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Relación causal entre la ingesta de té y la densidad mineral ósea a diferentes edades: un estudio de aleatorización mendeliana

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ABSTRACT

Introduction: bone mineral density (BMD) is strongly associated with the risk of osteoporosis and fractures. Furthermore, dietary tea consumption also has a great impact on the variation in BMD. The pathway mechanisms from tea consumption to BMD are not well known. Therefore, we applied a two-sample Mendelian randomization (MR) approach in an attempt to explore the causality between tea

consumption and BMD. And then examine whether the effects of tea intake on BMD are specific across different age groups.

Methods: we investigated the relationship between tea consumption and BMD using a two-sample Mendelian randomization analysis, utilizing 31 single nucleotide polymorphisms (SNPs) related to tea intake from pooled data from a gene-wide association study (GWAS) of 447,485 British Biobank of European Origin participants, with BMD derived from a meta-analysis of total body BMD and age-specific effects in the Lifelong Genetic Cohort Study (n = 66,628). Causal analysis between tea intake and BMD was performed using MR-Egger, inverse variance weighting (IVW), weighted median, and weighted mode.

Results: in IVW, tea consumption has a positive causal effect on total body BMD. However, in different age groups, BMD has a positive effect only within the 45-60-year group. There is no genetic pleiotropy effect of tea intake can have an effect on systemic BMD or among the five different age groups. The Cochran Q statistic and MR-Egger regression were applied to calculate heterogeneity in the IVW method, and no significant heterogeneity was indicated.

Conclusions: the results of the MR analysis showed a positive causal effect of tea intake on total body BMD, whereas among the different age groups, tea intake positively affected BMD only in the 45-60 age group, which implies that tea is beneficial in maintaining or increasing BMD in this age group and may reduce osteoporosis and fracture risk.

Keywords: Mendelian randomization. Tea intake. Bone mineral density.

RESUMEN

Introducción: la densidad mineral ósea (DMO) está fuertemente asociada con el riesgo de osteoporosis y fracturas. Además, el consumo de té dietético también tiene un gran impacto en la variación de la DMO. Los mecanismos de la vía desde el consumo de té hasta la DMO no son bien conocidos. Por lo tanto, aplicamos un enfoque de aleatorización mendeliana (RM) de dos muestras en un intento de explorar la causalidad entre el consumo de té y la DMO. Y luego examinar si los efectos de la ingesta de té en la DMO son específicos en diferentes grupos de edad.

Métodos: investigamos la relación entre el consumo de té y la DMO utilizando un análisis de aleatorización mendeliana de dos muestras, utilizando 31 polimorfismos de un solo nucleótido (SNP) relacionados con la ingesta de té a partir de datos agrupados de un estudio de asociación de genes (GWAS) de 447.485 participantes del Biobanco Británico de Origen Europeo, con la DMO derivada de un metaanálisis de la DMO corporal total y los efectos específicos de la edad del Estudio de Cohorte Genética de por Vida (n = 66 628). El análisis causal entre la ingesta de té y la DMO se realizó mediante RM-Egger, ponderación de varianza inversa (IVW), mediana ponderada y modo ponderado.

Resultados: en IVW, el consumo de té tiene un efecto causal positivo sobre la DMO corporal total. Sin embargo, entre los diferentes grupos de edad, la DMO tiene un efecto positivo solo en el grupo de 45 a 60 años. No existe un efecto de pleiotropía genética de la ingesta de té que pueda tener un efecto sobre la DMO sistémica o entre los cinco grupos de edad diferentes. Se aplicaron el estadístico Q de Cochran y la regresión MR-Egger para calcular la heterogeneidad en el método IVW, y no se indicó ninguna heterogeneidad significativa.

Conclusiones: los resultados del análisis de RM mostraron un efecto causal positivo del consumo de té sobre la DMO corporal total, mientras que, entre los diferentes grupos de edad, el consumo de té afectó positivamente la DMO solo en el grupo de 45-60 años, lo que implica que el té es beneficioso para mantener o aumentar la DMO en este grupo de edad y puede reducir el riesgo de osteoporosis y fractura.

Palabras clave: Aleatorización mendeliana. Ingesta de té. Densidad mineral ósea.

INTRODUCTION

Bone mineral density (BMD) is closely related to human health, especially its decline, which leads to osteoporosis and further increases the risk of fracture. Based on the Centers for Disease Control's NHANES data from 2005-2010, it is estimated that more than 9.9 million Americans have been diagnosed with osteoporosis, and 43.1 million have low BMD (1). Patients with osteoporosis are at a 40 % risk of fracture, which results in limited mobility and a severely degraded quality of life (2,3). With increasing age, bone mineral density generally tends to decline, while the prevalence of osteoporosis is estimated at 58 % in men aged over 64 years and 50 % in postmenopausal women (4). Low BMD is a key preventable risk factor for fracture (5). Although BMD is highly heritable (6) and the decline in BMD due to aging appears to be beyond our ability to alter, lifestyle factors can be modified to optimize BMD and reduce the fracture risk (7).

Daily dietary habits play a significant role in the alterations of bone

mineral density, with tea consumption being a notable factor. Tea contains various beneficial active substances, including tea polyphenols, caffeine, theanine, theanosine, and thean polysaccharides (8). Several studies have demonstrated that moderate tea consumption is advantageous for bone health (9,10), with tea polyphenols promoting skeletal well-being through direct antioxidant effects (11). Additionally, the ellagic acid present in tea counteracts some of the deleterious changes in bone caused by Cd and Pb in a dose-dependent manner by reducing exposure (12). However, studies assessing the association between tea consumption and BMD have yielded inconsistent results (13). One meta-analysis did not support this causal relationship (14), and some studies suggest that caffeine may have biological effects that adversely affect BMD (15). Therefore, the impact of tea consumption on bone health requires further in-depth exploration, including investigations into the underlying mechanisms, the quantity of tea consumed, and the duration of consumption.

Mendelian randomization (MR) is an approach that uses genetic variation as an instrumental variable to investigate causal relationships between modifiable risk factors and outcomes of interest. One of the main strengths of MR is its ability to overcome confounding and reverse causation, which is a common problem in observational studies (16). In this study, we adopted a two-sample Mendelian randomization approach using genome-wide association study (GWAS) summary statistics to investigate the relationship between tea intake and total body bone mineral density (TB-BMD), and further explore the causal relationship with BMD in different age groups (0-15; 15-30; 30-45; 45-60; over 60).

METHODS

Study design

This study employed two-sample MR to explore the relationship between tea intake and BMD, utilizing genome-wide association study (GWAS) summary statistics. In the MR analysis, tea intake was selected as the risk factor, while total body bone mineral density and changes in BMD at different ages were chosen as outcomes (Fig. 1). The study aimed to assess the causal relationship between tea intake and changes in BMD, as well as the specificity of different age groups. No ethical approval was required because publicly available data were used.

Data sources

Summary statistics of exposures and outcomes were obtained from the MRC IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/), which provides access to data through R packages for Mendelian randomization, genetic colocalization analyses, genetic correlations, and motif visualization (17). The GWAS dataset of exposure factor tea intake (ukb-b-6066) was obtained from the UK Biobank, which included sample sizes of 9,851,867 SNPs and 447,485 European pedigrees, with summary data on endpoints taken from the meta-analysis of the Whole Life Genetic Association Study on Whole Body BMD and the Age-Specific Effectiveness evaluation (18), this analysis included 56,284 individuals from European populations, and the five age groups comprised 66,628 individuals, predominantly Europeans (86 %), with a small proportion from US-Australian populations (14 %) (0-15 years: n = 11,807; 15-30 years: n = 4,108; 30-45 years: n = 10,062; 45-60 years: n = 18,805; 60 years and above: n = 22,504). A summary of the datasets used in this study is detailed in table I. In

clinical practice, regional bone mineral densities (aBMD) such as lumbar spine, total hip, femoral neck, and spine are commonly measured using dual-energy X-ray absorptiometry (DXA) (19) to assess the skeletal status of patients with or without osteoporotic fracture (20). The DXA measurement of TB-BMD is also used as a surrogate indicator of hip and spine BMD to draw conclusions about fracture risk (21). To comprehensively explore the overall effect of tea on human BMD, this study used TB-BMD as an analytical index, rather than limiting the analysis to specific sites like the hip and spine.

Statistical analysis

Selection of instrumental variables

In this study, we carefully selected instrumental variables (IVs) based on strict criteria, and the selected SNPs had to fulfill three indispensable assumptions: association, independence, and exclusivity (Fig. 1). SNPs were considered valid IVs if they showed a significant genome-wide association with exposure (p < 5e-8). Removing SNPs with an r2 greater than 0.001 linkage disequilibrium (LD) with the most significant SNP in the 10,000 kb range. We obtained summary statistics for 41 single nucleotide polymorphisms (SNPs).

The proportion of explained by each SNP was calculated, and the F statistic was computed to assess the strength of the IV (22). F > 10 indicates that the assumption of association is met, meaning the selected genetic variant is not a weak instrumental variable and there is no bias in the results. The F statistic was computed using the formula

$$F = \frac{(N-k-1)}{k} \times \frac{R^2}{(1-R^2)}$$

where k denotes the number of SNPs used in the analyses. The r² reflects the proportion of variance in the exposed variable that can be explained by the SNPs. The R² was calculated using a formula

$$R^2 = \frac{2\times\beta^2\times EAF\times(1-EAF)}{2\times\beta^2\times EAF\times(1-EAF)+2\times SE^2\times N\times EAF\times(1-EAF)}$$

where β denotes the effect size of the SNP, EAF denotes the minor allele frequency, SE² denotes the standard error of the effect size, and N denotes the total number of individuals in the GWAS study (23).

MR analysis

We investigated the causal relationship between tea intake and BMD at different ages using several different MR methods. Inverse variance weighting (IVW) was the most widely used method in MR analysis with random and fixed effects, and MR-Egger, weighted median, and weighted mode were also applied to assess the level multivariate validity of selected SNPs. A *p*-value of less than 0.05 was considered significant for the causal effect of exposure on the outcome, as well as for calculating the effect estimates reported in thermodynamics (OR) and the corresponding 95 % confidence interval (CI). Associations were considered statistically significant if all *p*-values for IVW were less than 0.05, and the results of the MR-Egger, Weighted median, and Weighted mode methods were consistent with IVW. R (version 4.3.1) and the R package "TwoSampleMR" were used for all statistical analyses in the MR analysis.

Heterogeneity analyses were performed using MR-Egger and IVW methods to calculate Cochran's Q statistic. *p*-values > 0.05 indicated no heterogeneous associations. Leave-one-out analyses were performed to assess the effect of individual SNPs on the causal effect of exposure on outcome. In the presence of heterogeneity, causality was estimated using a random-effects IVW approach. The MR-Egger method was used to test for pleiotropic effects in sensitivity analyses, and directional pleiotropy was assessed by estimating the deviation of the MR-Egger intercept from zero, $p > 0.05$ indicating that there was no potential for pleiotropy in IV (24). If horizontal pleiotropy was present, the causal effect was adjusted using the Causal Analysis Using Summary Effect (CAUSE) package to remove SNPs with horizontal multiplicity (25).

RESULTS

Instrumental variable

We identified a total of 41 SNPs associated with tea intake through the MR analysis process, and supplementary table I lists detailed information about each SNP, including chromosomal location, effector allele (EA) and effector allele frequency (EAF). Estimates of the association of each SNP with tea intake and BMD at each age are also shown, including β-values, standard errors (SE) and *p*-values. After excluding 10 SNPs associated with confounders (hypertension, BMI, smoking) using the Phenoscanner database, we ultimately included 31 SNPs as instrumental variables (Supplementary Table II). SNPs that did not meet the inclusion criteria were excluded at all ages, and the remaining IVs obtained, without the effect of linkage disequilibrium (r2 = 0.001, kb = 10,000), reached the genome-wide significance level ($p < 5e-8$), with all F statistics > 10 and no weak instrumental

variable bias.

Mendelian randomization results

We carried out two-sample MR across different age groups, from IVW, there was a positive causal effect between genetically predicted tea intake and TB-BMD, with a positive effect of (p = 0.018) seen as shown in table II. During the age-specific effect of BMD, according to the IVW analysis, it has been shown that there was no statistically significant causal relationship of tea intake on BMD in most of the considered age groups with OR greater than 1. Only the age group 45-60 years showed significant effect (p = 0.011), remaining groups didn't show the statistically significant evidence of effect on BMD. Similar results were observed in the MR-Egger, weighted median, and weighted mode analyses (Table II, Fig. 2), and a scatter plot of these results is shown in figure 3.

Heterogeneity test and pleiotropy analysis

In exploring the causal relationship between tea intake and TB-BMD, the MR-Egger and IVW methods, according to Cochran's Q test, showed $p > 0.05$, indicating no heterogeneity among SNPs and no possibility of genetic pleiotropy. In MR-Egger regression, the intercept term indicated no horizontal pleiotropy (Egger Intercept: 0.002, p-value: 0.673). The funnel plot (Fig. 4) was visually symmetrical, also indicating that pleiotropy had not been established. There was no heterogeneity in the Cochran's Q test across different age groups ($p >$ 0.05). All tests of MR-Egger and leave-one-out analyses were negative (p-value of MR-Egger intercept > 0.05) (Table II), indicating that our MR results were not biased by horizontal pleiotropy. Using the leave-one-out test (Fig. 5), the overall error line did not change significantly

after excluding each SNP, and the overall risk estimate was not significantly affected by any single SNP. This suggests that there were no unusually significant SNPs, the choice of instrumental variables in this study was justified.

DISCUSSION

In the present study, we investigated the effect of tea intake on TB-BMD by using a two-sample MR analysis with large-scale GWAS pooled data and further explored whether the effect was age-specific. Our findings indicated that genetically predicted increases in tea intake were positively correlated with increases in TB-BMD. This suggests that perhaps a trend exists in which the consumption of tea has a beneficial effect on BMD, and the average BMD of the tea drinkers was about 5 % higher compared to that of the non-tea drinkers (26). In looking at age group specificity more in-depth, our study showed a significantly positive causal relationship between levels of tea intake and BMD in people aged 45 to 60 years. This means that the increased intake of tea is in favor of maintaining or increasing BMD within this age group, and that this positive relationship might extend to a protective relationship of tea against fracture risk. However, this was not statistically significant in other age groups.

Our findings are in agreement with many previous studies (27) in that tea consumption has a positive effect on bone mineral density. Tea is rich in polyphenols, flavonoids, and alkaloids, which may improve the antioxidant capability of the body, reduce oxidative stress damage, and exert positive effects on bone metabolism (25). Tea polyphenols promote osteoclastogenesis and inhibit osteoclast formation by modulating growth factors, cytokines, chemokines, and their

receptors, and moderate intake of tea polyphenols can reduce bone loss and prevent microstructural deterioration, hence benefiting bone health (28). Flavonoids and catechins are the main constituents of tea polyphenols, and evidence suggests that flavonoid-rich foods may be associated with bone loss and fracture outcomes, with women with the highest flavonoid intake having the lowest risk of osteoporotic and hip fractures (29). Catechins exhibit a unique and powerful role in neutralizing free nitrogen and oxygen radicals owing to their antioxidant properties, scavenging a variety of reactive oxygen species, and inhibiting the generation of free radicals and lipid peroxidation, thus exerting a protective effect under a variety of physiological conditions (30). The effect of caffeine in tea on BMD remains controversial, with one cross-sectional study suggesting that caffeine intake may be beneficial for lumbar spine BMD in women aged 30-39 years (31). However, in a prospective cohort study of Swedish women aged 40-75 years it was noted that caffeine-containing tea was not significantly associated with fracture risk (32). Caffeine may also attenuate the benefits of other bioactive components in tea (33). The pharmacological relationship between caffeine and BMD is through nonspecific antagonism of adenosine receptors, which stimulate adenosine A2A and A2B receptors to activate osteoblasts and inhibit osteoclast differentiation to induce bone formation. Thus, competitive inhibition of adenosine A2 caffeine receptors inhibits bone formation and promotes bone resorption. However, antagonism of adenosine A1 receptors may have the opposite effect. Caffeine may also affect BMD through disturbances in calcium metabolism, altered vitamin D responses, and other mechanisms (34). Inconsistent findings may be due to individual differences in the response to caffeine; therefore, caffeine intake in

the diet should be carefully considered in light of individual health and genetic factors.

This study possesses several strengths. First, the MR study design minimizes residual confounding and reverse causation, which can exist in traditional observational studies. Second, using summary-level data and a sufficient number of cases, along with funnel plots and MR-Egger to test for potential horizontal pleiotropy and outliers, greatly improved the statistical power to detect causal effects. Third, all studies were genome-controlled, indicating that the results are less likely to be affected by genome inflation. Fourth, while previous studies focused on older age groups, our study targeted the entire age range. These results contribute to a better understanding of the role of tea intake in BMD research progression, facilitating future clinical trials for treating osteoporosis and providing lifestyle advice for the general public.

First and most important, the low statistical power in analyzing the effect of exposure factors on BMD across different age groups is the biggest limitation of the study. Without information on different types of tea, for example, it was impossible to know if these might have different effects. Third, though tea intake showed a positive effect on BMD across the entire population, it was statistically significant only for the 40-65 age group. Thus, the specific effect of tea intake on BMD requires further investigation. Fourth, most of the analysis in this study was based on available summary statistics; thus, it was not possible to stratify by gender, which might make it hard to draw any direct influence of gender on the causal relationship between tea intake and whole-body BMD. Besides, because of the lack of individual information, it was impossible to estimate the accurate sample overlap between exposure and outcome.

In conclusion, MR analysis showed that tea intake is positively associated with BMD in the overall population and especially in the age group of 45-60 years in our study. It may be useful to resolve some of the problems with a decrease in BMD in the middle-aged and aged populations. Our study also has limitations, and further studies need to be done to observe the association in other age groups.

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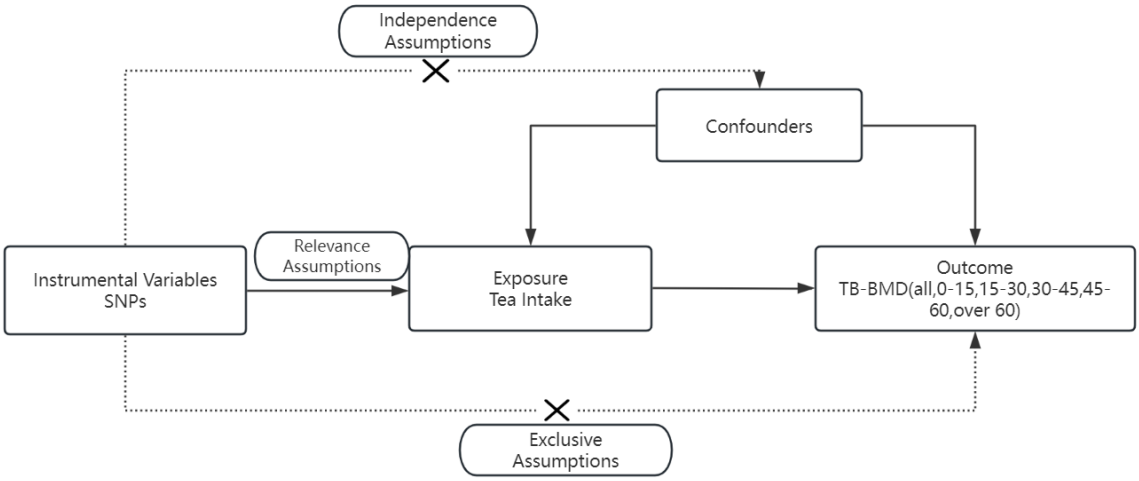

Figure 1.

Exposure	outcome.BMD.by.age.	method	nSNP	P.value	OR(95%CI)
Tea Intake	Total body bone mineral density	MR Egger	40	0.652	1.10(0.73 to 1.66)
		Weighted median	40	0.074	1.18(0.98 to 1.41)
		Inverse variance weighted	40	0.155	1.14(0.95 to 1.35)
		Weighted mode	40	0.094	1.18(0.98 to 1.43)
	15 or less	MR Egger	39	0.558	0.84(0.46 to 1.51)
		Weighted median	39	0.564	1.11(0.77 to 1.61)
		Inverse variance weighted	39	0.157	1.20(0.93 to 1.55)
		Weighted mode	39	0.680	1.09(0.73 to 1.63)
	15-30	MR Egger	40	0.800	1.16(0.38 to 3.50)
		Weighted median	40	0.497	1.28(0.63 to 2.61)
		Inverse variance weighted	40	0.977	0.99(0.63 to 1.57)
		Weighted mode	40	0.575	1.35(0.48 to 3.77)
	30-45	MR Egger	39	0.358	1.48(0.65 to 3.37)
		Weighted median	39	0.075	1.47(0.96 to 2.24)
		Inverse variance weighted	39	0.347	1.18(0.83 to 1.68)
		Weighted mode	39	0.092	1.66(0.93 to 2.94)
	45-60	MR Egger	39	0.333	1.29(0.77 to 2.16)
		Weighted median	39	0.025	1.43(1.04 to 1.96)
		Inverse variance weighted	39	0.007	1.36(1.09 to 1.70)
		Weighted mode	39	0.064	1.39(0.99 to 1.95)
	60 or more	MR Egger	40	0.778	1.08(0.62 to 1.90)
		Weighted median	40	0.920	0.98(0.74 to 1.31)
		Inverse variance weighted	40	0.720	0.96(0.75 to 1.22)
		Weighted mode	40	0.714	0.94(0.68 to 1.30)

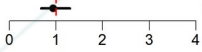

Figure 2. Forest plot of the MR analysis results.

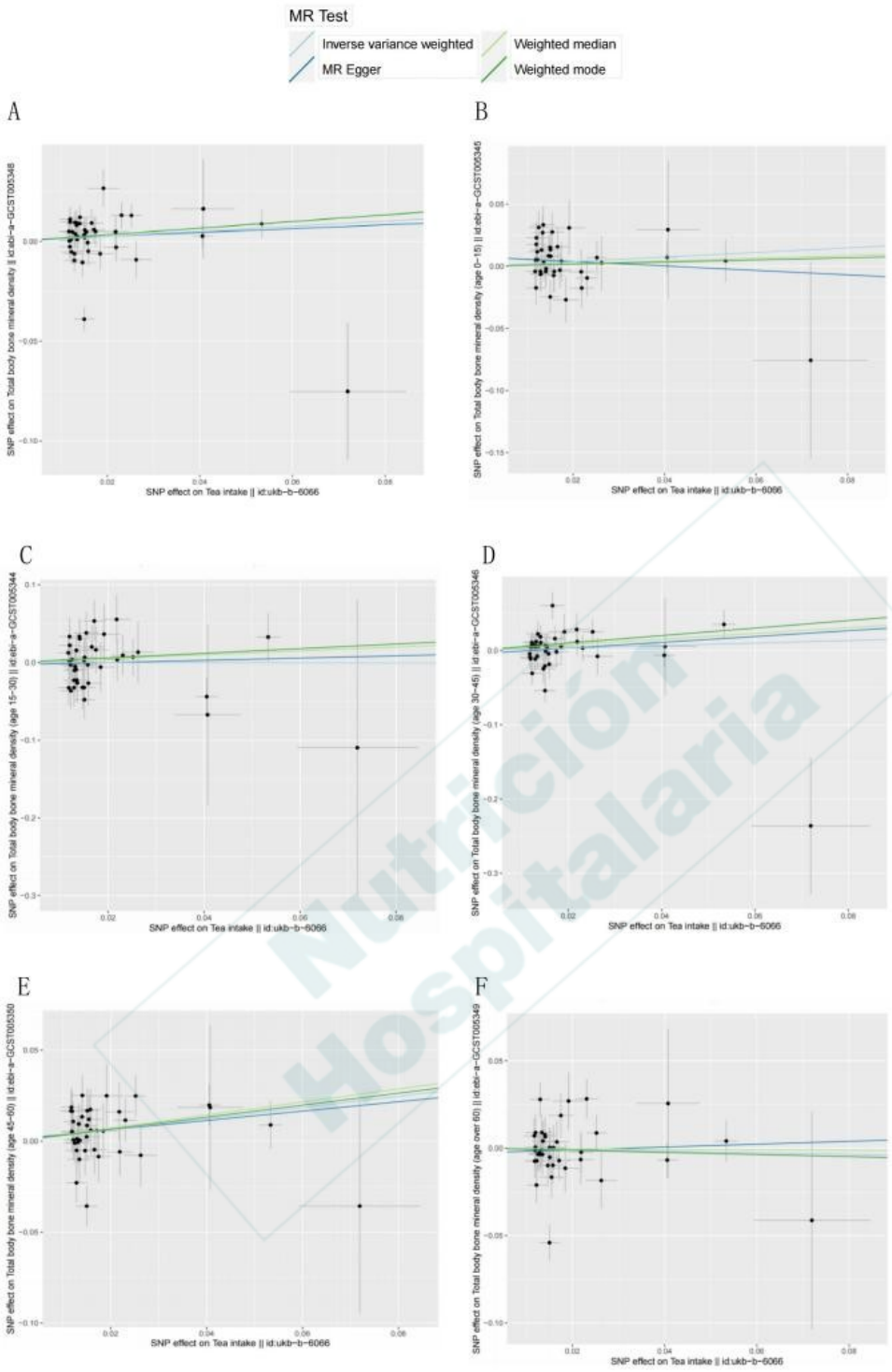

Figure 3. Scatter plot of genetic associations comparing tea intake to the genetic associations with total body bone mineral density. A. Total body bone mineral density. B. Total body bone mineral density (age, 0-15). C. Total body bone mineral density (age, 15-30). D. Total body bone mineral density (age, 30-45). E. Total body bone mineral density

(age, 45-60). F. Total body bone mineral density (age over 60).

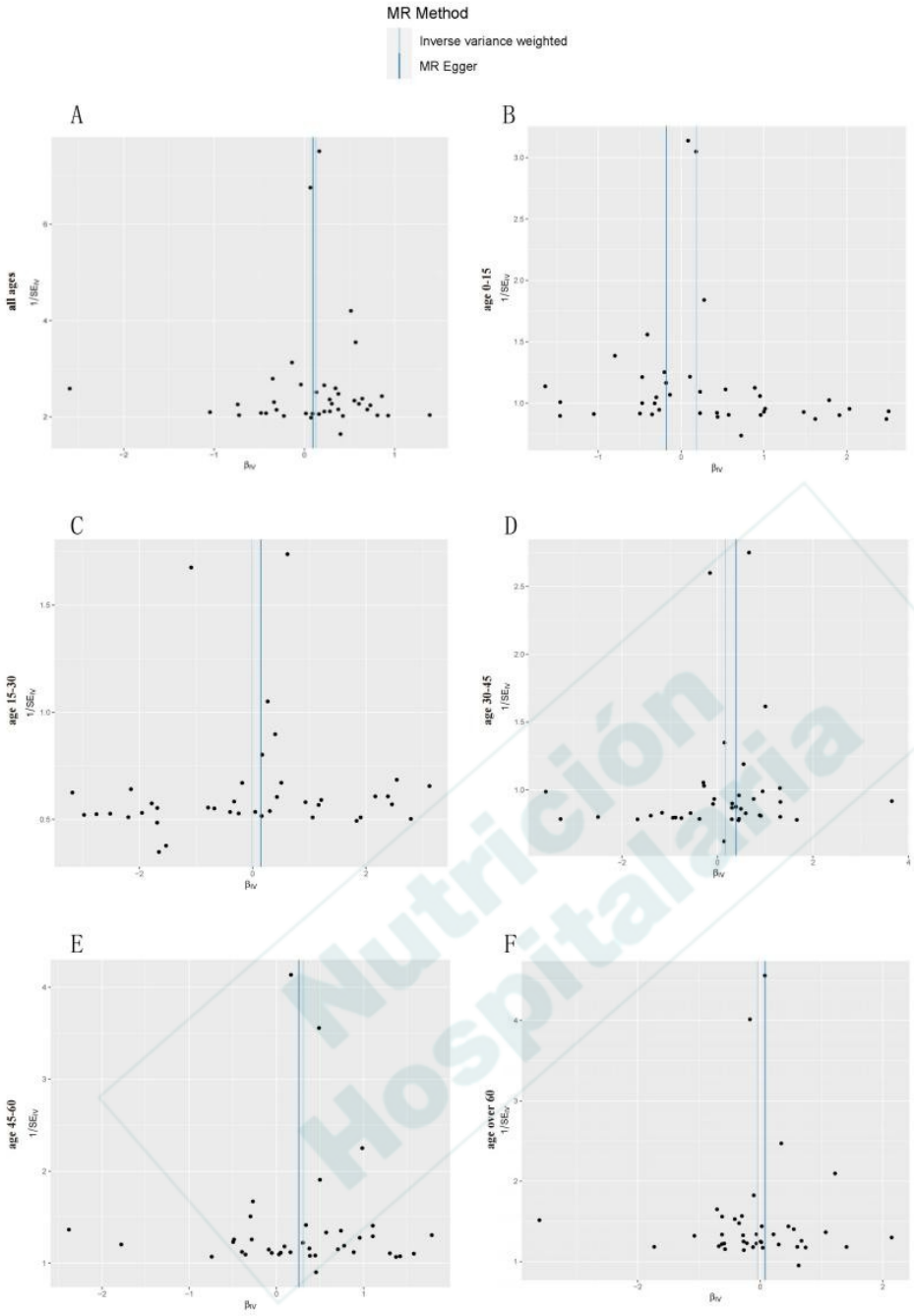

Figure 4. Funnel plot of individual causal effect between tea intake and total body bone mineral density. A. Total body bone mineral density. B. Total body bone mineral density (age, 0-15). C. Total body bone mineral density (age, 15-30). D. Total body bone mineral density (age, 30-45). E. Total body bone mineral density (age, 45-60). F. Total body bone mineral density (age over 60).

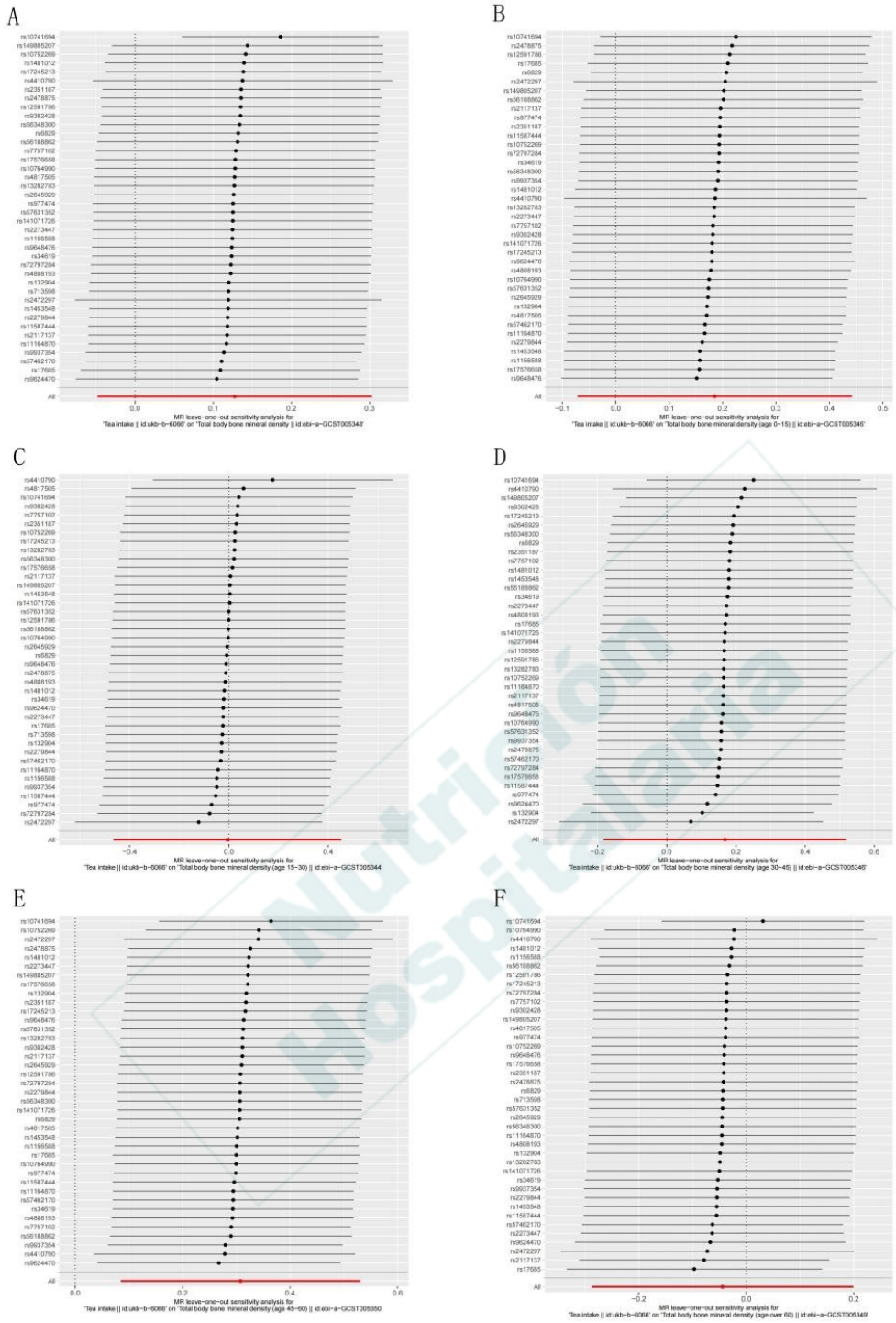

Figure 5. Leave-one-out sensitivity analysis for tea intake on total body bone mineral density. A. Total body bone mineral density. B. Total body bone mineral density (age, 0-15). C. Total body bone mineral density (age, 15-30). D. Total body bone mineral density (age, 30-45). E. Total body bone mineral density (age, 45-60). F. Total body bone

mineral density (age over 60).

Table I. Summary information of GWAS database study data

Traits	GWAS ID	Year	Sample size	Total number of SNPs tested	Population studied
Tea intake	ukb-b-6066	2018	447485	9851867	European
Total body bone mineral density	ebi-a-GCST00534	2018	56284	16162733	European
Total body bone mineral density (age 0-15)	ebi-a-GCST005345	2018	11807	9351693	European Australian
Total body bone mineral density (age 15-30)	ebi-a-GCST005344	2018	4180	8509502	European Australian
Total body bone mineral density (age 30-45)	ebi-a-GCST005346	2018	10062	9656698	European Australian
Total body bone mineral density (age 45-60)	ebi-a-GCST005350	2018	18805	10304110	European
Total body bone mineral density (age over 60)	ebi-a-GCST005349	2018	22504	11932096	European Australian

Table II. Summary of MR analysis results

Exposures	Outcomes (BMD or age)	No. of SNPs	Method	Beta (SE)	OR (95 % CI)	p	Heterogeneity test		Pleiotropy test	
							Cochran's Q	p-value	Egger intercept	p-value
Tea Intake	Total body bone mineral density	40	MR Egger	0.095 (0.210)	1.100 (0.729, 1.658)	0.652	99.44	2.119e-7	0.00066	0.866
		40	Weighted median	0.164 (0.092)	1.179 (0.984, 1.412)	0.074				
		40	Inverse variance weighted	0.127 (0.090)	1.136 (0.953, 1.354)	0.155	99.52	3.418e-7		
		40	Weighted mode	0.167 (0.097)	1.181 (0.977, 1.428)	0.094				
	15 or less	39	MR Egger	-0.179 (0.303)	0.836 (0.462, 1.514)	0.558	37.8	0.433	0.0074	0.191
		39	Weighted median	0.108 (0.187)	1.114 (0.772, 1.607)	0.564				
		39	Inverse variance	0.185 (0.13)	1.203 (0.931, a	0.157	39.61	0.398		

			weighted	1)	1.555)					
		39	Weighted mode	0.085 (0.205)	1.089 (0.728, 1.627)	0.68				
	15-30	40	MR Egger	0.144 (0.566)	1.155 (0.381, 3.502)	0.8	41.14	0.335	-0.003	0.77
		40	Weighted median	0.247 (0.363)	1.28 (0.628, 2.608)	0.497				
		40	Inverse weighted	-0.007 (0.234)	0.993 (0.628, 1.571)	0.977	41.24	0.373		
		40	Weighted mode	0.297 (0.525)	1.346 (0.481, 3.766)	0.575				
	30-45	39	MR Egger	0.391 (0.42)	1.478 (0.649, 3.368)	0.358	54.61	0.031	-0.0046	0.56
		39	Weighted median	0.385 (0.216)	1.47 (0.962, 2.244)	0.075				
		39	Inverse weighted	0.168 (0.179)	1.183 (0.833, 1.68)	0.347	55.12	0.036		
		39	Weighted mode	0.505 (0.29	1.657 (0.933,	0.092				

				3)	2.943)					
	45-60	39	MR Egger	0.257 (0.262)	1.293 (0.774, 2.161)	0.333	44.24	0.193	0.0011	0.831
		39	Weighted median	0.358 (0.16)	1.43 (1.045, 1.957)	0.025				
		39	Inverse variance weighted	0.308 (0.114)	1.361 (1.088, 1.701)	0.007	44.29	0.223		
		39	Weighted mode	0.329 (0.173)	1.39 (0.99, 1.95)	0.064				
	60 or more	40	MR Egger	0.082 (0.287)	1.085 (0.618, 1.905)	0.778	66.16	0.003	-0.0026	0.628
		40	Weighted median	-0.015 (0.145)	0.985 (0.741, 1.309)	0.92				
		40	Inverse variance weighted	-0.044 (0.124)	0.957 (0.75, 1.22)	0.72	66.58	0.004		
		40	Weighted mode	-0.06 (0.164)	0.942 (0.683, 1.299)	0.714				

SNP: single nucleotide polymorphisms; beta: the size of the effect of SNP on phenotype; SE: standard error of beta

value; OR: odds ratio; CI: confidence interval; forest plot of MR studies using genetically predicted tea intake with BMD at different ages. IVW, MR-Egger, Weighted median, and Weighted mode were used in this study.