Mendelian randomization study to assess causality between diet and phenotype of aging

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ABSTRACT

Background and Objectives: Observational research findings have demonstrated correlations between diet and the process of aging. Nevertheless, there remains uncertainty regarding possible disruption caused by confounding variables. To elucidate the connections between diet and aging, we employed the Mendelian randomization analysis. **Methods and Study Design:** The exposure factor was the daily diet, whereas accelerated aging was measured through telomere length, facial aging (FA), frailty index (FI), and senescence-associated secretory phenotypes (SASPs), representing the outcome factors. The primary analysis employed IVW analysis, with additional MR-Egger and Weighted Median analyses conducted to assess the reliability of the findings. Furthermore, we analyzed the heterogeneity and pleiotropy of the results. **Results:** The results revealed that the consumption of salad/raw vegetables and oily fish exhibited a negative correlation with FA, whereas coffee intake showed a positive correlation with FA. On the other hand, the intake of cheese, oily fish, dried fruit, and cereal showed negative associations with FI. Additionally, coffee, alcohol, and pork intake were positively associated with FI. Lastly, the intake of bread exhibited a positively correlated with SASPs, while the intake of cheese and coffee showed a negative correlation with SASPs. **Conclusions:** Our study revealed that the consumption of cheese, vegetables, oily fish, dried fruit, bread, coffee, and alcohol was associated with the aging process. Interestingly, our findings suggest that coffee intake may accelerate aging, whereas intake of oily fish may delay the aging process. However, it is important to note that further well-designed prospective studies are required to validate our findings in the future.

Key Words: Mendelian randomization, aging, facial aging, frailty index, SASPs

INTRODUCTION

Aging is an unavoidable and intricate biological process frequently accompanied by a decline in biological function and a range of prominent features, including mitochondrial dysfunction, DNA damage, telomere attrition, cellular senescence, and epigenetic changes.[1] Telomere length (TL) decreases with age in humans, and the resulting genomic instability caused by telomere shortening has been linked to age-related diseases.[2] Therefore, TL serves as a crucial indicator of cellular aging. In addition, chronic inflammation, frailty, and facial aging (FA) are also essential features of aging. In individuals, inflammation is characterized by escalated levels of circulating pro-inflammatory cytokines and heightened vulnerability to chronic ailments, precipitating frailness. Frailty, characterized by a decline in physiological reserves

and organ system dysfunction, is a prominent feature of pathological aging.[3,4] It is commonly measured using a frailty index (FI). The prevalence of frailty among elderly individuals is significant, leading to an increased susceptibility to falls, disability, hospitalization, and mortality. Hence, identifying and controlling factors that accelerate aging is crucial in preventing premature death, increasing healthy life expectancy, and improving the overall quality of life.

The influence of diet on aging has attracted considerable attention from researchers due to its accessibility and modifiability. Diet can affect various important aspects of cellular aging, including decreased ability to sense nutrients, genomic instability, disrupted proteostasis, epigenetic changes associated with aging, impaired mitochondrial function, senescence, and altered intercellular communication. A large-scale cross-sectional design research examined the correlation between the frequency of milk consumption, the intake of milk fat, and telomere length in the adult sample. The findings indicate no association between milk consumption frequency and telomere length. However, a robust relationship was observed between milk fat intake and telomere length.[5] Moreover, several studies have shown that the quality of dietary intake may affect the occurrence of frailty, and the dietary factors associated with frailty are intake of calories, protein, vitamin D and calcium. Furthermore, senescent cells secrete various inflammatory cytokines, chemokines, and matrix proteases, termed the senescence-associated secretory phenotypes (SASPs).[6,7] Nevertheless, the relationship between specific dietary intake and SASPs is unclear. Therefore, the effect of diet on aging needs to be further confirmed.

Mendelian randomization (MR) is a viable method for inferring associations between specific dietary intakes and aging. MR can use genetic variation as an instrumental variable (IV) for exposure (such as dietary intake) to make association inferences, which largely avoids the confounding factors common in observational studies. Many studies use MR to explore the correlation between dietary intake and diseases, including cardiovascular diseases, psychiatric disorders, and cancer. In this study, we performed MR analyses using pooled statistics from genome-wide association studies (GWAS) to characterize the associations between specific dietary components and aging comprehensively. This study provides further evidence for the value of diet as a modifiable factor in preventing aging.

MATERIALS AND METHODS

Design of experimental

MR is a research method that applies genetic tools as variables to study whether inferences about exposure factors affect outcomes. The following three principles guide the experimental design of Mendelian randomization. First, the association hypothesis - genetic mutations are strongly associated with exposure factors. Second, the exclusivity hypothesis - the genetic mutation affects the outcome only through the exposure factors pathway: no other pathway or mediator allows the effect of the genetic variant to act on the outcome. Third, the independence hypothesis – the genetic mutations are not associated with other factors.

Data source

The factors on diet-related exposures in this experiment were obtained from the UK Biobank. We chose four indicators for aging-related outcomes. Data on leukocyte mitochondrial length and facial aging were obtained from studies with Codd. The sample size for leukocyte mitochondrial length was 472,174 (216,187 males and 255,987 females, age 56.1 ± 7.90), and the sample size for facial aging was 423,999 (194,391 males and 229,601 females, age 40-69). The data related to the frailty index comes instead from an Atkins study. These factors are thought to be associated with reduced life expectancy. The SASPs-related GWAS data were obtained from the study by Ahola-Olli et al. have been uploaded to the mrcieu database (https://gwas.mrcieu.ac.uk/).[8]

Screening of genetic instrumental variables (IVs)

In order to obtain appropriate instrumental variables from different GWAS data. We first selected genome-wide significant single nucleotide polymorphisms (SNPs) ($p < 5\times10^{-8}$). We chose kb = 10000, $r^2 < 0.001$ as a condition to ensure linkage disequilibrium between instrumental variables.[9] Finally, to ensure that the study results were less likely to be affected by instrument bias, we evaluated the instrument strength F > 10 as instrumental variables. We then reconciled the exposure and outcome data sets to obtain the effect of genetic instruments on outcomes and removed palindromic SNPs.

Statistical analysis

We used the random-effects inverse variance weighting (IVW) method as the primary method for causality between dietary intake and aging. The IVW method is = the most potent method for causality detection in two-sample MR analyses when all MR assumptions are reasonable.

To prevent other factors from influencing the conclusions, we tested for heterogeneity in the IVW model through Cochran's Q test of $p < 0.05$, indicating the presence of heterogeneity. However, heterogeneity does not necessarily mean that the IVW model is invalid. The MR-Egger method allows for the presence of non-zero intercepts and is used to detect directional pleiotropy. Leave-one-out analyses were performed to assess whether the removal of individual SNPs significantly affected the results. We use the MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) method to detect outliers. As soon as outliers are detected, they will be removed. Once the removal of outliers, MR analysis will be performed again. The TwoSampleMR package in R software (version 4.3.0) was utilized to conduct all the analyses. Therefore, we performed sensitivity analyses using the MR-Egger and weighted median (WM) methods, allowing us to accurately estimate causality in the presence of invalid SNPs.

In addition, 95% confidence intervals (CIs) for the odds ratios (ORs) were used to estimate the association effect of dietary intake on the aging phenotype. $p < 0.05$ was considered suggestive of an association, whereas high-confidence associations were those that were multiple-tested with a Bonferroni-corrected critical value of 0.0029 (= 0.05/17).

RESULTS

Details of instrumental variables (IVs)

Firstly, we designed relevant experiments using different dietary intake characteristics as exposures and four aging phenotypes as endpoints. We selected 17 different dietary intakes as exposures and screened SNPs as instrumental variables based on solid correlation ($p < 5\times10^{-8}$) and mutual independence ($r^2 < 0.001$). Further calculations of the F-statistics of these IVs did not fall below the threshold of 10, suggesting that there was less evidence of weak instrumental bias in the present study. Therefore, we used these SNPs in subsequent analyses as the IVs to estimate the causal effect between dietary intake and aging.

Dietary factors on telomere length (TL)

TL is an essential marker of aging. The results are shown in Figure 1. According to the analysis conducted using IVW methodology, a causal association was identified solely between the consumption of dried fruits and the length of telomeres among the 17 dietary habits examined ($p = 0.0132$, $\beta = 0.109$, OR = 1.13， 95% CI, 1.01-1.26). Dry fruit intake appeared to be positively correlated with TL. However, the further analysis combined with MR-egger revealed that the direction of IVW and MR-egger ($p = 0.747$, $\beta = -0.0675$) did not

coincide, so the result was not meaningful. There was no causal association between dry fruit intake and telomere length.

Dietary factors on facial aging (FA)

FA is an outward manifestation of aging that involves skin laxity and superficial photodamage but also includes more profound loss of underlying structural volume of fat and muscle and even correlates with bone regression and remodeling.[10,11] Our research found that based on the results of the IVW analysis, salad / raw vegetable intake (p = 0.003, β = -0.0489, OR = 0.93, 95% CI, 0.87-0.99), oily fish intake (p = 0.006, β = -0.0488, OR = 0.95, 95% CI, 0.92-0.99) showed a negative correlation with FA whereas the intake of coffee (p = 0.028, β = 0.0391, OR = 1.04, 95% CI, 1.00-1.08) and pork (p = 0.003, β = 0.153, OR = 1.17, 95% CI, 1.05-1.29) showed a positive correlation with facial aging, as shown in Figure 2. Further analysis of the data's heterogeneity and pleiotropy revealed some pleiotropy in the analysis of pork intake and facial aging, and the results were not credible.

Dietary factors on the frailty index (FI)

Frailty has been ranked as one of the most critical risk factors for mortality in older people. It can be assessed for age-related phenotypic outcomes, with the FI being today's most commonly used indicator.[12,13] The results are shown in Figure 3. IVW analysis revealed that cheese intake (p = 8.03e-09, β = -0.219, OR = 0.8, 95% CI, 0.75-0.87), oily fish intake (p = 0.033, β = -0.109, OR = 0.9, 95% CI, 0.81-0.99), dried fruit intake (p = 1.46e-04, β = -0.310, OR = 0.73, 95% CI, 0.62-0.86), fresh fruit intake (p = 0.03, β = -0.152, OR = 0.86, 95% CI, 0.75-0.99) and cereal intake (p = 8.72e-08, β = -0.287, OR = 0.75, 95% CI, 0.68-0.83) exhibited negative associations with FI. Coffee intake (p = 0.009, β = 0.142, OR = 1.15, 95% CI, 1.04-1.28), alcohol intake (p = 2.52e-10, β = 0.148, OR = 1.16, 95% CI, 1.11-1.21) and pork intake (p = 2.52e-10, β = 0.313, OR = 1.37, 95% CI, 1.12-1.67) were positively associated with FI. However, the combination of MR-Egger and WM analyses revealed that the IVW for fresh fruit intake was not in the same direction as the MR-Egger analysis, and therefore this result is not credible.

Dietary factors on senescence-associated secretory phenotypes (SASPs)

Cellular aging is a distinctive feature of the aging process, and cells that become senescent produce SASPs, which initiate secondary senescence and disturb the balance of tissues, resulting in impaired tissue repair and regeneration.[14,15] Based on the MR analysis, it was

found that the bread intake was positively associated with levels of the interleukin-1 receptor antagonist (IL-1RA) (p = 0.05, β = 0.711, OR = 2.04, 95% CI, 1.01-4.10) and interleukin-17 (IL-7) (p = 0.006, β = 1.02, OR = 2.77, 95% CI, 1.35-5.71). Cheese intake negatively correlates with hepatocyte growth factor (HGF) (p = 0.026, β = -0.356, OR = 0.70, 95% CI, 0.51-0.96). Oily fish intake showed a positive correlation with levels of several SASPs, including macrophage inflammatory protein-1 β (MIP-1b) (p = 0.023, β = 0.175, OR = 0.67, 95% CI, 0.47-0.95), macrophage colony-stimulating factor (M-CSF) (p = 0.006, β = 0.328, OR = 2.45, 95% CI, 1.28-4.66), monocyte-chemotactic protein 3 (MCP3) (p = 0.039, β = 0.484, OR = 2.45, 95% CI, 1.28-4.66) and interleukin-1β (IL-1β) (p = 0.011, β = 0.532, OR = 1.70, 95% CI, 1.13-2.56). Coffee intake is negatively associated with M-CSF (p = 0.042, β = -0.714, OR = 0.49, 95% CI, 0.24-0.97). The results are shown in Figure 4.

DISCUSSION

Dietary intake has a close relationship with the process of aging. Various dietary habits have the ability to influence aging by regulating gut microbes and metabolites.[16,17] A growing body of evidence suggests that a sensible diet may slow down the aging process. In this research, we examined the effects of different dietary factors on aging using telomere length, facial aging, frailty index, and SASPs as markers. We discovered that the consumption of cheese, vegetables, oily fish, dried fruit, bread, coffee, and alcohol was associated with aging. Our findings indicate that coffee intake may accelerate aging, while oily fish intake may have a protective effect and delay the aging process.

Most of the current studies on dietary habits and aging phenotypes are based on clinical analyses, where genetic variation is used as a tool, compared to clinical analyses, and Mendelian randomization, which has the advantage over RCTs of incorporating larger sample sizes while allowing for the exclusion of as many confounding factors as possible.

Pork intake caused an increase in facial aging and frailty index, indicating a promoting effect of red meat intake on human aging. Multiple investigations have revealed a robust connection between the consumption of red meat and an increased susceptibility to various ailments.[18] Prolonged pork intake can alter the composition of gut microorganisms, thus affecting protein digestion and absorption.[19] In addition, red meat is rich in trimethylamine metabolized by gut microbes to form raw trimethylamine oxide (TMAO) and accelerate atherosclerosis.[20] Under the classification of the World Health Organization (WHO), red meat belongs to the group 2A carcinogens, which may potentially induce the development of cancer in individuals. Harmful substances such as N-nitroso compounds, heterocyclic amines

and heterocyclic aromatic amines are produced during high-temperature meat processing.[21] These substances are closely associated with the development of many types of cancer.[22] Furthermore, heme, abundant in red meat, catalyzes the production of N-nitroso compounds (NOCs) and lipid peroxidation products (LPOs). These carcinogens bind to DNA to form DNA adducts, interfering with DNA replication and repair, and causing cellular damage.[23] Clinical meta-studies have also found increased levels of interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) and other cytokines with red meat intake, suggesting that excessive red meat intake may cause chronic inflammation in the body, which can trigger aging.[24,25]

Analyses targeting the structure of the staple diet found that bread appeared to contribute to aging, while a cereal diet was negatively associated with frailty index. Lack of refined processes in cereals compared to bread. Bread has a lower fiber content compared to cereals. Higher refined carbohydrates can increase the burden of hyperglycemia and the risk of cardiovascular disease.[26] In contrast, a significant portion of the carbohydrates in whole grains is dietary fibers that cannot be digested. They can act on intestinal activity and transit and serve as valuable substrates for intestinal microorganisms, influencing their composition and structure. Typically, the digestible and indigestible carbohydrate profile and its complexity determine the nutritional quality of grains. Whole grains are more intricate compared to refined grains, and the significance of non-digestible carbohydrates and their markedly superior nutrient content in whole grains has resulted in the endorsement of whole grains as a component of a nourishing and environmentally friendly diet. Therefore, an increased consumption of whole grains is linked to reduced occurrences of cardiovascular disease, type 2 diabetes, certain cancers, and mortality.[27] Refined foods have also been found to have a risk of triggering shortening of telomere length in clinical studies. This is similar to the conclusion we reached. The occurrence of this phenomenon may be related to the additives contained in refined foods.[28]

Our findings point to vegetable and fruit intake as beneficial for longevity. Fruits and vegetables are acknowledged as crucial components of a nutritious diet for individuals of all ages. Enhanced consumption of these food groups diminishes the likelihood of cardiovascular disease, numerous degenerative disorders, diverse forms of cancer, and mortality.[29,30] Several meta-analytical studies have demonstrated a significant correlation between the consumption of vegetables and fruits and a decreased vulnerability to frailty. Our investigation also revealed an inverse association between the intake of fruits and vegetables and indices of frailty, which corroborates this finding.[31,32] Fruits and vegetables are rich in selenium, vitamin C, vitamin E and other antioxidants (e.g., carotenoids), which help reduce oxidative

stress levels, mitochondrial dysfunction and apoptosis.[33] In addition, fruit and vegetable intake is also thought to be effective in reducing the levels of inflammatory factors in the body, such as C-reactive protein (CRP) and TNF-α. The fact that aging is closely linked to inflammatory states may also be a mechanism by which fruit and vegetable intake affect aging.[34] The high levels of antioxidant-rich components such as vitamin C and carotenoids found in fruits and vegetables have been shown to be effective in mitigating oxidative stress in the body's cells, which is thought to potentially promote senescence by modulating mitochondrial length, as well as triggering chronic inflammation to promote cellular senescence.[35]

As we all know, we also found that alcohol intake promotes aging, while cheese intake inhibits aging. Alcohol consumption was powerfully associated with an increase in the frailty index. The effect of alcohol intake on life expectancy is currently inconclusive. Clinical studies have shown that long-term alcohol abuse damages several tissues and organs. It can develop different pathologies, like alcohol use disorder, alcoholic liver disease and alcohol-related brain damage, and increase the risk of gastrointestinal, respiratory, breast and liver cancers.[36–38] Some researchers have found that alcohol abuse may shorten telomere length, but moderate alcohol intake does not affect telomeres.[39]

On the other hand, cheese was negatively correlated with the risk of frailty and with levels of the SASPs factor HGF. Dairy intake is closely related to health, and dairy intake is beneficial for chronic diseases such as cancer. Cheese intake affects the metabolic synthesis of amino acids such as 3-phenyl lactate, methionine, proline, leucine, tyrosine, valine and isoleucine.[40] Casein has been shown to have potential anti-mutagenic and anti-cancer properties, while whey protein hydrolysate has been shown to prevent chemically induced mammary tumors in rats.[41,42] In addition, Bordoni et al. meta-analysis found that intervention with fermented dairy products reduced biomarkers of inflammation, while intervention with non-fermented dairy products did not. Some researchers have noted that dairy interventions appeared to have more potent anti-inflammatory activity in participants with metabolic disorders, including overweight and obesity.[43,44] In addition, studies have shown that cheese is rich in spermidine, which inhibits cellular oxidative stress and necrosis by enhancing cellular autophagy. Supplementation with spermidine has been shown to increase the lifespan of yeast, nematodes and fruit flies.[45]

Surprisingly, oily fish and coffee seem to have a bidirectional effect on aging. We found that the intake of oily fish reduces the risk of frailty index and facial aging but increases the risk of IL-1β, MCP3, M-CSF, and MIP-1b. Oily fish not only harbors ample omega-3

polyunsaturated fatty acids (PUFAs), but it also holds a plethora of nutrients consisting of high-quality proteins, vitamin A, vitamin D, selenium, and an array of minerals and elements.[46] The components found in oily fish have the potential to enhance collagen and elastin production, leading to stronger skin and a decelerated aging process.[47] Oily fish, abundant in long-chain Omega-3 fatty acids, exhibits diminished inflammatory markers and risk factors associated with cardiovascular disease.[48] However, our study discovered that the consumption of oily fish led to an increase in the expression of inflammatory factors. The above evidence indicates that lipophilic persistent organic pollutants, namely dioxins and dioxin-like polychlorinated biphenyls, might be found in fatty fish. These substances have the potential to harm cellular structures.[49]

Similarly, we found that coffee raised the risk of frailty and facial aging but reduced the risk of M-CSF in SASPs. The role of coffee in aging is not yet clear. The high caffeine content of coffee often causes anxiety, insomnia, headaches, tremors and palpitations, increasing the risk of cardiovascular disease.[50] Coffee also increases the risk of bone loss and fractures, which may cause changes in the facial bones that lead to facial aging.[51] Osteoporosis, in turn, is an essential factor that triggers an increase in the frailty index. However, coffee contains antioxidants such as tocopherols and chlorogenic acid that are thought to be beneficial for prolonging life. Coffee also protects the liver by increasing peroxisome proliferator-activated receptor α (PPAR-α) mediated fatty acid oxidation, reducing collagen deposition, and generally increasing protective antioxidants. In addition, coffee is thought to reduce both total mammalian target of rapamycin (mTOR) levels and phosphorylated (Ser2448) mTOR levels, thereby extending lifespan.[52]

We also found that dry fruit intake appeared to be positively associated with telomere length, but the results lacked statistical significance. Earlier studies have indicated a positive connection between the intake of fruits and vegetables and the length of telomeres.[53] The length of telomeres is a crucial indicator of aging, which decreases as individuals grow older. The length of telomeres is determined by a combination of factors, including the regulation of telomerase activity, telomere protection, and/or telomere structure. Therefore, further investigation is required to demonstrate the impact of dietary factors on telomere length.

Although our experimental results revealed some correlations between dietary habits and aging, it is important to note that telomere length, facial aging, frailty index, and SASPs are only partial indicators of aging. Therefore, further clinical research is needed to establish a clinical correlation between dietary habits and aging. Furthermore, it is noteworthy that most

of our samples within the cohort originate from European ethnicities, underscoring the need to enhance the inclusivity of racial diversities in forthcoming investigations.

Conclusion

The present research elucidates the association between dietary consumption and the process of aging. The purpose of this study was to evaluate the influence of different nutritional components on the process of aging through the analysis of indicators such as telomere length, facial aging, frailty index, and SASPs. Our study suggest that coffee consumption might hasten the aging process, whereas the consumption of oily fish may have a safeguarding effect, thereby delaying aging. It is crucial to interpret our results cautiously, as further well-designed prospective studies will be essential to validate and verify our findings in future research endeavors.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare that there is no conflict of interest.

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expourse	SNP	P. value	OR	95%CI
Alcohol intake	77	0.3030	1.01	（0.99-1.04）
Beef intake	14	0.7460	1.02	（0.91-1.15）
Bread intake	19	0.7480	1.02	（0.92-1.13）
Cereal intake	34	0.5470	1.03	（0.94-1.11）
Cheese intake	56	0.3460	1.03	（0.97-1.08）
Coffee intake	35	0.2360	0.96	（0.90-1.03）
Cooked vegetable intake	12	0.0595	1.12	（1.00-1.27）
Dried fruit intake	34	0.0132	1.11	（1.02-1.22）
Fresh fruit intake	45	0.6290	1.02	（0.93-1.12）
Lamb/mutton intake	27	0.5750	1.03	（0.93-1.13）
Non-oily fish intake	9	0.7410	1.03	（0.85-1.25）
Oily fish intake	54	0.1130	1.05	（0.99-1.11）
Pork intake	10	0.1510	1.11	（0.96-1.27）
Poultry intake	6	0.3220	1.13	（0.89-1.43）
Processed meat intake	20	0.6680	0.95	（0.75-1.20）
Salad/raw vegetable	15	0.9230	1.01	（0.89-1.14）
Tea intake	32	0.5490	1.01	（0.97-1.06）

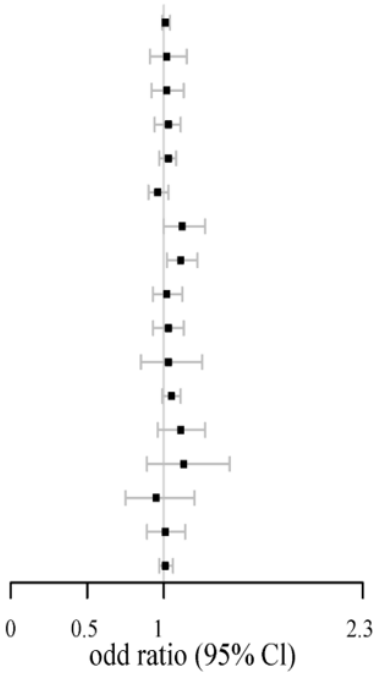

Figure 1. Forest plot of genetic associations of different dietary habits and telomere length. CI, confidence interval; OR, odds ratio.

expourse	SNP	P. value	OR	95%CI
Alcohol intake	92	0.85500	1.00	(0.99-1.01)
Beef intake	13	0.19700	1.07	(0.96-1.19)
Bread intake	26	0.70300	0.99	(0.94-1.04)
Cereal intake	36	0.46900	1.02	(0.97-1.06)
Cheese intake	57	0.41600	0.99	(0.96-1.02)
Coffee intake	37	0.02810	1.04	(1.00-1.08)
Cooked vegetable intake	13	0.31600	0.96	(0.89-1.04)
Dried fruit intake	35	0.94100	1.00	(0.95-1.05)
Fresh fruit intake	48	0.71200	1.01	(0.96-1.06)
Lamb/mutton intake	29	0.76700	0.99	(0.92-1.07)
Non-oily fish intake	9	0.01010	0.86	(0.77-0.97)
Oily fish intake	54	0.00635	0.95	(0.92-0.99)
Pork intake	13	0.00350	1.17	(1.05-1.29)
Poultry intake	5	0.24000	0.91	(0.78-1.06)
Processed meat intake	21	0.17900	1.04	(0.98-1.11)
Salad/raw vegetable intake	16	0.02780	0.93	(0.87-0.99)
Tea intake	37	0.32800	1.01	(0.99-1.04)

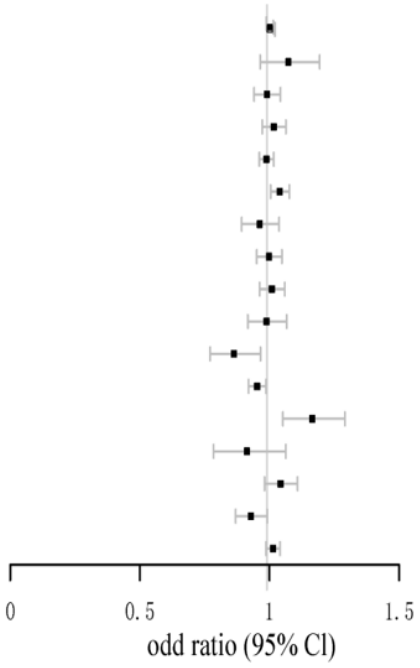

Figure 2. Forest plot of genetic associations of different dietary habits and facial aging. CI, confidence interval; OR, odds ratio.

expourse	SNP	P. value	OR 95%CI
Alcohol intake	91	2.52e-10	1.16 (1.11-1.21)
Beef intake	13	8.73e-01	1.02 (0.83-1.25)
Bread intake	23	5.39e-01	0.96 (0.83-1.11)
Cereal intake	36	8.72e-08	0.75 (0.68-0.83)
Cheese intake	60	8.03e-09	0.80 (0.75-0.87)
Coffee intake	34	9.21e-03	1.15 (1.04-1.28)
Cooked vegetable intake	14	5.13e-02	1.23 (1.00-1.53)
Dried fruit intake	36	1.46e-04	0.73 (0.62-0.86)
Fresh fruit intake	50	3.00e-02	0.86 (0.75-0.99)
Lamb/mutton intake	29	2.88e-01	0.91 (0.77-1.08)
Non-oily fish intake	10	5.69e-01	1.07 (0.84-1.36)
Oily fish intake	57	3.32e-02	0.90 (0.81-0.99)
Pork intake	13	2.16e-03	1.37 (1.12-1.67)
Poultry intake	4	2.62e-01	1.48 (0.75-2.91)
Processed meat intake	19	8.13e-01	1.02 (0.86-1.22)
Salad / raw vegetable intake	17	3.95e-01	0.91 (0.73-1.14)
Tea intake	38	7.86e-01	1.01 (0.93-1.10)

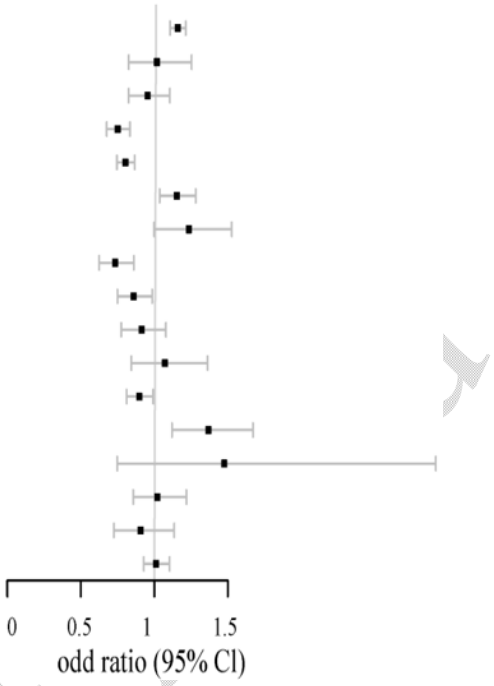

Figure 3. Forest plot of genetic associations of different dietary habits and frailty index. CI, confidence interval; OR, odds ratio.

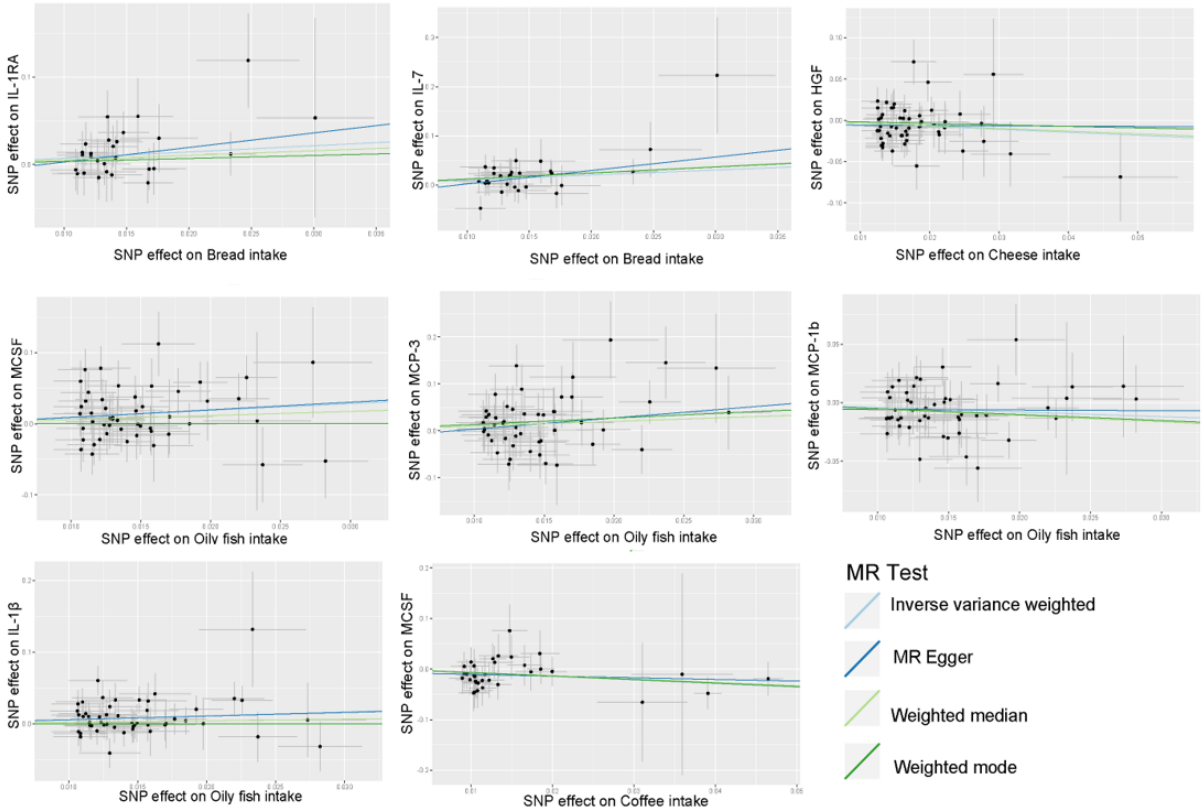

Figure 4. The MR analyses: Casual effect of different dietary on SASPs. Lines in light blue, blue, light green, and green represent IVW, MR - Egger, weighted median, and weight mode methods