A Mild Causal Relationship between Tea Consumption and Decreased Risk for Obesity in General Population: A Two-Sample Mendelian Randomization Study

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Research

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Abstract

Background

Tea consumption is considered as a protective factor for obesity. This study aimed to verify the casual association between tea consumption and obesity through a two-sample Mendelian randomization (MR) analysis in general population-based datasets.

Methods

The genetic instruments, single nucleotide polymorphisms (SNPs) associated with tea consumption habits, were obtained from genome-wide association studies (GWAS): UK Biobank, Nurses' Health Study, Health Professionals Follow-up Study and Women's Genome Health Study. The effect of the genetic instruments on obesity was analyzed using UK Biobank dataset (among ~ 500,000 participants). The causal relationship between tea consumption and obesity risk was analyzed by five methods of MR analyses: inverse variance weighted (IVW) method, MR-Egger regression method, weighted median estimator (WME), weighted mode and simple mode.

Results

Ninety-one SNPs were identified as genetic instruments in our study. A significant result was observed in IVW analysis (odds ratio [OR] = 0.998, 95% confidence interval [CI] = 0.996 to 1.000, $P = 0.049$), which is the commonly used approach of two-sample MR analysis.

Conclusion

Our findings evidenced a mild causal relationship between tea consumption and the decreased risk for obesity. Further studies are needed to clarify the effects of tea consumption on obesity-related health problems in detail.

Background

Obesity is a nutrition-related metabolic disorder caused by genetic and environmental determinants [1, 2]. Obesity and obesity-related diseases have been public health burdens worldwide, especially in developed countries. In the United States, the healthcare expense was about \$1,901 per year for each obese person, which extrapolated to about \$149,4 billion at the national level [3]. Due to the continuous rise of incidence in the past 50 years, obesity has now reached pandemic proportion [2, 4], and is predicted to 20% by 2025 [5]. Moreover, obesity increases the risk of various severe complications, such as type 2 diabetes, cardiovascular disease, dementia and cancers [2]. In spite of the crucial role of diet and exercise in the treatment of obesity, supportive herbal remedies are of increasing concerns [6].

Tea is one of popular beverages globally, which is consumed up to 2 billion cups per day [7]. Tea is considered as an anti-obesity beverage attributed to three main components: tea polyphenols, tea polysaccharide and caffeine [8–10]. Although growing researches have focused on the relationship between tea and anti-obesity, the findings are inconsistent [11–14] .

Conventional epidemiological studies are susceptible to the potential confounders and inverse causality, which over- or under-estimate the causal relationship between determinants and outcomes. Mendelian randomization (MR) analysis is able to control the biases by introducing instrumental variables [15]. In MR studies, genetic variants that are closely associated with exposure factor are defined as instrumental variables, by which the causation between exposure factor and outcome is measured by genetic variants as substitution [16]. Since the formation of gametes follows the Mendelian law of “parental alleles randomly assigned to offspring”, genetic variation is not affected by traditional confounding factors, and is associated with outcomes in a time-sequential manner [17]. In the current study, a two-sample MR analysis was used to assess the causal relationship between tea consumption and obesity in general population-based databases.

Methods

Datasets

For the database of exposure, significant single nucleotide polymorphisms (SNPs) related to tea consumption ($P < 5 \cdot 10^{-8}$) were obtained from a genome wide association study (GWAS) among ~ 370,000 participants of European ancestry, which included participants in UK Biobank, Nurses’ Health Study, Health Professionals Follow-up Study and Women’s Genome Health Study [18]. The linkage disequilibrium (LD) of significant SNPs linked to tea consumption was set to meet $r^2 < 0.001$ to avoid the effect of strong LD on the results. The outcome datasets of obesity were obtained from the UK Biobank study which recruited about 500,000 European participants in 2006–2010. The relevant data were extracted from two databases respectively, including SNP sites, alleles, effect estimates for exposure and outcome, standard error (SE), and P values.

Statistical analysis

There are three premises for two-sample MR [17, 19]: 1) Genetic variation as an instrumental variable must be closely related to exposure. 2) Instrumental variables are not associated with any known confounders. 3) The instrumental variables are not directly related to the outcome, that is, the instrumental variables cannot affect the outcome in other ways except through the exposure factors.

Prior to two-sample MR analysis, there is a need to unify the effect-value directions of exposure data and outcome data. Exposure and outcome data are unified into a dataset by removing the intermediate allele frequencies of SNPs containing palindromes [20]. In addition, SNPs with A/T or G/C alleles are defined as palindromic SNPs, “intermediate allele frequencies” referred to $0.01 < \text{allele frequency} < 0.30$ [21].

Inverse variance weighted (IVW) method, MR-Egger regression method, weighted median estimator (WME), weighted mode and simple mode were used to evaluate the causal effect between tea consumption and obesity risk, and subsequently checked the stability and reliability of the results. The IVW model is a weighted linear regression model, which is based on the premise that all genetic variants are valid instrumental variables [22]. MR-Egger regression method can obtain unbiased estimation when there is pleiotropy in instrumental variables, measure average pleiotropy through intercept term, and perform sensitivity analysis [23]. WME can still calculate the causal association effect when the genetic variation below 50% violates the core assumptions of MR [24].

The intercept of the MR-Egger regression line illustrated the magnitude of the genetic pleiotropy. It was considered that there was no pleiotropic effect if no significant difference between intercept and 0 ($P > 0.05$) [23]. Cochran's Q statistic was used to assess the heterogeneity among the estimates from included SNPs. Funnel plot showed the relationship between the individual Wald ratio of each SNP and its accuracy, and whether its symmetry indicated whether the results had directional horizontal pleiotropy [25]. The "leave-one-out" method was used for sensitivity analysis. By gradually eliminating each SNP and calculating the combined effect of the remaining SNPs, the influence of individual SNP on results and the stability of the results were evaluated [26].

All data analyses were performed by the "TwoSampleMR" package in R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set as two-tailed $P < 0.05$ unless otherwise specified.

Results

Instrumental variable selection

A total of 108 significant SNPs ($P < 5 \times 10^{-8}$, $LD\ r^2 < 0.001$) were obtained from the GWAS about tea consumption [18]. Among them 16 SNPs were removed for being palindromic with intermediate allele frequencies, and one SNP was removed because of no corresponding outcome data. Finally, 91 SNPs were selected to perform the following MR analysis. The detailed information of these SNPs was shown in Additional file 1: Table S1, mainly including effect allele (EA), other allele (OA) and summary statistics (beta coefficient, SE and P -value).

MR analysis

The causation between tea consumption and obesity was analyzed using the methods of IVW, MR Egger, WME, weighted mode and simple mode, independently. As shown in Table 1 and Fig. 1, a statistical significance was observed in IVW method analysis [odds ratio (OR) = 0.998, 95% confidence interval (CI) = 0.996 to 1.000, $P = 0.049$] (Table 1, Figs. 1 and 2). No significant causal relationships were observed in the analyses of MR Egger (OR = 1.003, 95%CI = 0.998 to 1.008, $P = 0.255$), WME (OR = 0.998, 95%CI = 0.996 to 1.001, $P = 0.262$), weighted mode (OR = 0.999, 95%CI = 0.994 to 1.003, $P = 0.505$) or simple mode (OR = 0.999, 95%CI = 0.993 to 1.005, $P = 0.747$) (Table 1, Figs. 1 and 2).

Table 1
Two-sample Mendelian Randomization for tea consumption on obesity risk

Method	N SNPs	Beta coefficient	SE	OR (95%CI)	<i>P</i>
IVW	91	-0.002	0.001	0.998 (0.996-1.000)	0.049
MR-Egger	91	0.003	0.003	1.003 (0.998–1.008)	0.255
WME	91	-0.002	0.001	0.998 (0.996–1.001)	0.262
Weighted mode	91	-0.001	0.002	0.999 (0.994–1.003)	0.505
Simple mode	91	-0.001	0.003	0.999 (0.993–1.005)	0.747
N SNPs indicates the number of single nucleotide polymorphisms; SE, standard error; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted; WME, weighted median estimator.					

Sensitivity analysis

The leave-one-out method displayed that the results of two-sample MR analysis were strong (Fig. 3), indicating that no instrumental variables influenced the causal inference. No significant heterogeneity was found across the estimates of included SNPs (Cochran's $Q = 86.692$, $P = 0.550$). The funnel plot analysis showed a symmetry result (Fig. 4), by which non-significance in directional and horizontal multipolarity was observed. In addition, genetic pleiotropy test was carried out by the MR-Egger regression analysis. A non-significant intercept was obtained [intercept=-5.885727e-05 (SE = 2.995104e-05), $P = 0.053$] in this test, illustrating that our findings were not influenced by the polymorphisms.

Discussion

Our two-sample MR analyses are conducted in five independent approaches. The result of IVW analysis evidenced that tea consumption has a mild causal relationship with decreased risk for obesity in general population. The results of MR Egger, WME, weighted mode and simple mode analyses did not show causal relationship between tea and obesity. Nevertheless, IVW is the most widely used and usually provides predominant results [22, 27]. The results of sensitivity analyses showed no statistical difference, which proved that these two-sample MR results were reliable.

As a popular, economical and safe drink, the effect of tea on anti-obesity is widely understood, especially among overweight and obese individuals [8–10, 28]. The potential mechanisms of tea on anti-obesity are as follows: 1) reducing food intake and energy absorption [29], 2) regulating the expression of lipid metabolism genes and inhibiting fat accumulation [30], 3) enhancing the activity of antioxidant defense enzymes [31, 32], 4) regulating intestinal microflora disturbance and attenuating intestinal inflammation [33, 34], and 5) maintaining intestinal barrier integrity [35].

In recent years, a growing number of studies have begun to explore the association between tea consumption and obesity. Two reviews showed no-significant link between tea and weight loss in obese

people [11, 12]. On the other hand, some randomized controlled trials (RCTs) proved the anti-obesity effect of tea on obesity [36–38]. In addition, two meta-analyses published in 2020 came up with similar results [13, 14]. Our study, a two-sample MR analysis based on general population-based datasets, verified the casual relationship between tea consumption and decreased obesity risk.

Traditional epidemiological studies, consisting of case-control studies and cohort studies, provide representative findings on the relationship between exposures and outcomes. However, these studies are usually biased by confounding factors and adverse causal effects [39–41]. MR analysis can control the biases by introducing instrumental variables [25, 42]. MR analysis on general population-based datasets is a novel approach to provide evidence on causation. Our MR study based on UK Biobank, Nurses' Health Study, Health Professionals Follow-up Study and Women's Genome Health Study validated that tea consumption have a mild causal relationship with decreased risk for obesity.

Limitations

There are inevitable limitations that should be notified. First, potential horizontal pleiotropy could not be comprehensively assessed even though multiple sensitivity analyses were performed. However, Cochran's Q statistic and MR-Egger intercept test found that there were no heterogeneity or pleiotropy in this MR analysis. Second, we did not carry out subgroup analysis due to the lack of demographic information in detail. In addition, the study population were of European ancestry, which might lead to ethnic bias.

Conclusion

Our findings evidenced that tea consumption has a mild causal relationship with decreased risk for obesity in general population. More studies are needed to clarify the effects of tea and its components on obesity-related health problems.

Abbreviations

MR

Mendelian randomization, SNPs:nucleotide polymorphisms, GWAS:genome-wide association studies, LD:linkage disequilibrium, IVW:inverse variance weighted, WME:weighted median estimator, OR:odds ratio, CI:confidence interval, EA:effect allele, OA:other allele.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data of obesity is available at <http://www.nealelab.is/uk-biobank>.

Competing interest

The authors declare no conflict of interest.

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Author Contributions

C.L. did the data analysis and explained the results, C.L., M.N. and Z.G. wrote the manuscript, P.L., Y.Z., D.L., S.Y., and W.W. reviewed manuscript. Y.L. and H.H. decided the idea of the research and were responsible for the whole research. All authors had read and approved the final manuscript.

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Figures

Figure 1

Scatter plot to visualize the causal effect between tea consumption and obesity risk. The slope of the straight line indicates the magnitude of the causal association, scatter plot of inverse variance weighted (IVW) method, MR-Egger regression method, weighted median estimator (WME), weighted mode and simple mode. MR, Mendelian randomization; SNP, single nucleotide polymorphism.

Figure 2

Forest plot to show the casual effect of tea consumption on obesity risk. Forest plot of IVW and MR-Egger regression method. MR, Mendelian randomization.

Figure 3

Forest plot of “leave-one-out” sensitivity analysis method to show the influence of individual SNP on the results. MR, Mendelian randomization.

Figure 4

Funnel plot to visualize overall heterogeneity of Mendelian randomization assessment for the effect of tea consumption on obesity risk. MR, Mendelian randomization; SE, standard error; IV, instrument variable.

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