Association between dried fruit intake and DNA methylation: A Multivariable Mendelian Randomization Analysis

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Research Article

Keywords: Dried fruit intake, DNA methylation, GWAS, Mendelian randomization, causality

Posted Date: May 17th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2925798/v1

Abstract

Background

Observational studies have reported associations between dried fruit intake and DNA methylation(DNAm). However, inherent flaws in observational study designs make them susceptible to confounding and reverse causality bias. Consequently, it is unclear whether a causal association exists. In the present study, we aimed to investigate the causal associations between dried fruit intake and DNAm.

Methods

We performed two-sample Mendelian randomization (MR) using the IEU Open GWAS database aggregated data. Forty-three single nucleotide polymorphisms (SNPs) associated with dried fruit intake as instrumental variables (IVs) were selected as exposure. DNAm outcomes include Gran (estimated granulocyte proportions); AgeAccelGrim(GrimAge acceleration); Hannum (Hannum age acceleration); IEAA(Intrinsic epigenetic age acceleration), AgeAccelPheno(PhenoAge acceleration), and DNAmPAIadjAge (DNAm-estimated plasminogen activator inhibitor-1 levels). Inverse variance weighted (IVW) method was the primary method for MR analysis, complemented by four other MR methods to ensure the stability and reliability of the results. Additional sensitivity analyses were also performed. The direct effects of dried fruit intake on DNAm were estimated using multivariable mendelian randomization (MVMR).

Results

Univariate MR results showed that for each standard deviation increase in dried fruit intake, the risk of AgeAccelGrim was reduced by 77.7% [odds ratio (OR) = 0.223, 95% confidence interval (CI) = 0.081–0.612; P_{IVW}=3.588×10^{-3}], and the risk of AgeAccelPheno was reduced by 81.7% (OR = 0.183, 95%CI = 0.054–0.621, P_{IVW}=6.426×10^{-3}). However, the effects on Gran(P_{IVW}=0.264), Hannum(P_{IVW}=0.299), IEAA(P_{IVW}=0.700), and DNAmPAIadjAge(P_{IVW}=0.051) were not statistically significant. MVMR results adjusting for the potential effects of confounders showed that the causal relationship between dried fruit intake and AgeAccelGrim (P_{IVW}=2.482×10^{-2}) persisted, but the effect on AgeAccelPheno (P_{IVW}=0.052) was not statistically significant. Sensitivity analysis showed that our results were stable and reliable.

Conclusion

Our MR findings suggest that increased dried fruit intake is associated with slower AgeAccelGrim, providing a promising avenue for exploring the beneficial effects of dried fruit intake on lifespan extension.

Introduction

DNAm is one of the most widely studied epigenetic mechanisms characterized by the addition of methyl groups to cytosine-guanine dinucleotides (CpG), which are responsible for the regulation of gene expression and play an important role in physiological processes such as normal cell differentiation, embryonic development, and adult maintenance(1–3). In recent years, DNAm-based epigenetic clocks (Gran, Hannum, IEAA, AgeAccelGrim, and AgeAccelPheno) and DNAmPAI adjAge measurements have been used as biomarkers of aging and correlated with healthy lifespan with a precision that has been shown to be superior to other common indicators of physiological age, such as biological age, chromosome telomere length, etc(4, 5).

Diet is an influential modifiable factor affecting DNAm. Food can alter DNA methylation patterns by modulating enzyme activity and altering substrates(6, 7). Dried fruits (raisins, dried plums, dried apricots) are foods rich in various nutrients, including vitamins, minerals, dietary fiber, and antioxidants that protect cells and biomolecules from the effects of aging by fighting free radicals and other forms of oxidative damage(8). Studies have shown that raisin intake can reduce oxidative stress, improve cell function and slow the signs of aging(9, 10). Other studies have shown that eating more polyphenol-rich foods, which can help fight free radical damage, can reduce the risk of DNAm (11, 12). In addition, polyphenols have anti-inflammatory and antioxidant properties that can help reduce cell damage and promote cell regeneration, thereby delaying aging(13). Likewise, dried apricots are a rich source of antioxidants, including vitamin A and beta-carotene, which may help protect cells from oxidative damage(14). Thus, observational studies suggest that increased intake of dried fruits could be an effective means of preventing DNA methylation.

Potential confounding factors and reverse causality in observational studies affect the ability to make causal inferences. In contrast, MR follows Mendel's law of inheritance - random assignment of parental alleles to offspring - and is the use of exposure-related genetic variation as an instrumental variable (IV) to infer causal relationships between risk factors (exposure) and disease risk (outcome). The use of genetic variants as instrumental variables avoids some of the limitations of observational studies (confounding, reverse causality, regression dilution bias) and RCTs (representativeness and feasibility issues) in making causal inferences(15, 16). Therefore, studies on the risk of DNA methylation reduction by dried fruit intake need to be supported by additional evidence and should be further confirmed in clinical trials.

This study used a multivariate MR design to investigate whether there is a causal relationship between dried fruit intake and DNA methylation and to estimate its effect to provide scientific evidence for delaying the primary prevention of DNA methylation.

Materials and methods

Study design and data sources

We used a 2-sample MR model to evaluate the causal effect of exposure(dried fruit intake) on the outcome(DNAm). Before conducting MR analysis, the following three core assumptions were considered(17, 18). Assumption 1: Robust correlations between instrumental variables(IVs) and exposure factors. Assumption 2: The IVs are independent of the confounding factors affecting the exposure-outcome relationship. Assumption 3: IVs can only affect outcomes through exposure factors and cannot influence outcome occurrence through other means. Data on the associations of single nucleotide polymorphisms (SNPs) with dried fruit intake and DNAm were obtained from published genome-wide association studies (GWAS). Each original research received the appropriate ethical approval and patient informed consent. Therefore, no additional ethical approval or informed consent was required for this study(4).

Dried fruit intake was obtained from the UK BioBank cohort, which included 421,764 individuals of European ancestry(Supplementary Table S1). The study design and methodology of UKB have been previously reported in detail (http://www.ukbiobank.ac.uk/resources/). In brief, information on the Dried fruit intake was collected retrospectively by a shortened food frequency touchscreen questionnaire(ACE) at baseline. ACE touchscreen question "About how many pieces of DRIED fruit would you eat per DAY? (Count one prune, one dried apricot, and ten raisins as one piece; put '0' if you do not eat any)". The following checks were performed: If the answer > 100, then rejected. If the participant activated the Help button, they were shown the message: Please provide an average considering your intake over the last year. If you are unsure, please provide an estimate or select Do not know.

The summary statistics of GWAS data (DNAm) comprised 28 cohorts of people of European ancestry, including 34,710 participants(4). An outlier threshold for methylation values of +/-5 standard deviations was applied for each cohort, and outlier samples were excluded from the analysis, including Gran dataset (N = 34,470), AgeAccelGrim dataset (N = 34,467), Hannum dataset (N = 34,449), IEAA dataset (N = 34,461), DNAmPAladjAge dataset (N = 34,448), and AgeAccelPheno dataset (N = 34,463)(Supplementary Table S1).

Selection of instrumental variables

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guideline (15). The IV selection criteria for this study were as follows: First, we extracted SNPs closely and significantly associated with the traits in the GWAS summary data of dried fruit intake ($P<5\times10^{-8}$). Considering that some SNPs are in linkage disequilibrium (LD) with each other, the LD between SNPs was further estimated using MRBase (https://mrcieu.github.io/TwoSampleMR/)(19). Removed possible linkage disequilibrium ($LDR^2<0.001$, kb = 10,000), palindromic structural SNPs (SNPs with a minor allele frequency > 0.42), and incompatible SNPs, 43 independent SNPs were obtained(Supplementary Table S2). To assess the strength of each instrumental variable, we calculated the F-statistic ($F = \beta^2/se^2$) for each SNP(Supplementary TableS2) (20); F > 10, suggesting the absence of weak instrumental bias. MR assumptions and study design(FIGURE 1) .

Mendelian randomization analyses

We used five MR methods to analyze the causal effects of dried fruit intake on DNAm. In univariate MR, The IVW method was used as the primary analysis. MR Egger, weighted median, weighted mode, and penalized weighted median methods were performed to further validate the reliability of results. IVW method has the advantage of considering the heterogeneity of SNPs used in the IVs and providing reliable causal estimates without directional polymorphisms(21, 22). MR-Egger provides unbiased estimates of causal effects even if all SNPs in the IVs are invalid due to polymorphism(23). Weighted Median (WM) still produces robust estimates when at least half of the instruments used in the MR analysis are valid(24). Weighted mode is sensitive to the problematic bandwidth selection for mode estimation, and it weighed the contribution of each SNP to the cluster, and the penalized weighted median for further analysis(25).

For significant estimates, we further assessed horizontal pleiotropy using MR-Egger intercept test, and $p > 0.05$ indicates no pleiotropy(23). The Cochran's Q test was adopted for IVW analysis and also used to identify heterogeneity, and $p > 0.05$ indicates no heterogeneity. Moreover, the leave-one-out method to analyze the influence of a single SNP and evaluate the reliability of the results. A funnel plot was used to assess the possible directional pleiotropy. In addition, MR pleiotropy residual sum and outlier (MRPRESSO) global tests and RadialMR were used to detect multi-effect outliers at any level for exposures with significant causal associations and reassessed the causal associations' estimates after removing outliers(21, 26). In MVMR, dried fruit intake, Tea intake, Coffee intake, Current tobacco smoking, and Alcohol intake frequency were used as exposures simultaneously to explore their effects on AgeAccelGrim and AgeAccelPheno. Finally, we used the Phenoscanner (www.phenoscanner.medschl.cam.ac.uk, last accessed on January 13th, 2023) tool to check whether each SNP of IV used in the MR study was associated with other phenotypic affecting DNAm(27), including tea intake(28), coffee intake(29), current tobacco smoking(30, 31), and alcohol intake frequency(32) and remove SNPs related to any potential confounders at genome-wide significance.

Statistical analysis

The statistical significance threshold was defined as *P-value* < 0.008 (0.05/6 tests) after Bonferroni correction to address the multiple testing issues. If a *P-value* was between 0.008 and 0.05, we regarded it as nominally significant for a potential causal association. All statistical analyses were performed by the package "TwoSampleMR" (https://github.com/MRCIEU/TwoSampleMR) (33),"MRPRESSO"(version 1.0), and "Radial MR" (version 1.0), in R (version 4.2.2).

Results

43 SNPs were identified as IVs for predicted dried fruit intake. The F-statistics for each SNP ranged from 17.79 to 47.90, reflecting a low possibility of weak instruments. After the Bonferroni correction, univariate MR results showed that for each genetically identified standard deviation increase in dried fruit intake, the

risk of AgeAccelGrim was reduced by 77.7% (OR = 0.223, 95%CI = 0.081–0.612; P_{IVW}=3.588×10^{-3}), and the risk of AgeAccelPheno was reduced by 81.7%(OR = 0.183, 95%CI = 0.054–0.62 1, P_{IVW}=6.426×10^{-3}). However, the effects on Gran(OR = 1.011,95%CI = 0.991–1.032, P_{IVW}=0.264), Hannum (OR = 0.583, 95%CI = 0.209–1.617, P_{IVW}= 0.299), IEAA(OR = 0.832, 95%CI = 0.326–2.123, P_{IVW}= 0.700), and DNAmPAladjAge (OR = 0.108, 95%CI = 0.012–1.007, P_{IVW}=0.051) were not statistically significant.Similarly, the MR-Egger, Weighted median, Weighted mode, and Penalised weighted Median yielded similar results and directions, respectively(Supplementary Table S3).

In addition, we used the MRPRESSO and Radial-MR test to identify any level of multi-effect outliers and reassessed the causal effect estimates after removing outliers. The results still indicated that genetically predicted increased dried fruit intake was associated with reduced risk of AgeAccelGrim (OR = 0.255, 95%CI = 0.104–0.627, P_{IVW}=2.985×10^{-3}) and AgeAccelPheno(OR = 0.145, 95%CI = 0.046–0.449, P_{IVW}=8.371×10^{-4}) (Supplementary Table S4). Moreover, we found that SNPs were associated with other traits by searching the Phenoscanner(last accessed on January 14th, 2023) (Supplementary Table S5). After excluding potential pleiotropic SNPs, we also observed genetically predicted increased dried fruit intake was associated with reduced risk of AgeAccelGrim (OR = 0.176, 95%CI = 0.058–0.542, P_{IVW}=2.483×10^{-3}), and AgeAccel Pheno (OR = 0.163, 95%CI = 0.040–0.669, P_{IVW}=0.012) (Supplementary Table S6). This suggested that dried fruit intake can slow AgeAccelGrim and AgeAccel Pheno. The Cochran Q test for IVW(p = 0.932 and P = 0.602) and MR-Egger regression(P = 0.921 and P = 0.556) showed that there was no heterogeneity in SNPs(Table 1). Besides, there was no significant statistical difference in MR-Egger-intercept(p = 0.578 and p = 0.995), so we can assume that SNPs have no horizontal pleiotropy. Moreover, the funnel plot shows that when a single SNP is used as IV, the points representing the causal association effect are largely symmetrically distributed, indicating that the causal association is less likely to be affected by potential bias. The leave-one-out analyses suggested that the effect estimates were not influenced by a single outlying variant (FIGURE 2 and FIGURE 3).

Table 1
Sensitivity analysis dried fruit intake on DNA methylation.

Exposure	Horizontal pleiotropy test				Heterogeneity test			
	MR-Egger regression		MR-PRESSO		IVW		MR-Egger	
	Egger intercept	*P value*	*Global Test RSSobs*	*Global test p value*	*Q value*	*P value*	*Q value*	*P value*
Dried fruit intake								
Gran	-0.000831	0.162	26.739	0.937	25.524	0.939	23.491	0.958
AgeAccelGrim	0.014094	0.578	24.827	0.935	23.386	0.932	23.071	0.921
Hannum	0.009884	0.699	42.568	0.333	40.179	0.331	40.011	0.296
IEAA	0.041946	0.112	49.130	0.216	46.592	0.219	43.626	0.281
DNAmPAIadjAge	0.023098	0.699	22.609	0.965	21.438	0.966	21.286	0.956
AgeAccelPheno	0.000187	0.995	36.249	0.586	34.160	0.602	34.159	0.556

Abbreviation: **Gran**, DNA methylation-estimated granulocyte proportions; **AgeAccelGrim**, DNA methylati on GrimAge acceleration;**Hannum**, DNA methylation Hannum age acceleration; **IEAA**, Intrinsic epigenetic age acceleration; **DNAmPAIadjAge**,DNA methylation-estimated plasminogen activator inhibitor-1 levels, adjusted for age; **AgeAccelPheno**,DNA methylation PhenoAge acceleration; MR-PRESSO, MR pleiotropy residual sum and outlier .

According to the MVMR analyses adjusting for tea and coffee intake, there was still significant evidence of associations of dried fruit intake with AgeAccelGrim (OR = 0.178, 95%CI = 0.069–0.464; P_{IVW} =4.023×10^{-4}), and AgeAccelPheno (OR = 0.126, 95%CI = 0.038–0.426; P_{IVW}=8.558×10^{-4}). When Plus Current tobacco smoking, the MR estimates were attenuated, AgeAccelGrim (OR = 0.298,95%CI = 0.108–0.819; P_{IVW}=1.914×10^{-2}), and AgeAccelPheno (OR = 0.115, 95%CI = 0.029–0.442; P_{IVW}=1.672×10^{-3}). Nevertheless, When Plus alcohol intake frequency, the MR estimates continued to weaken or not significant, AgeAccelGrim (OR = 0.328,95%CI = 0.124–0.867; P_{IVW}=2.482×10^{-2}), and AgeAccelPheno (OR = 0.280, 95%CI = 0.029–1.012; P_{IVW}=0.052)(Table 2) indicating that the effect of dried fruit intake on AgeAccelGrim, and AgeAccelPheno can be disturbed by the frequency of smoking and alcohol consumption.

Table 2
Multivariate MR results of Dried fruit intake with AgeAccelGrim and AgeAccelPheno (IVW).

Exposure	AgeAccelGrim		AgeAccelPheno	
	OR (95% CI)	*P value*	*OR (95% CI)*	*P value*
Adjusted for Tea intake, Coffee intake				
Dried fruit intake	0.178(0.069–0.464)	**4.023×10^{-4}**	0.126(0.038–0.426)	**8.558×10^{-4}**
Tea intake	1.592(0.681–3.719)	0.282	0.614(0.260–1.448)	0.454
Coffee intake	0.647(0.329–1.274)	0.208	1.503(0.515–4.384)	0.265
Plus Current tobacco smoking				
Dried fruit intake	0.298(0.108–0.819)	**1.914×10^{-2}**	0.115(0.029–0.442)	**1.672×10^{-3}**
Tea intake	1.798(0.813–3.978)	1.473×10^{-1}	0.575(0.246–1.348)	0.201
Coffee intake	0.639(0.337–1.211)	1.703×10^{-1}	1.632(0.572–4.658)	0.360
Current tobacco smoking	35.76(6.867–186.29)	**2.159×10^{-5}**	1.481(0.164–13.35)	0.726
Plus Alcohol intake frequency				
Dried fruit intake	0.328(0.124–0.867)	**2.482×10^{-2}**	0.280(0.029–1.012)	0.052
Tea intake	0.587(0.308–1.119)	1.035×10^{-1}	0.734(0.317–1.703)	0.472
Coffee intake	2.247(1.010–5.001)	**4.731×10^{-2}**	1.890(0.663–5.385)	0.233
Current tobacco smoking	27.27(5.619–132.39)	**4.134×10^{-5}**	4.678(0.583–37.50)	0.146
Alcohol intake frequency	1.246(0.893–1.738)	1.947×10^{-1}	1.312(0.842–2.044)	0.229

Abbreviations: **AgeAccelGrim**, DNA methylation GrimAge acceleration;**AgeAccelPheno**, DNA methylation PhenoAge acceleration.

Discussion

To our knowledge, this is the first study to focus on the causal relationship between dried fruit intake and DNAm through MR analysis. Our study suggests that the intake of dried fruits has potential preventive value for AgeAccelGrim and AgeAccelPheno acceleration. MVMR results adjusted for dried fruit intake, Tea intake, Coffee intake, Current tobacco smoking, and Alcohol intake frequency found that there was still significant evidence of associations of dried fruit intake with AgeAccelGrim. However, the association with a reduced risk of AgeAccelPheno was not significant. Uncovering this association could contribute to elucidating the pathophysiological mechanisms underlying dried fruit intake and DNAm.Therefore, active health education based on dried fruit intake and rationalization of dietary ratios may contribute to delaying aging.

Dried fruits (raisins, dried plums, dried apricots) are rich in many bioactive components and phytochemicals (34, 35). Traditionally, dried fruits are dried by sunlight or heat processing without added sugars or fruit juices and retain to a large extent the nutrients and bioactive found in their fresh counterparts. Several studies have shown that oxidative stress and inflammation can lead to changes in DNA methylation patterns, and dried fruits rich in polyphenols and antioxidants may help prevent these changes(36–38).One of the most commonly consumed and dried fruits rich in polyphenols and antioxidants, raisin intake has been shown in studies to reduce oxidative stress, improve cellular function, and slow down the signs of aging(39, 40). Polyphenols, in particular, protect cells and biomolecules from the effects of aging by fighting free radicals and other forms of oxidative damage, and also have anti-inflammatory and antioxidant properties that can help reduce cellular damage and promote cell regeneration, thereby slowing aging(41). Dried plums are also a traditional dried fruit rich in antioxidants. They are rich in fiber, vitamins, potassium, iron, minerals and antioxidants, providing the body with a rapid source of energy while also having potential anti-aging benefits through a variety of mechanisms(42). Dried apricots are a good source of antioxidants, including vitamin A and beta-carotene. The antioxidants in dried apricots may help protect cells from oxidative damage, help reduce oxidative stress and inflammation, and may also help prevent DNA methylation changes associated with inflammation(43).

While there may be some potential benefits to aging from consuming dried fruits as part of a balanced diet, it is important to remember that diet is only one of many factors that influence aging and more research is needed to fully understand the relationship between dried fruits and aging. More evidence is needed to support the research on the risk of reduced DNA methylation with dried fruit intake and should be further confirmed in clinical trials.

The strength of this study is that the MR design minimizes confounding and reverse causality in observational studies and comprehensively assesses the causal relationship between dried fruit intake and DNAm. Nevertheless, our study has several limitations. First, although this study used multivariate correction to further demonstrate the independent effect of increased dried fruit intake on AgeAccelGrim and AgeAccelPheno acceleration, it did not completely exclude the confounding of some unknown confounding factors including those not yet reported in the literature. Second, the population included in

this study was mainly European, and since the results of the analysis of causal associations may be influenced by different races, further studies with the same MR in other races are still needed to verify the stability of the results of this study. In addition, the exposure variance explained by genetic variation is only a fraction of the total exposure variance, and the effect values obtained are only the effects of this fraction of exposure variance on outcome determined by instrumental variables, whereas the effects of exposure variance on outcome determined by other non-genetic factors cannot be obtained by MR models. Strictly speaking, the estimates of the effect of exposure on outcome obtained from MR cannot be fully equated with the true causal effect. Similarly, it is worth noting that dietary surveys may be subject to some bias, as participants may have difficulty recalling their food intake accurately. Therefore, data on dried fruit intake need to be interpreted and used with appropriate vigilance. The true causal association should be explored in the context of the biological mechanisms of the disease and the results of well-established trials and clinical studies.

Conclusion

In conclusion, this MR study provided genetic evidence that higher dried fruit intake was associated with reduced risk of AgeAccelGrim. This data informs the design and implementation of future prospective studies on diet-related DNAm. Nevertheless, further studies are needed to validate our findings, including studies with larger sample sizes, racially and ethnically diverse populations, and should also comprehensively assess other lifestyle, social determinants, environmental exposures and effects of genetic variation that may influence the methylation process, as well as studies on the causal role of dried fruit intake on epigenetic regulation.

Declarations

Data availability statement

The datasets presented in this study can be found in online repositories. They can also be downloaded from the IEU Open GWAS project, https://gwas.mrcieu.ac.uk/datasets/.

Ethics statement

The GWAS summary data used in this study were publicly available for download, and each original study received the appropriate ethical approval. Therefore, no additional ethical approval or informed consent was required for this study.

Author contributions

LW and HP contributed to the study design. YZ and XZ conducted data acquisition. MF, LY, and MG analyzed the data and drafted the manuscript. YW and ZT revised the draft. ZT and XX interpreted the results. All authors read and approved the final manuscript.

Acknowledgments

We thank the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/datasets/) for providing summary results data for the analyses.

Funding

This study was supported by the Shanghai municipal health commission Foundation(No.20204Y0181), and Fengxian District Science and Technology Commission Project (No.20211805, No.20211602, and No.20211838).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary tables

Supplementary Tables s1-s6 are not available with this version

Figures

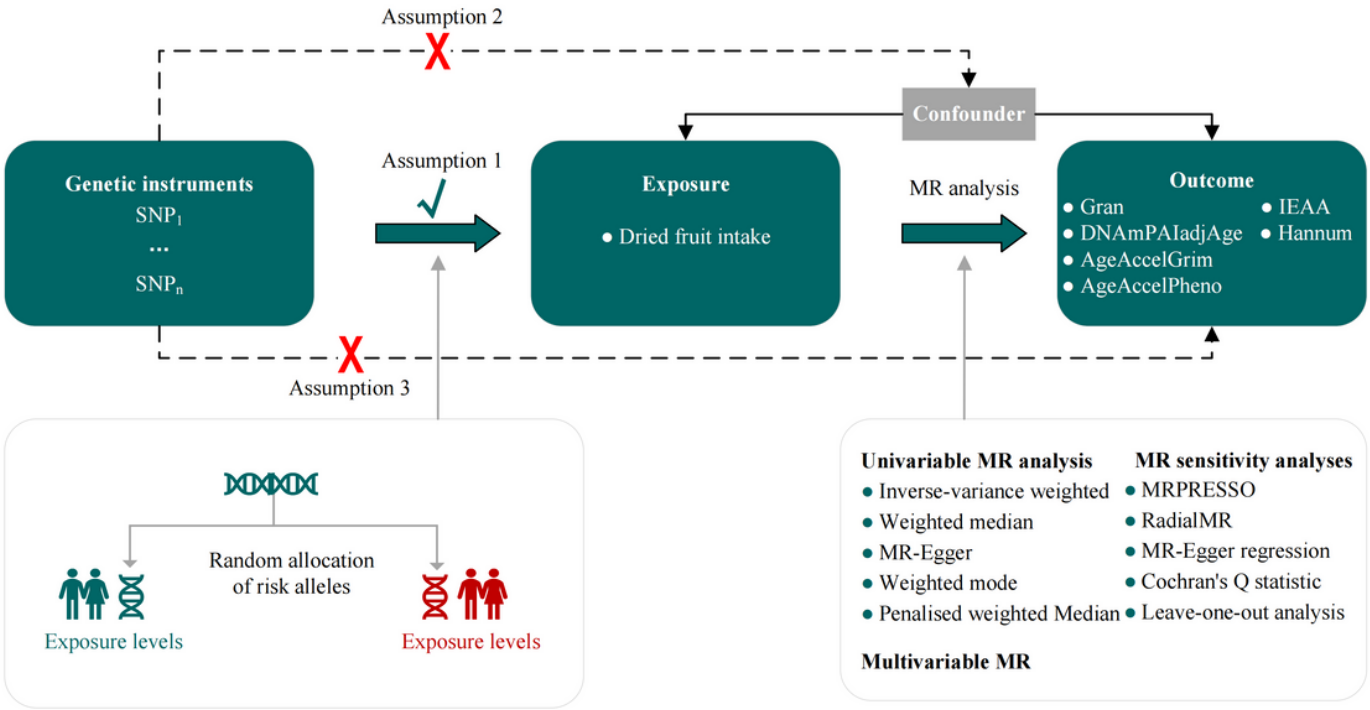

Figure 1

MR assumptions and study design.

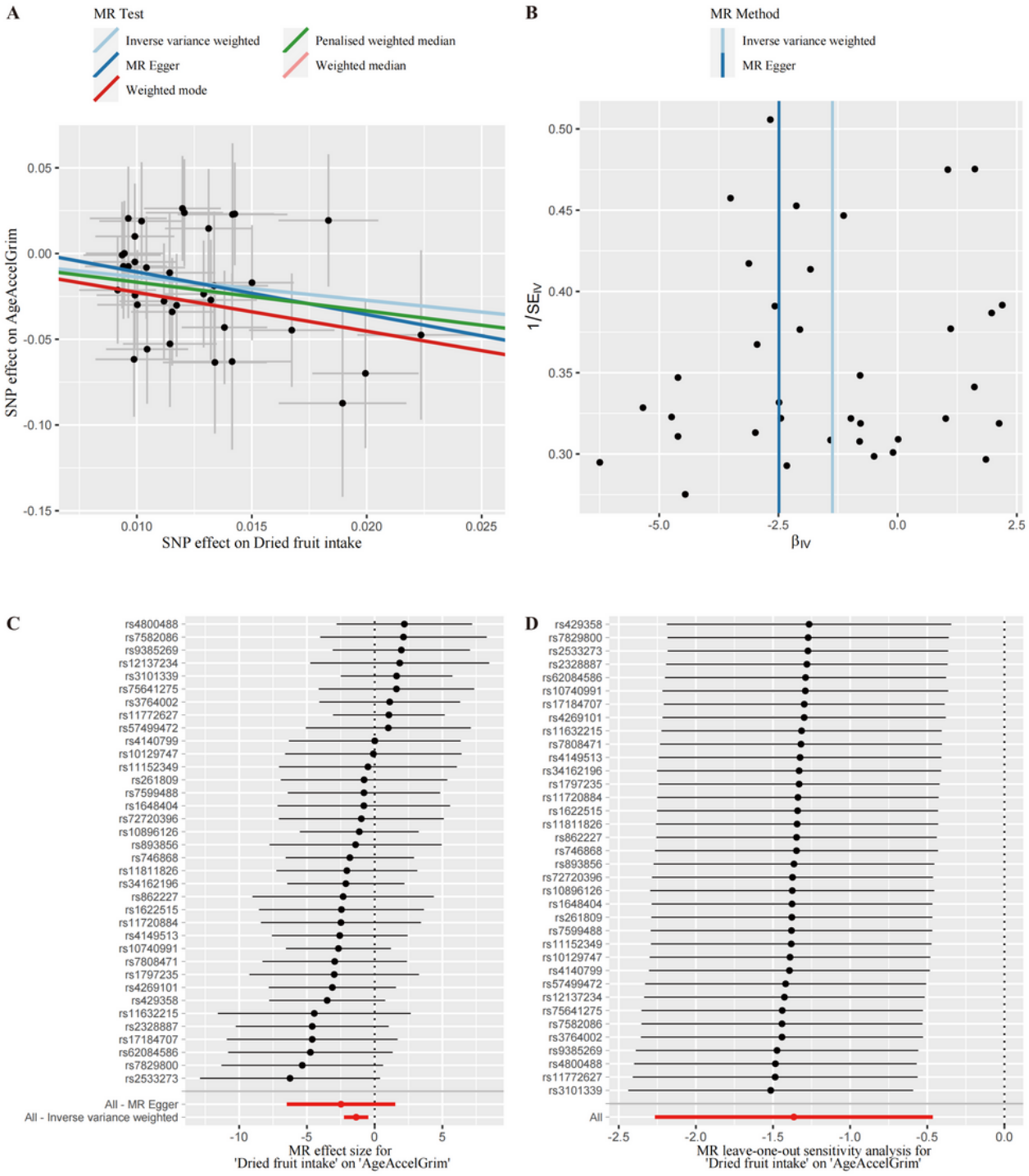

Figure 2

MR results of Dried fruit intake on AgeAccelGrim.

(A) Scatter plot of SNPs associated with Dried fruit intake on AgeAccelGrim.

(B) Forest plot of SNPs associated with Dried fruit intake on AgeAccelGrim.

(C) Funnel plot of SNPs associated with Dried fruit intake on AgeAccelGrim.

(D) Leave-one-out analysis of SNPs associated with Dried fruit intake on AgeAccelGrim.

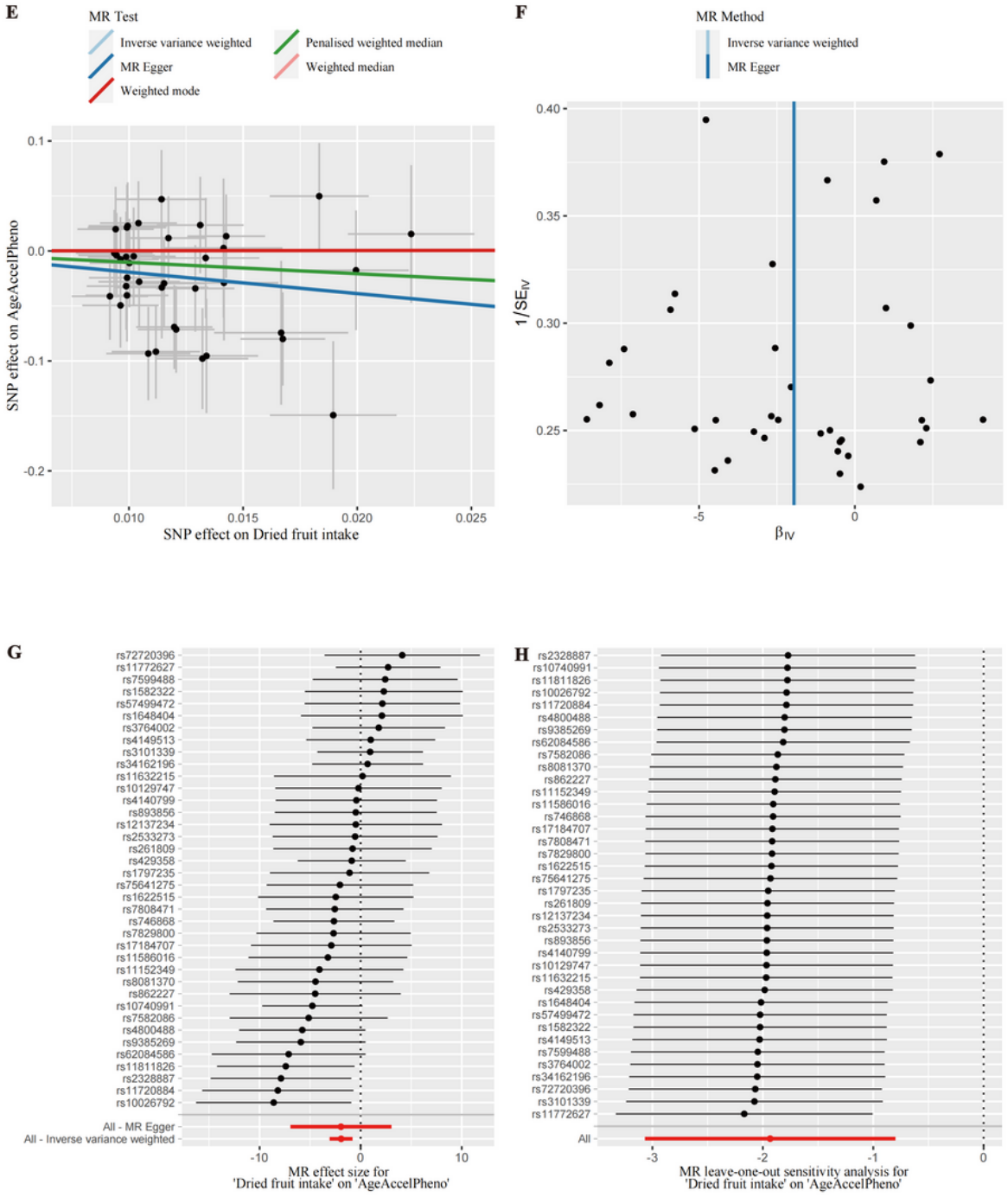

Figure 3

MR results of Dried fruit intake on AgeAccelPheno.

(A) Scatter plot of SNPs associated with Dried fruit intake on AgeAccelPheno.

(B) Forest plot of SNPs associated with Dried fruit intake on AgeAccelPheno.

(C) Funnel plot of SNPs associated with Dried fruit intake on AgeAccelPheno.

(D) Leave-one-out analysis of SNPs associated with Dried fruit intake on AgeAccelPheno.