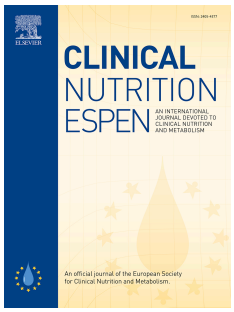

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Excess energy intake causally increases the blood pressure and hypertension risk: A Two Sample Mendelian Randomization Analysis

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Running title: Excess Energy Intake and Hypertension Risk: Causal Analysis

Abstract

Background/Aim: The impact of excess energy intake on blood pressure(BP) and hypertension(HTN) has not been extensively studied. This study aimed to evaluate the causal link between energy intake and systolic and diastolic BP(SBP and DBP) and HTN, using a Mendelian randomization(MR) approach.

Methods: We conducted an MR analysis using summary statistics from large-scale genome-wide association studies(GWAS) datasets of European ancestry. Several MR methods were applied, including inverse-variance weighted(IVW), weighted median and mode, and MR-Egger regression. Genetic variants associated with energy intake were obtained from a published GWAS of the UK Biobank(N=64,979). GWAS datasets for SBP, DBP, and HTN included 436,419; 436,424; and 361,194 individuals (1,237 cases and 359,957 controls), respectively, all from the UK Biobank. Effect estimates were reported as beta coefficients(β) with 95% confidence intervals(CIs) for continuous outcomes and odds ratios(ORs) with 95% CIs for binary outcomes.

Results: The IVW analyses indicated that each SD increase in energy intake was causally associated with one SD increase in SBP(β=0.093,95%CI:0.027–0.160,P=0.006) and DBP(β=0.070,95%CI:0.014–0.126,P=0.014), based on 10 and 8 included SNPs, respectively. These significant associations were confirmed by the weighted median MR method for SBP(β=0.096,95%CI:0.032–0.169,P=0.012) and DBP(β=0.077,95%CI:0.006–0.148,P=0.044). Furthermore, a causal relationship between energy intake and HTN was observed using the IVW(OR=1.004,95%CI:1.002–1.006,P=0.012) and the MR Egger method(OR=1.012,95%CI:1.004–1.020,P=0.045), based on 9 included SNPs. No evidence of weak instrument bias, heterogeneity, or horizontal pleiotropy was detected. The significant findings were consistent across most applied MR methods.

Conclusions: Our findings support a direct causal relationship between excess energy intake and both BP and HTN.

Keywords: Energy intake, blood pressure, Hypertension, Mendelian randomization**,** Causal association

Introduction

Hypertension (HTN), characterized by chronically elevated blood pressure (BP) levels, is a major public health issue that affects millions of people worldwide [1]. It poses a risk for cardiovascular diseases and other negative health consequences [2, 3]. The causes of high BP are multifaceted, with factors such as lifestyle choices, genetic predisposition, and dietary habits playing a role in its development [4]. Previous research highlights the role of dietary factors in the development and progression of HTN [5, 6]. Recently, caloric restriction has been under speculation as a promising nutritional strategy for the management of high systolic blood pressure (SBP), diastolic blood pressure (DBP), and HTN [7, 8]. Calorie intake is the most fundamental dietary factor and the primary source of the body's energy. However, most prior studies have focused on individual dietary components such as specific nutrients (e.g., carbohydrates [9], omega-3 fatty acids [10], sodium [11]) or dietary patterns rather than overall energy intake.

The effects of excess energy consumption on chronic conditions such as high BP and HTN, independent of body weight and the energy-providing nutrients themselves, remain poorly understood. Although calorie-restricted diets have consistently been associated with improvements in metabolic profiles, reductions in oxidative stress, and lower levels of inflammation, several studies have also shown that excessive energy intake can independently elevate oxidative stress and inflammatory markers and increase the risk of metabolic disorders [12-15]. At least three observational studies have reported a positive association between higher energy intake and increased HTN risk [16-18]. While analyzing individual nutrients remains important, it is equally essential to consider the practical challenges of implementing dietary changes, especially given the cost and accessibility of certain nutrients. Therefore, examining the overall effect of total energy intake on HTN is critical to ensure its role is not overlooked amid the focus on specific nutrients [19].

However, determining whether energy intake directly causes elevated BP has been challenging due to confounding variables and the potential for reverse causality in observational studies. To date, it remains unclear whether energy intake independently contributes to elevated BP or HTN risk. Given the limitations of observational research and the scarcity of causal evidence in the literature [20], this study aims to investigate the potential causal relationship between energy intake and HTN using a more robust analytical approach.

Mendelian randomization (MR) is a novel epidemiological method that uses genetic variants, specifically single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to assess causal relationships between exposures and health outcomes [21]. Unlike traditional observational studies, MR reduces bias from confounding and reverse causality, offering more reliable causal inferences. The growing availability of biobank and genome-wide association study (GWAS) data has enabled broader applications of MR to explore genetic contributions to common diseases [22]. A recent extension of MR, known as two-sample Mendelian randomization (TSMR), enhances this approach by using summary statistics from two independent samples, further strengthening the validity of causal inference [23].

Therefore, the present study employed TSMR analysis to examine the causal relationship between energy intake and BP as well as HTN, using genetic summary data from two large-scale GWASs.

Methods

Genome-wide association study (GWAS) statistics of exposure

SNPs related to energy intake were extracted from the UK Biobank, a large cohort of approximately 500,000 individuals aged 40-69 years that collects extensive genotype and phenotypic data [24]. Dietary intake was assessed using a web-based 24-hour dietary recall tool, *'Oxford WebQ'* [25, 26], which includes questions on the consumption of 206 food and

32 beverages over the previous 24 hours. To better estimate habitual intake, participants who provided an email address were invited to complete the 24-hour diet recall survey online on several occasions. Energy intake from dietary data was calculated based on the frequency, standard serving size, and nutritional composition of the reported foods. For this study, we used publicly available genome-wide association summary statistics for energy intake as a continuous variable from 64,979 participants of European ancestry of the UK biobank.

GWAS summary statistics of the outcome

In the present study, SBP, DBP, and HTN were used as outcome variables in the MR analysis. GWAS summary statistics for these outcomes were obtained from the UK Biobank [22]. In the UK Biobank, two BP measurements were taken after a 5-minute rest in a seated position, with at least a 1-minute interval between readings. Measurements were performed using an appropriately sized cuff and an Omron 705IT automatic digital BP monitor. The mean of the two readings was used to derive SBP and DBP values. For individuals with only one available reading, that single measurement was included in the analysis [27]. For HTN, we used GWAS results from the Neale Lab's analysis of UK Biobank phenotypes (Round 2), available at [http://www.nealelab.is/uk-biobank/]. The HTN phenotype was defined using electronic health records (EHRs) to identify cases of essential hypertension, based on the International Classification of Diseases, 9th Revision (ICD-9). The GWAS included 436,419 individuals for SBP, 436,424 for DBP, and 361,194 for HTN (1,237 cases and 359,957 controls), all of European ancestry.

Instrumental SNPs selection

The MR assumptions were considered for selecting SNPs as instrumental variables (IVs) (**Figure S1**). For extracting significant related SNPs with energy intake, we used a relaxed GWAS threshold to p-value $< 5 \times 10^{-6}$ because we observed any SNPs with higher significance

[28]. In the final sets, we performed linkage disequilibrium (LD) clumping restricted to $r^2 <$ 0.2 in a clumping distance = 1000 kb window to minimize correlations between the selected SNPs. The exposure and outcomes data were harmonized to ensure alleles were aligned, and the presence of ambiguous and/or palindromic variants was checked.

The associations of selected SNPs with other traits at genome-wide significance levels were checked using the PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk/). The F-statistics with the threshold of 10 (<10=weak IV, >10=strong IV), was applied for assessing the selected SNPs in terms of being weak instruments using the F-statistics [29]. The relevant information was extracted, including SNP, effect allele, non-effect allele, effect allele frequency, effect sizes, standard error, sample size, and p-value.

The core assumptions of Mendelian Randomization were carefully examined to ensure the validity of the selected instruments. In summary, MR depends on three main assumptions. First, the relevance assumption requires that the SNPs are strongly associated with the exposure, which we confirmed using F-statistics > 10. Second, the independence assumption indicates that the SNPs should not be associated with confounding variables, which we assessed using the PhenoScanner database and linkage disequilibrium clumping. Third, the exclusion restriction assumption states that the SNPs should influence the outcome only through energy intake and not through other pathways. We evaluated this assumption using the MR-Egger intercept, MR-PRESSO global test, RadialMR, and leave-one-out analysis, as illustrated in Supplementary Figure S1.

Statistical analysis

A two-sample MR analysis was conducted to evaluate the causal association of energy intake with SBP, DBP, and HTN. We considered the inverse variance weighted (IVW) method as the main analysis to estimate the associations of the IVs. Additionally, we conducted several

sensitivity analyses including MR-Egger, weighted median, and weighted mode estimators to address the validity and consistency of our results [30]. Moreover, several other MR methods, including the various IVW and median MR estimators, debiased inverse variance weighted, the Robust adjusted profile score (RAPS), the MR-Losso, and constrained maximum likelihood (MRcML) were performed to detect the robustness of our results [31].

The heterogeneity of IVs was assessed using Cochran's Q statistic and the I^2 index for MR-inverse-variance weighted analyses, and Rucker's Q statistic for MR-Egger [32]. To quantify horizontal pleiotropy, we used the MR-Egger method by intercept tests [33].

Several assessments were applied to detect the outliers SNPs and influential points in driving the analysis such as Cook's distance, MR-PRESSO, RadialMR (using Cochran's Q-statistic), Leverage test, Mendelian Randomization-Contour Enhanced Meta-Analysis (Mr-CML), and finally leave-one-out analysis as a sensitivity analysis to identify SNPs that significantly changes the estimated causal effect and have a large impact on the result. SNPs that were identified as outliers or influential points or had adverse effects in more methods were excluded from the analysis.

We drew a forest plot of MR for the association of each energy intake-related SNPs with SBP, DBP, and HTN. The Leave-one-out analysis and its plot were also performed to assess the influence of each SNP on the pooled causal estimates by systematically removing one SNP at a time [34]. In addition, we depicted a funnel plot to identify if the presence of directional pleiotropy can be observed, indicating a tendency for causal estimates from weaker variants to be biased in a particular direction (36).

All data analyses were carried out using the "TwoSampleMR", "MendelianRandomization", "MRPRESSO", "RadialMR", and " mr. raps" packages of the R4.3.1 software [20, 33, 35]. The measure of association was reported as a beta coefficient (β) 95% confidence interval (CI)

150 expressed as standard deviation (SD) change in SBP and DBP per one SD increment of the
151 energy intake. For HTN, the results were expressed as odds ratios (ORs) with 95% CIs,
152 reflecting the odds of HTN per one SD increase in energy intake.

153 To account for multiple testing, the Bonferroni correction was performed on the energy intake
154 association with three outcomes. So, a conservative corrected threshold was calculated (α =
155 0.05/3 outcomes=0.016), and considered P-values < 0.016 as strongly associated, and P-values
156 between 0.016 and 0.05 were regarded as suggestive evidence of associations.

157 To account for multiple testing across the three outcomes (SBP, DBP, and HTN), we applied
158 Bonferroni correction, resulting in a conservative adjusted threshold ($\alpha = 0.05/3 = 0.016$).
159 Although alternative approaches such as false discovery rate (FDR) may yield fewer
160 conservative cutoffs, Bonferroni was retained to enhance stringency and reduce the likelihood
161 of type I error. Accordingly, P-values < 0.016 were considered strongly associated, and those
162 between 0.016 and 0.05 were regarded as suggestive.

163 **Results**

164 ***Instrumental variables selection***

165 We used a relaxed genome-wide significance threshold ($P < 5\times10^{-6}$) for SNP selection due to
166 the absence of genome-wide significant variants ($P < 5\times10^{-8}$) for energy intake in the original
167 GWAS. Similar thresholds have been used in prior MR studies involving complex traits such
168 as dietary intake. Instrument strength was confirmed using F-statistics (all >10), and multiple
169 sensitivity analyses (MR-Egger, MR-PRESSO, RadialMR) were conducted to assess potential
170 bias and pleiotropy. From 9,851,867 SNPs of energy intake, we reached 41 SNPs after selection
171 based on $P< 5 \times 10-6$ and then 13 SNPs after LD clumping of r2<0.2. The range of the F
172 statistic was from 20.8 to 27.1 (the median of 23.3) for these SNPs all was >10 as the
173 conventional threshold, indicating that the instrument's bias could not have a significant effect

on estimating causal effects. All SNPs remained in the harmonizing step with outcomes. None of the SNPs were excluded due to being palindrome, and checks using the PhenoScanner database indicated that none were associated with BP or HTN, thereby minimizing concerns regarding pleiotropy. Moreover, no SNPs were located within the human leukocyte antigen (HLA) region. The Cochran heterogeneity test revealed significant heterogeneity for energy intake-SBP harmonized data (Q = 33.9, p=0.006) and energy intake-DBP (Q = 24.4, p=0.017), but not for energy intake-HTN (Q = 14.4, p=0.275). No evidence of directional pleiotropy was detected in any of the exposure–outcome associations (P>0.05).

Based on the results of different analyses to detect SNPs with potential outlier, influential, or adverse effects in our MR analyses, we excluded three SNPs for SBP (rs11224098, rs35237101, and rs752690); five SNPs for DBP (rs11224098, rs35237101, rs752690, rs12528606, and rs7911565); and four SNPs for HTN (rs35237101, rs13048538, rs45322636, and rs62347998). Consequently, we obtained 10, 8, and 9 SNPs for SBP, DBP, and HTN, respectively. The characteristics of identified SNPs for SBP, DBP, and HTN were provided in Supplementary Excel Files 1, 2, and 3, respectively. After excluding the mentioned SNPs, we repeated the analyses. We observed no significant heterogeneity among the remaining SNPs for energy intake-SBP (Q=15.8, p=0.070), energy intake-DBP (Q=3.4, p=0.845), and energy intake-HTN (Q = 6.6, p=0. 576). No significant pleiotropy was observed in any of the exposure-outcome datasets (P>0.05).

Mendelian Randomization and sensitivity analysis

The results of the MR analysis are indicated in **Table 1**. The findings of IVW analyses indicated that genetically predicted each SD increment in energy intake was causally associated with increased one SD in SBP (β= 0.093, 95% CI = (0.027 – 0.160), P=0.006) and DBP (β= 0.070, 95% CI = (0.014 – 0.126), P=0.014). These significant results were confirmed by the weighted

198 median method, which showed a positive association between energy intake and SBP (β =
199 0.096, 95% CI= (0.032 – 0.169), P=0.012) and energy intake and DBP (β = 0.077, 95% CI=
200 (0.006 – 0.148), P=0.044). However, the results of MR-Egger, simple, and weighted mode
201 methods showed no significant causal relation between energy intake with SBP and DBP
202 (P>0.05).

203 Furthermore, we observed a causal relationship between the increment of one SD of energy
204 intake with the odds of HTN by IVW (OR= 1.004, 95% CI = (1.002 – 1.006), P=0.012) and
205 MR Egger method (OR= 1.012, 95% CI = (1.004 – 1.020), P=0.045). However, this significant
206 association was not observed by the results of weighted median, simple mode, and weighted
207 mode methods(P>0.05).

208 A sensitivity analysis was performed on the relationship between energy intake and SBP using
209 other MR methods (Figure 1 and Supplementary Figure S2, A). Except for MR Egger and
210 model-based methods (with P-values>0.05), all applied methods showed a significant direct
211 causal association between energy intake and SBP (P-values<0.016 as the corrected threshold).

212 Moreover, a sensitivity analysis was conducted using other MR methods to assess the
213 relationship between energy intake and DBP (Figure 2 and Supplementary Figure S3, A). Of
214 the sixteen methods applied, only the MR Egger, Penalized MR-Egger, and mode-based
215 methods did not confirm a causal relation between one SD increment of energy intake and one
216 SD increase in DBP (most P-values were<0.016 as the corrected threshold).

217 For the energy intake-HTN relationship, sensitivity analysis using other MR methods
218 confirmed a direct causal association between one SD increment of energy intake and higher
219 odds of HTN in most methods (the majority of significant P-values were <0.016 as the
220 corrected threshold). However, the median-based methods, Robust IVWs, and Debised

Inverse-variance weighted did not show any significant causal association between energy intake and the odds of HTN (P-values > 0.05) (Figure 3 and Supplementary Figure S4, A).

Leave-one-out analysis was used to analyze the results of the IVW method. After removing each SNP individually, the results were consistent with the IVW method in causal effect analysis for energy intake association with SBP and DBP (Supplementary Figure S2 and S3, C), indicating that no single SNP affected the causal estimation results. However, the results of the leave-one-out analysis on selected SNPs for the energy-HTN MR showed that excluding rs149006866 resulted in the IVW result being statistically non-significant (see Supplementary Figure S4, C).

The funnel plot assessment of all outcomes showed no evident asymmetry in SNP distribution, indicating that directional and horizontal pleiotropy was not observed (see Supplementary Figures S2-S4, D).

Discussion

This study is the first to investigate the causal relationship between energy intake and BP using MR analyses with large GWAS summary statistics. Our findings suggest that genetically predicted higher energy intake is associated with elevated BP and an increased risk of HTN.

Although there have been studies investigating the relationship between dietary components, nutrients, food groups, and dietary patterns with HTN [36-39], research specifically focusing on the influence of calorie consumption as a significant factor on BP or HTN is limited and outdated. Some observational studies have explored the association between energy intake and BP or HTN from various perspectives. In a case-control study, Kazemian et al. found that women with high energy intake during pregnancy (>3,000 kcal/day) had more than a ninefold increased risk of developing gestational hypertension [18]. Other studies have highlighted the timing of calorie consumption as a relevant factor [17, 40]. A cohort study in the UK reported

245 that higher calorie intake at breakfast was associated with a lower prevalence of HTN, while
246 greater late evening calorie consumption correlated with increased BP and HTN risk [17].
247 Additionally, some investigations have examined how total energy intake may interact with
248 key nutrients that affect BP. For example, one study found that sodium's effect on BP was
249 modified by total energy intake. Specifically, a sodium intake of 2,300 mg/day increased BP
250 more in the context of a low-energy diet than in a high-energy one [41]. This suggests that total
251 energy intake may amplify or attenuate the influence of nutrients such as sodium, magnesium,
252 and potassium on BP regulation.

253 Moreover, genetic variations influence metabolic pathways involved in BP regulation and may
254 interact with energy intake. Certain genes associated with BP could increase the risk of
255 hypertension when combined with a high-energy diet. For example, variations in the catechol-
256 O-methyltransferase (COMT) gene have been linked to altered catecholamine levels, which
257 can affect sympathetic nervous system activity and, in turn, BP regulation. In a study by Htun
258 Nc et al., the Met allele of the rs4680 variant in the COMT gene was associated with higher
259 BP and a greater prevalence of hypertension. Notably, when individuals with this allele
260 consumed higher amounts of calories, the risk of hypertension was further elevated [42]. This
261 indicates that higher energy intake may increase HTN risk through interactions with
262 hypertension-related genetic variants.

263 Our MR study provides the first robust genetic evidence supporting a causal relationship
264 between higher energy intake and elevated BP, demonstrating that genetically predicted
265 increases in energy consumption significantly raise both SBP and DBP and also increasing
266 hypertension risk. Notably, our MR approach overcomes key limitations of prior nutritional
267 epidemiology by minimizing reverse causation and confounding—issues pervasive in
268 traditional observational studies. Mechanistically, these results suggest that chronic positive
269 energy balance may independently contribute to hypertension pathogenesis. Also, clinically,

these findings reinforce the importance of caloric restriction interventions for hypertension prevention, particularly in high-risk populations. Although, our MR study does not directly address biological pathways to illustrate potential links between energy intake and blood pressure, the finding that genetically predicted greater energy intake leads to higher BP aligns with established epidemiological evidence linking excess caloric consumption to HTN, likely mediated through mechanisms such as increased body weight, metabolic dysregulation, and vascular changes [43-46].

The link between obesity and the activation of the sympathetic nervous system and the renin-angiotensin system, both of which contribute to the development of HTN, is well established [45]. Some studies suggest that the effects of energy intake on BP are mediated by factors such as visceral fat accumulation, obesity, and insulin resistance. For example, increased energy intake can elevate visceral fat and insulin resistance, leading to higher levels of catecholamines and enhanced sympathetic activity, which in turn may raise BP [47]. However, excess calorie intake may also affect BP through alternative mechanisms, including mitochondrial dysfunction and oxidative stress. Overeating disrupts energy balance, overwhelms mitochondria, and increases the production of reactive oxygen species, which causes cellular damage [46, 48-50]. Diets high in fat and sugar can trigger chronic low-grade inflammation [51, 52], which further intensifies oxidative stress by disrupting the body's antioxidant defenses [53]. The expansion of adipose tissue also promotes the release of pro-inflammatory cytokines, known as adipokines, which amplify both oxidative stress and inflammation [54]. Oxidative stress and inflammation can damage the vascular endothelium, impair nitric oxide production, and reduce the ability of blood vessels to relax, resulting in persistent vasoconstriction and increased vascular resistance [43, 44]. Additionally, high energy intake may enhance sympathetic nervous system activity and catecholamine secretion, leading to further vasoconstriction and elevated BP [55, 56]. Although our study does not directly examine these

295 mechanisms, the observed causal relationship between energy intake and BP highlights the
296 importance of further mechanistic research.

297 ***Strengths and Limitations***

298 A key strength of our study is the use of the TSMR approach to explore the causal relationship
299 between calorie consumption and BP. To the best of our knowledge, this is the first study to
300 employ this approach in examining the association between energy intake and BP, offering
301 new perspectives on the potential impacts of energy consumption on BP regulation.
302 Furthermore, the substantial sample size drawn from the UK Biobank database adds strength
303 to our study. Compared to other dietary factors, energy intake tends to show relatively
304 consistent variability, which improves the accuracy and reliability of our estimates. This
305 stability contrasts with the greater fluctuations seen in other nutrient intakes, further
306 strengthening the precision of our analysis. Another advantage of our study is the use of precise
307 and reliable methods to measure BP.

308 Some limitations of this study should be considered. First, energy intake was calculated based
309 on data obtained from 24-hour dietary recalls, which may be subject to recall bias and may not
310 accurately represent long-term dietary habits. However, several key methodological strengths
311 help minimize these measurement errors. The energy intake data came from publicly available
312 genome-wide association summary statistics based on a large sample of 64,979 European-
313 ancestry participants from the UK Biobank. The large sample size helps reduce recall bias by
314 averaging out random errors, yielding more reliable population-level estimates than smaller
315 studies prone to individual reporting inaccuracies. Moreover, using a web-based 24-h dietary
316 assessment (Oxford WebQ) [25, 26], is an automated self-administered tool, resulting in reduce
317 social desirability bias by allowing unannounced recalls in neutral settings. This also
318 incorporate portion-size images, improving estimation accuracy. As a fully automated

platform, Oxford WebQ has the potential to revolutionize dietary assessment by enhancing the feasibility and cost-effectiveness of collection of high-quality dietary data [57]. Furthermore, the Oxford WebQ as a 24-h dietary assessment has been administered multiple times to UK Biobank participants that included questions on the consumption of 206 different food items and 32 types of beverages and focused on intake during the previous 24 hours. This detailed and repeated approach allows for the estimation of individual consumption amounts for each item separately, using grams or various household portion sizes. As a result, the total energy intake calculated from these food components achieves acceptable accuracy. Second, the relatively small number of HTN cases (1,237), identified based on ICD codes in electronic health records (EHRs), may underestimate the true prevalence of HTN. While this strict case definition improves diagnostic specificity, it may limit statistical power to detect small effect sizes. Nevertheless, the large control group and strict quality control measures mitigate this issue. Additionally, consistent results across multiple sensitivity analyses and the use of SBP and DBP as complementary outcomes strengthen the validity of our findings. Third, although Mendelian randomization can establish a causal relationship between energy intake and blood pressure, it cannot reveal the underlying biological mechanisms. Further experimental studies are needed to clarify how energy intake influences blood pressure regulation.

Conclusions

Our research provides evidence supporting a causal relationship between energy intake and BP. Although the observed effect sizes were modest at the individual level, they remain highly relevant from a public health perspective. Even a slight reduction in SBP at the population level has been associated with significant decreases in cardiovascular morbidity and mortality [58]. Therefore, controlling caloric intake, despite modest individual effects, represent an important public health strategy for BP control. However, these findings should be interpreted with caution due to the inherent limitations of Mendelian randomization studies and the complex

mechanisms underlying the relationship between energy intake and BP. Further research, including large prospective studies and well-designed RCTs, is necessary to validate the effects and clarify the mechanisms by which higher dietary energy intake increases HTN risk.

List of abbreviations

BP: blood pressure

CIs: confidence intervals

COMT: catechol-O-methyl transferase

DBP: diastolic blood pressure

EHRs: electronic health records

GWASs: genome-wide association studies

HTN: Hypertension

IVs: instrumental variables

IVW: inverse variance weighted

LD: linkage disequilibrium

MR: Mendelian randomization

MRcML: MR-Losso, and constrained maximum likelihood

Mr-CML: Mendelian Randomization-Contour Enhanced Meta-Analysis

OR: odds ratio

SBP: systolic blood pressure

SNPs: nucleotide polymorphisms

TSMR: Two-sample Mendelian randomization

IR: insulin resistance

ROS: reactive oxygen species

Ethics approval and consent to participate

The current analysis used published or publicly available summary data. No original data were collected for the present study. Ethical approval for each of the studies included in the present analysis can be found in the original publications, including informed consent from each participant. The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Data availability statement

Not applicable.

Declaration of competing interest

The authors declared that there is no conflict of interests.

Authors' contributions

F.T., **M.A.,** and **D.H.** contributed to the conception, design, and statistical analysis. **N.S., M.KJ., H.F., M.Z., and P.M.** contributed to manuscript drafting. **MS.D.** and **MR.V.** supervised the study. All authors approved the final version of the manuscript.

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Legend 1 to Figure 1. The beta coefficient and 95%CI for the causal relationship of energy intake with systolic blood pressure calculated by different MR methods

Legend 2 to Figure 2. The beta coefficient and 95%CI for the causal relationship of energy intake with diastolic blood pressure calculated by different MR methods.

Legend 3 to Figure 3. The odds ratio and 95%CI for the causal relationship of energy intake with hypertension calculated by different MR methods.

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Table 1. Two-sample MR of energy intake relationship with systolic blood pressure, diastolic blood pressure, and hypertension

Outcome	Nsnp	Methods	Beta	SE	P-value	OR	95%CI	P-value	Horizontal pleiotropy			Heterogeneity	
									Egger intercept	SE	P-value	Q	P-value
SBP	**10**												
		MR Egger	0.04	0.09	0.657				0.001	0.003	0.572	15.1	0.055
		Weighted median	0.09	0.03	**0.012**								
		IVW	0.09	0.03	**0.006**							15.8	0.070
		Simple mode	0.10	0.06	0.177								
		Weighted mode	0.10	0.06	0.150								
DBP	**8**												
		MR Egger	0.11	0.07	0.176				-0.001	0.002	0.533	2.96	0.812
		Weighted median	0.07	0.03	**0.044**								
		IVW	0.07	0.02	**0.014**							3.40	0.845
		Simple mode	0.08	0.05	0.187								
		Weighted mode	0.08	0.06	0.218								
Hypertension	**9**												
		MR Egger	0.01	0.004		**1.012**	**(1.004, 1.020)**	**0.045**	-0.0002	0.0001	0.146	3.95	0.784
		Weighted median	0.001	0.002		1.001	(0.998, 1.003)	0.685					
		IVW	0.004	0.001		**1.004**	**(1.0007, 1.0073)**	**0.012**				6.63	0.576
		Simple mode	0.000	0.003		1.004	(0.996, 1.013)	0.924					
		Weighted mode	0.000	0.004		1.000	(0.992, 1.009)	0.927					

MR; Mendelian randomization, SBP; Systolic blood pressure, DBP; Diastolic blood pressure, IVW; Inverse variance weighted.

Figure 1

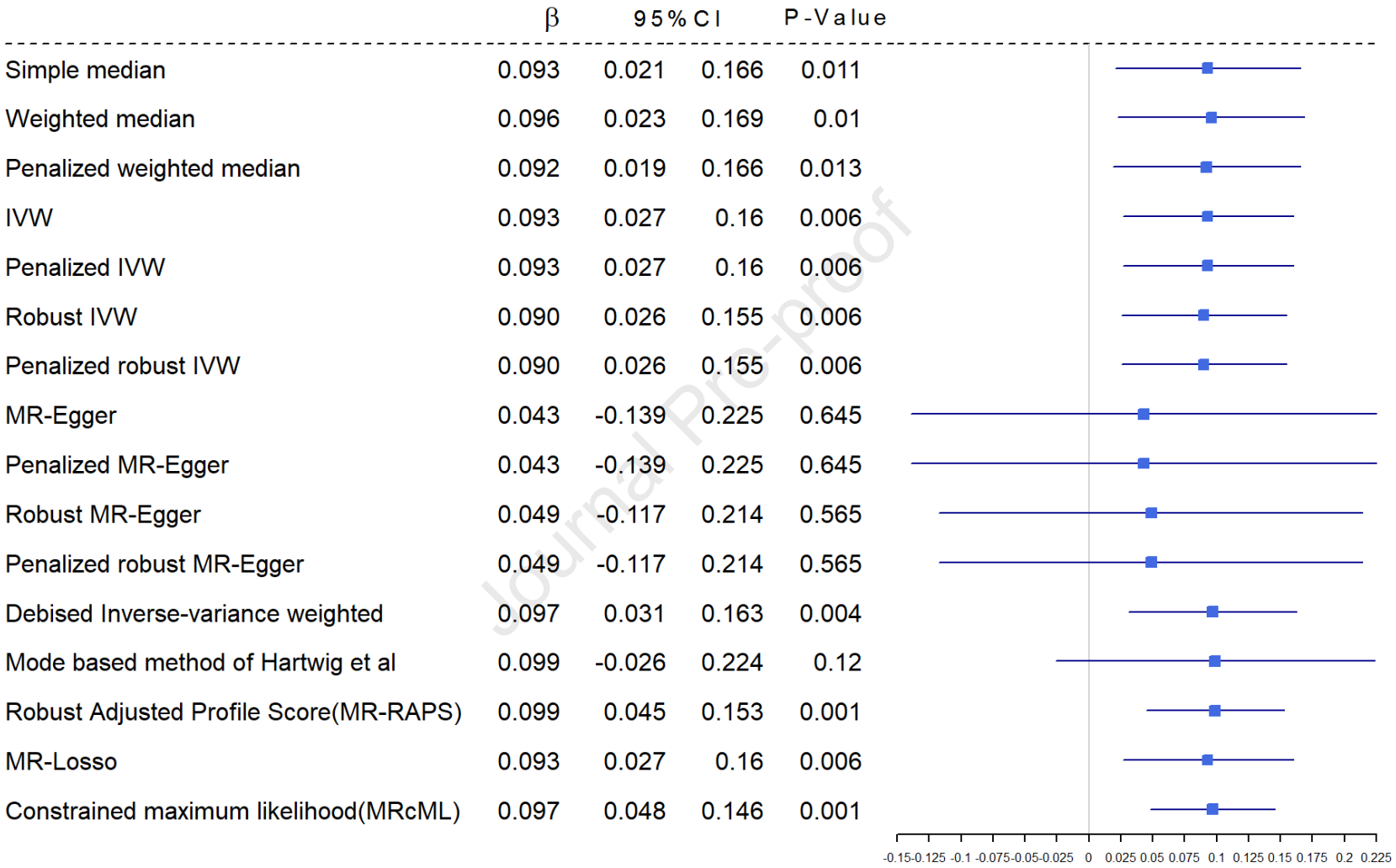

Figure 2

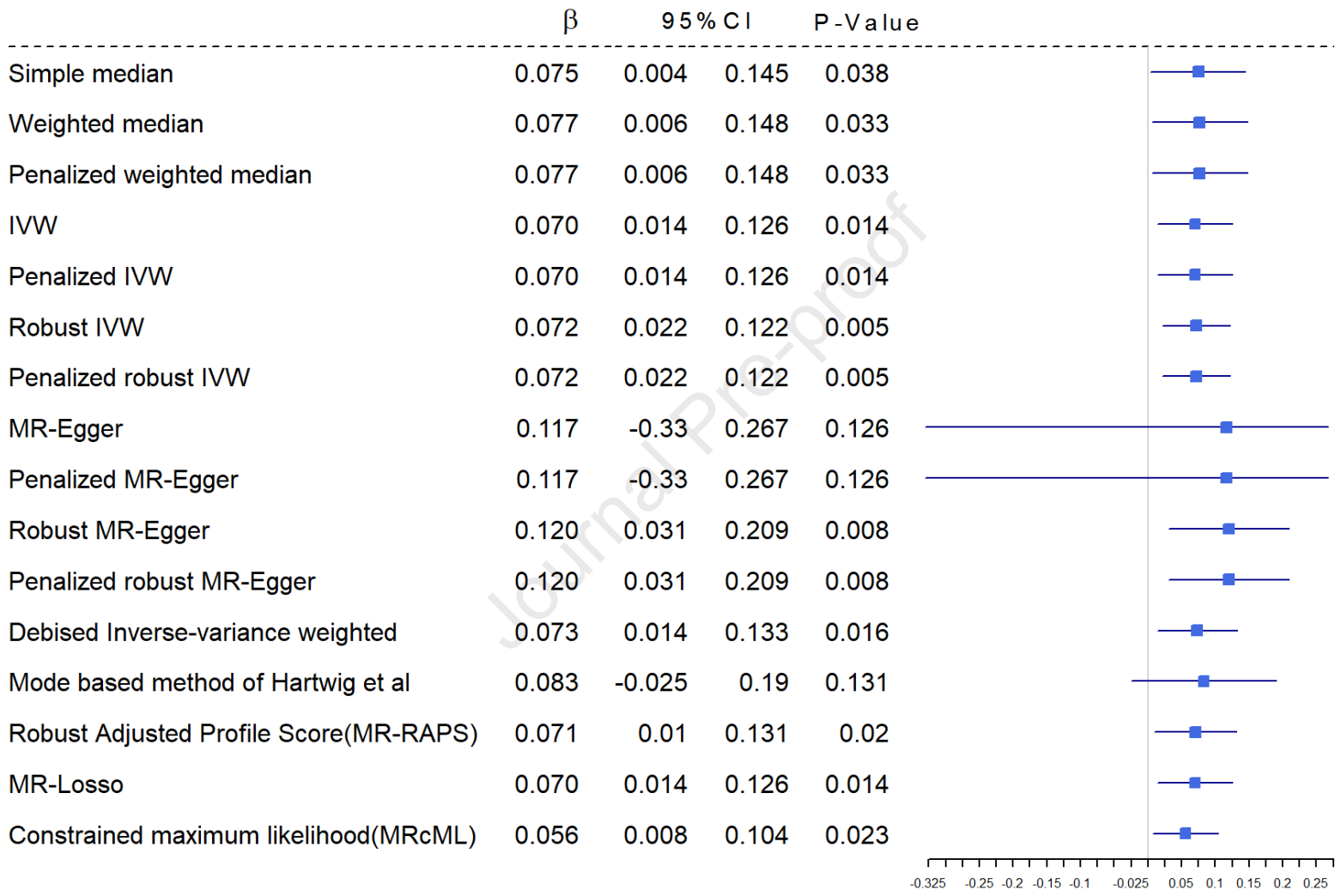

Figure 3