (BMR) is the rate of energy expenditure per unit time by endothermic animals at rest.(Schrödinger 1944) BMR plays a role in energy balance.(Anthanont, Jensen 2016) Assessing its relationship with MS is beneficial to our understanding of the causes of MS and its potential preventative measures.

Given the long latency period between exposure and outcome and the unethical approaches to controlling BMR, randomized controlled trials, the gold standard in causal inference,(Jones, Podolsky 2015) are not feasible.

Observational studies may be biased due to methodological limitations, including confounding factors, reverse causation, and measurement error.(Lawlor, Davey Smith, Kundu, Bruckdorfer, Ebrahim 2004) Mendelian randomization (MR) provides an analytical approach, utilizing genetic variants such as single nucleotide polymorphisms (SNPs), as instrumental variable to minimize an exposure's confounding bias, strengthening the causal inference of an exposure-outcome association.(Davies, Holmes, Davey Smith 2018; Emdin, Khera, Kathiresan 2017)

To assess BMR's effect on MS susceptibility, we performed a two-sample MR analysis using genetic associations from the most recent GWAS summary statistics for MS from the International Multiple Sclerosis Genetics Consortium (IMSGC)(International Multiple Sclerosis Genetics 2019) and the largest GWAS summary statistics database for BMR.(Hemani, Zheng, Elsworth, Wade, Haberland, Baird, Laurin et al. 2018) We explored whether participants with genetic variants associated with higher BMR also have a greater risk of MS.

Methods

Genetic variants associated with BMR

The data used for the GWAS of BMR correlation study included 9,851,867 SNPs (single nucleotide polymorphism) from 454,874 participants in the UK Biobank, found through the MR-Base platform in Europe.(Hemani, Zheng, Elsworth, Wade, Haberland, Baird, Laurin et al. 2018) All Mendelian randomization studies were analyzed using the R package '*TwoSampleMR*'.(ibran Hemani PH 2020) We screened the GWAS data of these participants for significant signaling loci associated with BMR whether the level of association with BMR was significant ($P < 5\times10^{-8}$) by using R function '*extract_instruments*'. We selected participants in a low-linkage disequilibrium state ($r^2 < 0.001$, kb distance > 10,000) and with a minor allele frequency (MAF) > 5% by using function '*clump_data*' and '*extract_outcome_data*', respectively.(Ference, Robinson, Brook, Catapano, Chapman, Neff, Voros et al. 2016) For SNPs that were not available in the outcome GWAS summary data, we used proxy SNPs with a minimum linkage disequilibrium $r^2 = 0.8$. If the regression dilution I^2(GX) estimates were less than 90%, simulation extrapolation (SIMEX) corrections were applied. We obtained the effect, standard error, and *P* values of the screened SNP numbers, effective allele, effective allele frequency, and effective allele with BMR and MS. We unified the direction of effect values for BMR and MS data, and performed two-sample Mendelian randomized causal association and sensitivity analyses. To reduce bias and ensure the validity of the conclusions, we performed a reverse causality test. SNPs associated with these characteristics in populations of European ancestry with significant genome-wide expression levels ($P < 5\times10^{-8}$, MAF > 5%) were included. BMR in UK Biobank was calculated according to the Oxford equation with the unit being Kilo-Joule.(Henry 2005) The specific formula is detailed in Table S1.

GWAS summary data on MS

Population selection and SNPs screening process of the study is provided in Fig. 1 and Table S2. We retrieved GWAS data of a total of 115,803 MS participants of European descent from the IMSGC, including 47,429 MS patients and 68,374 controls. Eligible KPNC (Kaiser Permanente Medical Care Plan, Northern California Region) cases were defined as current members with a diagnosis of MS by a neurologist (ICD-9 code 340.xx), age 18–69 years, and membership in KPNC at initial contact. Diagnoses were validated using electronic health record EHR review and individual interviews. Controls were current KPNC members without a diagnosis of MS or related condition (optic neuritis, transverse myelitis, or demyelinating disease. ICD-9 codes: 340, 341.0, 341.1, 341.2, 341.20, 341.21, 341.22, 341.8, 341.9, 377.3, 377.30, 377.39 and 328.82) confirmed through EHR data. We used a

set of 378 independent SNPs as instrumental variables to demonstrate a causal relationship between BMR and MS. We also considered the major histocompatibility complex (MHC) genome region with polymorphic loci, and checked the 378 SNPs we used against the 32 MHC loci reported by IMSGC and found no overlap between them(International Multiple Sclerosis Genetics 2019). The details of the 378 SNP final choosed are detailed in Table S3. In addition, the dataset used to generate the results in the current study is available from the corresponding author on request.

Statistical analysis

We analyzed and examined three assumptions of the MR application: that the instrumental variables are related to BMR, that the instrumental variables affect MS only through the causal pathway of BMR, and that there is no association between the instrumental variables and confounding factors. To assess the MR estimates of BMR for MS, we used four MR methods. We performed an MR analysis using mainly inverse variance weighting (IVW) for traits. We also estimated the effects using other statistical tests: the MR-Egger, Weighted median, and Weighted mode. Furthermore, we tested the “no measurement error” assumption in the MR-Egger analysis. If the regression dilution I^2(GX) estimates were less than 90%, SIMEX corrections were applied.

Sensitivity analysis

The lasso penalization method was used to correct for the heterogeneity of the traditional MR analysis between exposure and outcome variables. We also tested the instrumental variables for heterogeneity, with $P < 0.05$ representing the presence of heterogeneity. We used the leave-one-out method to remove SNPs one by one, using the remaining SNPs as the new instrumental variables to calculate the odds ratio (OR) for the causal effect of BMR on MS, to evaluate the effect of the removed SNP on the outcome, and to determine whether the MR estimate was heavily biased by the effect of a single SNP. The results of the MR were analyzed using the Two-Sample MR package, and(Hemani, Haycock, Zheng, Gaunt, Elsworth 2020) statistical analyses were performed in R statistical software (version 4.0.2).(Team 2019)

Results

Participant characteristics

We selected GWAS summary data on MS from the IMSGC (47,429 MS cases and 68,374 controls, European ancestry). The GWAS summary data on the BMR of 454,874 participants was extracted from MRC-IEU(Elsworth, Lyon, Alexander, Liu, Matthews, Hallett, Bates et al. 2020.08) (Table 1). The number required for 80% power in MS with an OR of 1.283 was at least 111,066 participants (see Table 2 for power calculations). We conducted the power calculations of the MR analysis according to the method described by Brion *et al.*(Brion, Shakhbazov, Visscher 2013) With a total of 115,803 MS participants, our study provided a statistical power of 0.9999, sufficient to verify a causal effect of BMR on MS. Therefore, it was sufficient to generate a strong genetic instrument based on the SNPs of the BMR.

Table 1
Description of GWAS consortiums used for each phenotype

Phenotype	MRbaseID	First author (year)	Consortium	Sample size	Population	Sex	Category
Basal metabolic rate	ukb-b-16446	Ben Elsworth(2018)	MRC-IEU	454,874	European	Males and females	Continuous
Multiple sclerosis	ieu-b-18	Patsopoulos NA(2019)	IMSGC	115,803	European	Males and females	binary

IMSGC: International Multiple Sclerosis Genetics Consortium; MRC-IEU = MRC Integrative Epidemiology Unit

Table 2
Power for conventional Mendelian randomization analysis (two-sided $\alpha = 0.05$)

Exposure/genetic instrument	R-squared	Actual n	Proportion of cases (%)	Observational OR (per SD)	n required for 80% power	Power
Basal metabolic rate/378 SNPs	0.47%	115,803	41%	1.283	111,066	0.99990

Causal effect between BMR and MS

Genetically predicted higher BMR was significantly associated with greater risk of MS (Fig. 2 and Table 3). BMR was associated with a 28.3% greater risk of MS (OR: 1.283, 95% CI; 1.108–1.486; $P = 0.001$; Q statistic: 384.58, $P = 0.370$). Supplementary Fig. 1 shows individual causal estimates for each of the 378 SNPs. However, the associations disappeared using the MR-Egger method (OR: 1.147, 95%: CI 0.797–1.651; $P = 0.459$), weighted median (OR: 1.224, 95% CI: 0.959–1.561; $P = 0.104$), and weighted mode (OR: 1.142, 95% CI: 0.779–1.673; $P = 0.498$). Nevertheless, the direction and magnitude of the causal estimates were similar. MR regression slopes are displayed in Supplementary Fig. 2. No single SNP strongly influenced the overall effect of BMR on MS in the leave-one-out sensitivity analysis (Supplementary Fig. 3). Supplementary Fig. 4 shows that when a single SNP is used as the instrumental variable, the points representing the causal association effect are symmetrically distributed, indicating that the causal association is less likely to be affected by potential bias. No evidence suggested the presence of directional pleiotropy in the MR-Egger regression analysis. The *P*-values for the intercept were large, and the estimates adjusted for pleiotropy suggested null effects (Intercept $\beta = 0.002$, $P = 0.512$). Since we were unable to obtain eligible SNPs using a threshold of $P < 5\times10 - 8$ for the MS GWAS dataset, reverse causality for this study was invalid.

Table 3
Causal effects from basal metabolic rate on multiple sclerosis

Exposure	Method	N SNPs	β	SE	OR	95%CI	*P* value	I^2	mean F
Basal metabolic rate	IVW	378	0.249	0.075	1.283	1.108–1.486	0.001*		79.76
	MR-Egger	378	0.138	0.186	1.147	0.797–1.651	0.459	0.92	
	Weighted median	378	0.202	0.124	1.224	0.959–1.561	0.104		
	Weighted mode	378	0.132	0.195	1.142	0.779–1.673	0.498		

* *P* value < 0.05, IVW = inverse variance weighted

Heterogeneity exists between basal metabolic rate and multiple sclerosis, so mendelian randomization was performed using the lasso method to eliminate heterogeneity (Q statistic = 384.58, *P* = 0.370).

Discussion

Using summary-level data for MS and BMR levels from large European populations, our study demonstrated that a genetic increase in BMR by 1 SD (a unit SD = 1358.36 KJ) was associated with a 28.3% increase in risk of MS, providing strong evidence in support of a causal role of BMR in MS susceptibility.

The success of the MR approach in MS has been demonstrated in several relevant studies; increased BMI and low serum vitamin D point to a causal association with increased MS susceptibility.(Jacobs, Noyce, Giovannoni, Dobson 2020; Mokry, Ross, Timpson, Sawcer, Davey Smith, Richards 2016) (Mokry, Ross, Ahmad, Forgetta, Smith, Goltzman, Leong et al. 2015) These epidemiological studies provide more substantial evidence than intervention studies, and account for a range of neurological diseases with significant lifestyle determinants. However, the risk factors identified in these studies only partially explain the epidemiological findings like latitude and ancestry. Epidemiological data suggest that the global distribution of MS generally increases with distance from the equator.(Walton, King, Rechtman, Kaye, Leray, Marrie, Robertson et al. 2020) In addition, although the disease is common in areas inhabited by Northern Europeans, this effect is modified according to where people live in their early lives. Migration studies show that childhood migration from low-risk areas to high-risk areas is associated with a lower risk of developing MS, and vice versa.(Dean, Kurtzke 1971) The risk factors currently identified by MR are not sufficient to systematically explain these phenomena; exposure risks may be greater than initially thought, or the better indicators that encapsulate exposure risks have not yet been identified.

BMR represents the energy expenditure necessary to maintain basic physiological functions, including the activity of the heart, respiration, conduction of nerve impulses, ion transport across membranes, and metabolic activity. Age, body size, and environmental temperature are the main factors affecting BMR.(Johnstone, Murison, Duncan, Rance, Speakman 2005)·(Blakemore, Burnett, Dahl 2010) The origins of endothermy in mammals are important events in vertebrate evolution, and BMR is the most reported estimate of energy expenditure in endotherms. According to the second law of thermodynamics, the core temperature drops when the body is exposed to low temperatures, and the BMR rises in mammals to maintain the core temperature.(Jeffery, Rovelli 2020) Over the course of the evolution of mammals, climate influences have generated changes in body structure.(Avaria-

Llautureo, Hernandez, Rodriguez-Serrano, Venditti 2019; Norin, Metcalfe 2019) Even after controlling for body size and composition, inhabitants living in warmer climates tend to have lower BMR values than those living in colder climates,(Froehle 2008) which is consistent with the world map representing MS incidence.(Walton, King, Rechtman, Kaye, Leray, Marrie, Robertson et al. 2020) It has been proven that BMR is positively associated with proinflammatory status among both normal weight and overweight people, suggesting that it is a marker of metabolic health, independent of obesity.(Drabsch, Holzapfel, Stecher, Petzold, Skurk, Hauner 2018) We imagine that BMR is better suited as a predictor of MS incidence.

Myelin comprises a membrane wrapped spirally around an axon, forming a sheath. This membrane is synthesized by oligodendrocytes in the CNS and interrupted at intervals by the nodes of Ranvier. Voltage-dependent sodium channels are clustered at the nodes of Ranvier, and the action potential jumps from one node to the next. This mode of saltatory conduction allows for the rapid transmission of the action potential along the axon. Accumulating evidence indicates that the increased energy demand for impulse conduction along excitable demyelinated axons and reduced axonal ATP production induces a chronic state of virtual hypoxia in chronically demyelinated axons.(Trapp, Stys 2009) The demyelinating state is associated with the inactivation of voltage-dependent potassium channels in oligodendrocytes.(Lubetzki, Zalc, Williams, Stadelmann, Stankoff 2020) It has been proven that myelination can be inhibited by blocking the action potential of neighboring axons or enhanced by increasing their electrical activity, clearly linking neuronal electrical activity to myelinogenesis.(Demerens, Stankoff, Logak, Anglade, Allinquant, Couraud, Zalc et al. 1996) Furthermore, the in vitro model has proven that a low glycolytic metabolic rate promotes oligodendrocyte survival; distinct energy utilization properties of human adult brain-derived oligodendrocytes and oligodendrocyte progenitor cells under conditions of metabolic stress can model the initial relapsing and subsequent progressive phases of MS.(Rone, Cui, Fang, Wang, Zhang, Khan, Bedard et al. 2016) In this MR study, we provide novel evidence that a high BMR is an independent causal risk factor in the demyelination of CNS; we believe that when the BMR increases beyond the compensable range, it might induce abnormal axonal electrical activity and thereby damage the myelin sheath. The specific mechanism needs to be further confirmed by scientific biophysical and biochemical experiments.

The principal determinant of BMR includes body mass and a variety of behavioral and ecological factors. (Johnstone, Murison, Duncan, Rance, Speakman 2005; Norin, Metcalfe 2019) Observational and prospective studies have demonstrated that individuals who are obese have an increased risk of MS.(Munger, Bentzen, Laursen, Stenager, Koch-Henriksen, Sorensen, Baker 2013),(Wesnes, Riise, Casetta, Drulovic, Granieri, Holmoy, Kampman et al. 2015) For smoking, our finding is consistent with the meta-analyses that have found an increased risk for MS in smokers versus nonsmokers.(Belbasis, Bellou, Evangelou, Ioannidis, Tzoulaki 2015; Degelman, Herman 2017) Our study indicates that smoking has a direct effect on BMR, which in turn increases the risk of MS, thus accounting for the lifetime effects of genetic variants on smoke. Environmental risk factors such as vitamin D deficiency might be related to reduced exposure to sunlight. Correction of vitamin D insufficiency could be important for the prevention of MS(Ascherio, Munger, White, Kochert, Simon, Polman, Freedman et al. 2014); sun exposure correlated with latitudes, which might also relate to BMR, as mentioned above. It appears that BMR and high-risk factors form part of the same causal biological pathway. The association of the selected genetic variants with these exposures might represent an example of pleiotropy due to shared biological underpinnings and thus does not bias the MR estimates. The identification of BMR as a causal susceptibility factor for MS may have important public health implications; people can change their food intake or activity patterns to counterbalance the risks in BMR elevation.

The advantages of our study include the application of two-sample MR to control for confounding factors, the use of large, novel GWAS datasets to improve power, and the alignment of our findings with previous epidemiologic risk factors and MR studies in MS. Our findings may contribute to the establishment of informed public health guidelines providing preventive measures against the adverse effects of BMR for prevention of MS. However, there are few reports focused on basic vivo experiments that can clarify how BMR mechanisms are correlated with demyelination in the CNS. In the future, basic medical experiments may pay greater attention to these aspects.

This study has some limitations. First, it focused on populations of European ancestry, which may restrict its generalizability. Second, we were unable to quantitatively analyze the factors that affect BMR to determine a precise cutoff due to the limitations of existing data.

In conclusion, there were primarily highlight from our finding that we provided evidence of an association between higher genetically predicted BMR and an increased risk of MS; specific OR values could predict the level of severity. Research on BMR will enable a greater appreciation of the genetic epidemiology of MS and has remarkable implications for preventive measures.

Declarations

Acknowledgments

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author on reason- able request.

Author Declarations

The authors declare that they have no conflict of interest. All participants provided written informed consent.

Standard protocol approvals, registrations, and patient consents

The data sources used in this study (IMSGC and MRC-IEU) obtained informed consent from all participants. Separate institutional review board approval was not required for this study.

Author Contributions

Chunxin Liu, Wei Qiu contributed equally to the study.

Conception and design: Chunxin Liu and Wei Qiu,.

Analysis and interpretation: Chunxin Liu, Yaxin LU and Jingjing Chen.

Data collection: Chunxin Liu, Yaxin LU and Jingjing Chen.

Critically revised the manuscript: Zifeng Liu and Yiqiang Zhan.

Obtained funding: Wei Qiu.

Overall responsibility: Zifeng Liu and Yiqiang Zhan

Ethics approval

Not applicable. Separate institutional review board approval was not required for this study.

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Figures

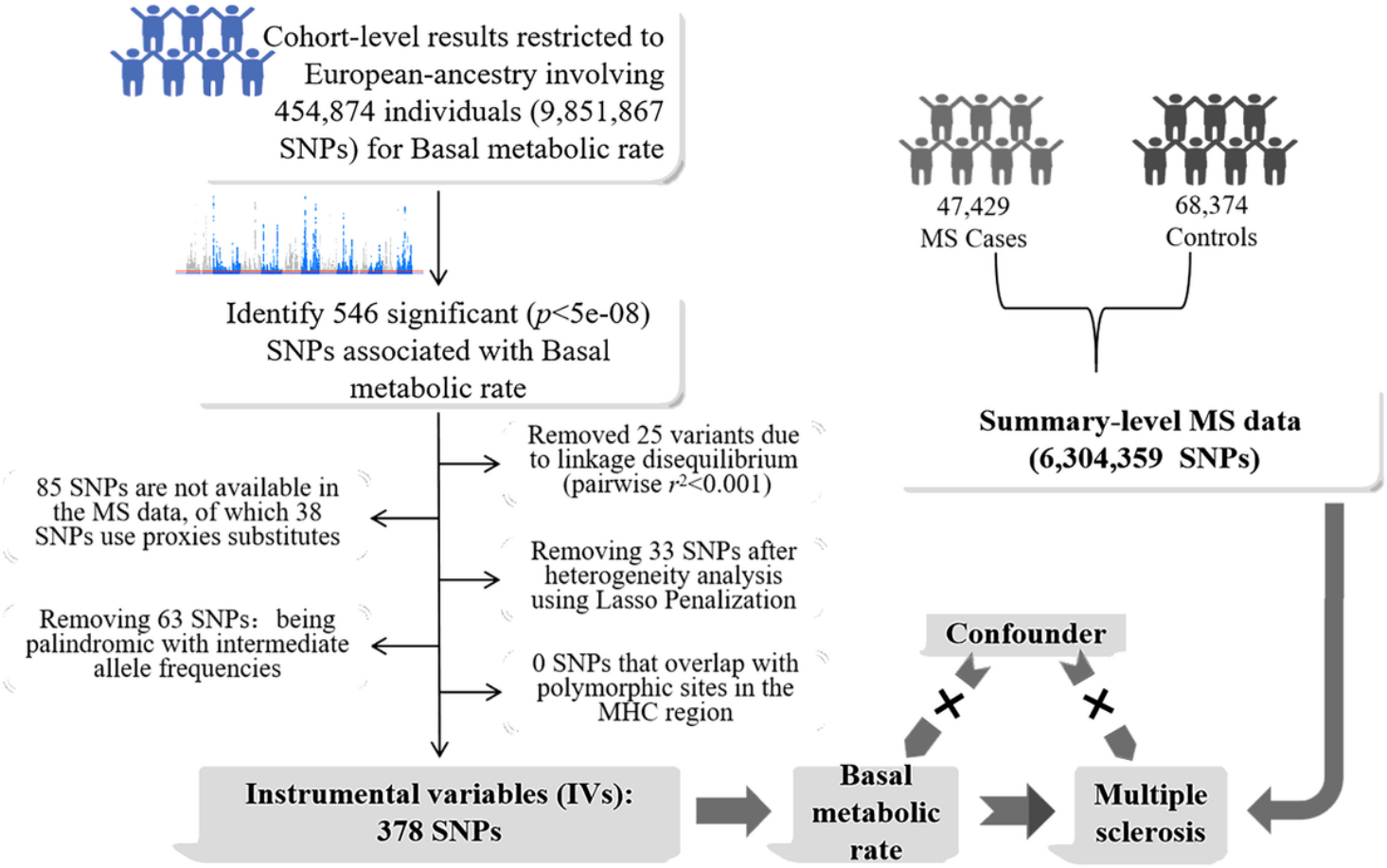

Figure 1

Schematic representation of the study.

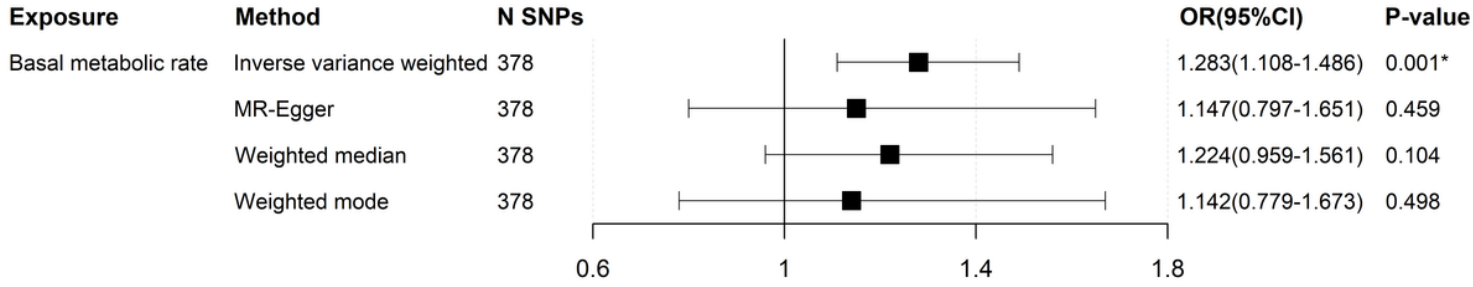

Figure 2

Causal effects from basal metabolic rate on multiple sclerosis *P-value<0.05, IVW=inverse variance weighted; # Heterogeneity exists between basal metabolic rate and multiple sclerosis, so Mendelian randomization was performed using the lasso method to eliminate heterogeneity (Q statistic=384.58, P=0.370).