Original Article

Causal association of dietary intake habits and telomere lengths: A Mendelian randomization study

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Background and Objectives: Healthy diets are crucial in disease prevention and balanced diets can slow telomere shortening. Currently, it is still unclear which dietary factors are causally related to telomere length. **Methods and Study Design:** The inverse variance weighted, Mendelian Randomization-Egger, weighted median, simple mode, and weighted mode methods were used. Additionally, heterogeneity, pleiotropy, MR-PRESSO and leave-one-out tests were conducted to ensure accuracy. Outcomes included granulocyte, lymphocyte, naive T-cell, memory T-cell, B-cell, and natural killer-cell telomere lengths. Exposures included alcohol intake frequency, alcoholic drinks per week, average weekly beer plus cider intake, average weekly red wine intake, intake of beef, bread, cereal, coffee, cooked vegetable, dried fruit, fresh fruit, lamb/mutton, non-oily fish, oily fish, pork, processed meat, salad/raw vegetable, tea and water. **Results:** The positive causal relationships were found between dried fruit intake and granulocyte telomere length (OR: 4.31; 95% CI: 1.29 to 14.4; $p = 0.02$), lymphocyte telomere length (OR: 4.22; 95% CI: 1.21 to 14.7; $p = 0.02$), naive T-cell telomere length (OR: 5.49; 95% CI: 1.58 to 19.0; $p = 0.01$). Oily fish intake was positively associated with memory T-cell telomere length (OR: 2.55; 95% CI: 1.16 to 5.58; $p = 0.02$). No significant causal relationships were found between other exposures and outcomes. **Conclusions:** This study found positive causal associations between telomere length and the intake of dried fruit and oily fish. No significant causal relationships were observed with other dietary factors. These findings provide insights into how specific dietary components may help maintain telomere length.

Key Words: dietary factors, telomere length, Mendelian randomization, causal relationship, healthy diet reference

INTRODUCTION

Telomeres are complex structures located at the ends of chromosomes, composed of DNA sequences and associated proteins.[1] Telomeres maintain chromosome stability during cell division and tend to shorten over time, and this shortening ultimately leads to cellular senescence or death.[2] An important property of telomeres is their role in the aging process. Moreover, telomere length (TL) has been associated with various types of tumors as well as several non-cancerous diseases.[3] In brief, TL plays a crucial role in human health, as maintaining TL helps safeguard chromosomes, cells, and overall health.

An unhealthy lifestyle accelerates telomere shortening.[4] Thus, adopting a healthy lifestyle is crucial for slowing this process. As a part of a healthy lifestyle, balanced and nutritious dietary patterns contribute to slowing down telomeres shortening.[5] Dietary patterns are a crucial modifiable risk factor in preventing diseases, with dietary risks causing 11 million deaths globally in 2017 alone—accounting for 22% of all adult deaths.[6] However, the specific dietary habits beneficial for maintaining TL have not yet been fully established. Therefore, the aim of this study was to explore the potential impact of common dietary habits on TL. It aimed to provide guidance for healthier dietary habits.

The Mendelian randomization (MR) analysis, a statistical method, uses genetic variants as instrumental variables to assess causal relationships between exposures and outcomes, thereby reducing confounding factors and reverse causation.[7] It is widely applied in biomedical research, such as studying the association between dietary vitamin C intake and endometrial cancer,[8] which highlights its potential to guide public health strategies. With continued advancements in genetic data and analytical methods, MR plays an increasingly important role in elucidating causal pathways and supporting evidence-based interventions.

In this study, the causal relationships between various dietary factors and TLs were studied using MR. The purpose of this study was to acquire a more in-depth understanding of whether dietary factors might influence TL by examining the causal relationship between them. This study provided more valuable information regarding the potential influence of diet on telomeres and laid a foundation for understanding the potential mechanisms.

METHODS

Study design

The MR analysis is established on the following basic assumptions (Figure 1): 1. Instrumental variables (IVs) are strongly associated with dietary factors. 2. IVs are not influenced by identified confounding factors, which are identified based on the studies by Bountziouka et al.[4] 3. The influence of IVs on TL is restricted to their impact through dietary factors. IVs are not directly associated with TL. The statistical analyses were performed using the Two SampleMR packages within the R software environment (version 4.0.4).

Data sources

The Genome-wide association studies (GWAS) data used in this study were acquired from the open GWAS project of the Medical Research Council Integrative Epidemiology Unit at the University of Bristol. The data on granulocyte, lymphocyte, naive T-cell, memory T-cell, B-cell, and natural killer-cell (NK-cell) telomere lengths were obtained from a study conducted by Andreu-Sánchez et al. (2022), which included a total of 902 participants.[9] Regarding dietary factors, data were drawn from studies conducted by Elsworth et al. (2018) and Liu et al. (2019).[10] The number of cases was as follows: alcohol intake frequency (462,346 cases); alcoholic drinks per week (335,394 cases); average weekly beer plus cider intake (327,634 cases); average weekly red wine intake (327,026 cases); beef intake (461,053 cases); bread intake (452,236 cases); cereal intake (441,640 cases); coffee intake (428,860 cases); cooked vegetable intake (448,651 cases); dried fruit intake (421,764 cases); fresh fruit intake (446,462 cases); lamb/mutton intake (460,006 cas-

es); non-oily fish intake (460,880 cases); oily fish intake (460,443 cases); pork intake (460,162 cases); processed meat intake (461,981 cases); salad/raw vegetable intake (435,435 cases); tea intake (447,485 cases); and water intake (427,588 cases). The data used in this study were publicly available, anonymous, and de-identified. Consequently, this study was not subject to approval by an ethics review board. For further information about dietary factors and TL, reference was made to Supplementary Table 1.

IVs selection

Firstly, SNPs selected as IVs should apply the three assumptions mentioned above. In this study, SNPs with strong correlations ($p < 5e-08$) were selected. These SNPs were input into Phenoscanner to examine their associations with confounding factors and telomere length. These confounding factors were identified based on the study by Bountziouka et al.[4] The SNPs associated with confounding factors or telomere length were excluded. Secondly, linkage disequilibrium could introduce bias in the results.[11] Therefore, in this study, a threshold of $r^2 = 0.001$ and kb = 10000 was set, which meant that within a 10000 kb range, SNPs were removed if the r^2 between these SNPs and the most significant SNP was > 0.001. This helped to reduce the potential bias due to linkage disequilibrium. Next, the F-statistic, which was calculated to assess the strength of the relationship between IVs and exposure, was considered sufficient for a strong correlation if it exceeded 10.[12] Then, based on the SNPs from the extracted exposure data, and the outcome data was retrieved from the designated outcome database. If the SNPs lacked the effect allele frequencies, the correspond-
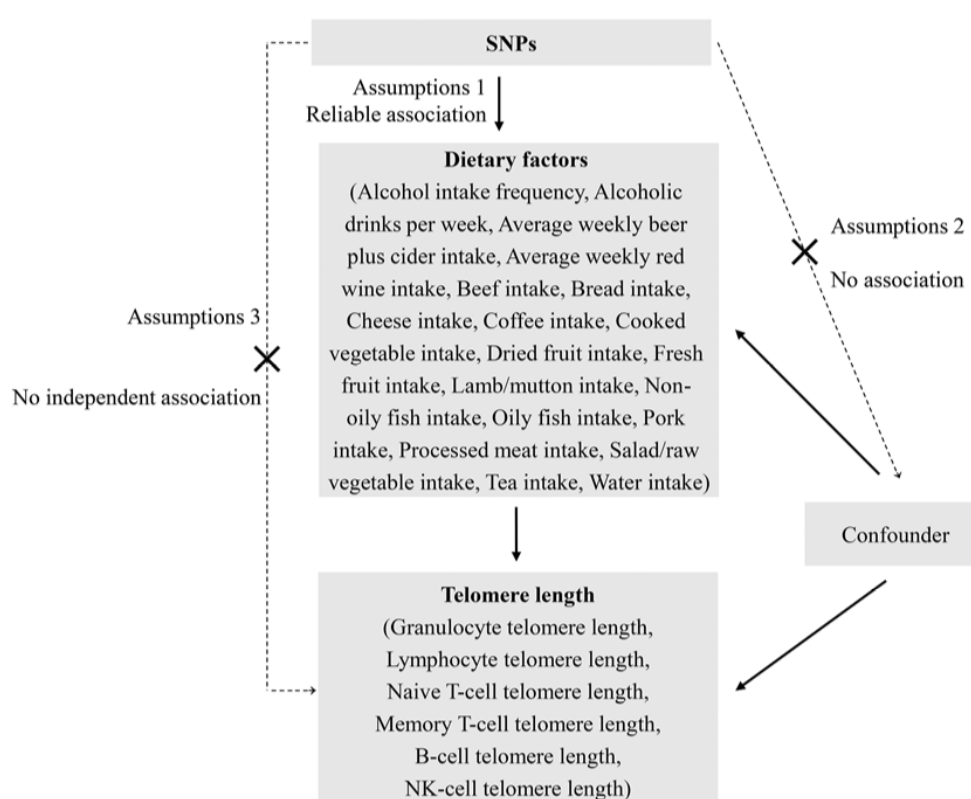

Figure 1. Three assumptions of the MR study

ing information was sought on the National Center for Biotechnology Information. Lastly, the alleles in the exposure data and the outcome data were aligned, and SNPs with palindromic structures were eliminated. The statistical analysis was conducted based on these aligned data.

Statistical analysis

The inverse variance weighted (IVW), Mendelian Randomization-Egger (MR-Egger), and weighted median (WM), simple mode, and weighted mode were used in this study. The IVW method provides an overall estimate of the causal effect by weighting SNPs inversely to their variances, meaning that SNPs with smaller variances are assigned larger weights.[13] By integrating the effect estimates of these SNPs, the method provides a comprehensive estimate of the causal relationship between exposure and outcome.[13] This method is consistent with the theoretical foundation of MR, as it can make full use of the genetic variants to assess the causal association between exposure and outcome. The MR-Egger method is based on a linear regression model and uses regression analysis to obtain the causal relationship between the exposure and the outcome.[14] It detects and corrects for pleiotropy, providing a more robust estimate of the causal effect when pleiotropy exists.[14] The WM method estimates causal effects by assigning varied weights to genetic variants based on their precision and derives the median of causal estimates.[15] When pleiotropy exists, it can also obtain a more reliable causal effect through reasonable weight assignment.[15] The simple mode and the weighted mode mainly focus on the identification and analysis of data patterns. They may be relatively weak in detecting causal relationships and are more used as supplementary analysis methods. The primary analysis method chosen for this study was the IVW method. Additionally, the results of the MR-Egger, WM, simple mode, and weighted mode were used as a supplement.

Sensitivity analysis

The first step was to perform a heterogeneity test. The purpose is to determine whether there are differences in causal effects among different SNPs, which is tested using Cochran's Q test.[16] In this study, a fixed-effects model was used, and in the presence of heterogeneity ($p < 0.05$), a random-effects model was used.[17] The second step was to conduct a pleiotropy test. Pleiotropy can lead to spurious correlation results. In MR, pleiotropy means that besides influencing the outcome through the exposure, an SNP can also affect the outcome via confounding factors. If pleiotropy is present, then SNPs can affect the outcome without acting through exposure, which violates the assumption of MR.[16] And MR-PRESSO test was conducted. The MR-PRESSO test is used to detect and correct for pleiotropy and outliers. It helps rule out the bias caused by reverse causation.[18] Finally, the leave-one-out analysis was performed. The evaluation of how removing a SNP from all SNPs would affect the model's results is conducted. It is used to check for the existence of outlier SNPs.[8]

RESULTS

IVs selection

This study included 19 dietary factors. 11 to 99 SNPs were retrieved from publicly available GWAS data using R programming, and these SNPs were strongly associated with exposures ($p < 5e-08$) and independent ($r^2 < 0.001$ and kb > 10000). After inputting these SNPs into Phenoscanner, the SNPs associated with confounders were removed. The F-statistics ranged from 28.8 to 647. All F-statistics exceeded 10, with no weak IVs, as shown in Supplementary Table 2. The principle of strong association for SNPs was satisfied. The SNPs for being palindromic with intermediate allele frequencies, and those for incompatible alleles were removed. The number of SNPs used ranged from 7 to 62, as shown in Figure 2.

Statistical analysis outcomes

According to the IVW method results, dried fruit intake was positively correlated with granulocyte telomere length (OR: 4.31; 95% CI: 1.29 to 14.4; $p = 0.02$), lymphocyte telomere length (OR: 4.22; 95% CI: 1.21 to 14.7; $p = 0.02$), naive T-cell telomere length (OR: 5.49; 95% CI: 1.58 to 19.0; p = 0.01), while oily fish intake was positively correlated with memory T-cell telomere length (OR: 2.55; 95% CI: 1.16 to 5.58; $p = 0.02$) (Figure 2). Dried fruit intake was not correlated with memory T-cell telomere length, B-cell telomere length, and NK-cell telomere length. Oily fish intake was not correlated with granulocyte telomere length, lymphocyte telomere length, naive T-cell telomere length, B-cell telomere length, and NK-cell telomere length. Alcohol intake frequency, alcoholic drinks per week, average weekly beer plus cider intake, average weekly red wine intake, beef intake, bread intake, cereal intake, coffee intake, cooked vegetable intake, fresh fruit intake, lamb/mutton intake, non-oily fish intake, pork intake, processed meat intake, salad/raw vegetable intake, tea intake, and water intake were not correlated with granulocyte telomere length, lymphocyte telomere length, naive T-cell telomere length, memory T-cell telomere length, B-cell telomere length, and NK-cell telomere length (Figure 2). Additional information on MR-Egger, WM, simple mode, and weighted mode was detailed in Supplementary Table 3. The forest plots illustrated the causal effects of each SNP on outcomes, with all-IVW > 0, indicating a positive causal relationship. The SNPs with the largest causal effects were rs10129747 for dried fruit intake and rs552234 for oily fish intake (Figure 3). In the scatter plot (Supplementary Figure 1), the slope of IVW trend line was greater than 0, confirming the positive causal relationship between dried fruit intake and granulocyte telomere length, lymphocyte telomere length, naive T-cell telomere length, as well as between oily fish intake and memory T-cell telomere length.

Sensitivity analysis outcomes

In the heterogeneity test (Table 1), the p-values ranged from 0.07 to 0.99 and were all greater than 0.05, indicating no heterogeneity. The even distribution of SNP points on both sides of the IVW line in the funnel plot indicated the absence of heterogeneity between dried fruit intake and granulocyte telomere length, lymphocyte telomere length, naive T-cell telomere length, as well as between
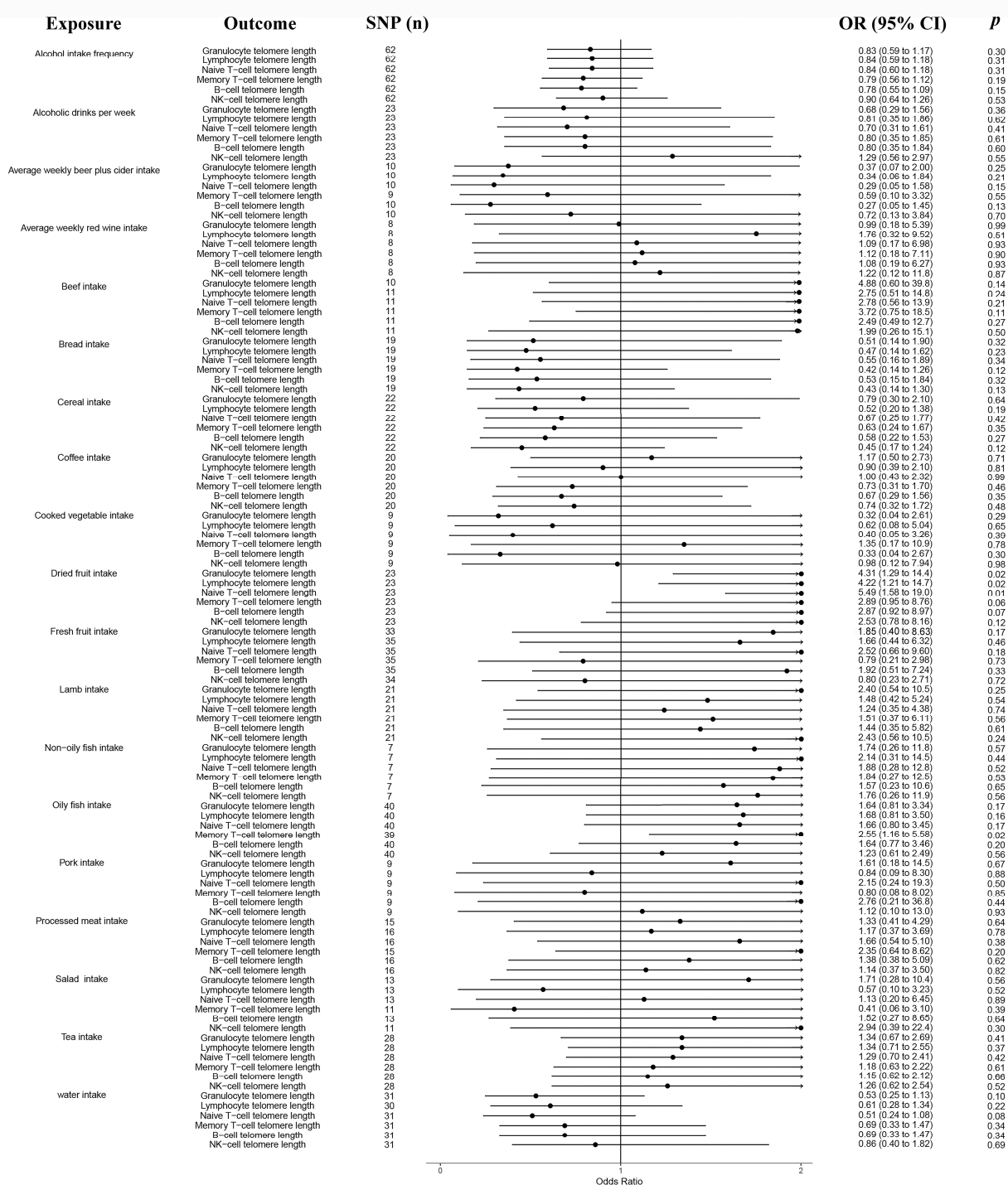
Exposure	Outcome	SNP (n)	OR (95% CI)	p
Alcohol intake frequency	Granulocyte telomere length	62	0.83 (0.59 to 1.17)	0.30
	Lymphocyte telomere length	62	0.84 (0.59 to 1.18)	0.31
	Naive T-cell telomere length	62	0.84 (0.60 to 1.18)	0.31
	Memory T-cell telomere length	62	0.79 (0.56 to 1.12)	0.19
	B-cell telomere length	62	0.78 (0.55 to 1.09)	0.15
	NK-cell telomere length	62	0.90 (0.64 to 1.26)	0.53
Alcoholic drinks per week	Granulocyte telomere length	23	0.68 (0.29 to 1.56)	0.36
	Lymphocyte telomere length	23	0.81 (0.35 to 1.86)	0.62
	Naive T-cell telomere length	23	0.70 (0.31 to 1.61)	0.41
	Memory T-cell telomere length	23	0.80 (0.35 to 1.85)	0.61
	B-cell telomere length	23	0.80 (0.35 to 1.84)	0.60
	NK-cell telomere length	23	1.29 (0.56 to 2.97)	0.55
Average weekly beer plus cider intake	Granulocyte telomere length	10	0.37 (0.07 to 2.00)	0.25
	Lymphocyte telomere length	10	0.34 (0.06 to 1.84)	0.21
	Naive T-cell telomere length	10	0.29 (0.05 to 1.58)	0.15
	Memory T-cell telomere length	9	0.59 (0.10 to 3.32)	0.55
	B-cell telomere length	10	0.27 (0.05 to 1.45)	0.13
	NK-cell telomere length	10	0.72 (0.13 to 3.84)	0.70
Average weekly red wine intake	Granulocyte telomere length	8	0.99 (0.18 to 5.39)	0.99
	Lymphocyte telomere length	8	1.76 (0.32 to 9.52)	0.51
	Naive T-cell telomere length	8	1.09 (0.17 to 6.98)	0.93
	Memory T-cell telomere length	8	1.12 (0.18 to 7.11)	0.90
	B-cell telomere length	8	1.08 (0.19 to 6.27)	0.93
	NK-cell telomere length	8	1.22 (0.12 to 11.8)	0.87
Beef intake	Granulocyte telomere length	10	4.88 (0.60 to 39.8)	0.14
	Lymphocyte telomere length	11	2.75 (0.51 to 14.8)	0.24
	Naive T-cell telomere length	11	2.78 (0.56 to 13.9)	0.21
	Memory T-cell telomere length	11	3.72 (0.75 to 18.5)	0.11
	B-cell telomere length	11	2.49 (0.49 to 12.7)	0.27
	NK-cell telomere length	11	1.99 (0.26 to 15.1)	0.50
Bread intake	Granulocyte telomere length	19	0.51 (0.14 to 1.90)	0.32
	Lymphocyte telomere length	19	0.47 (0.14 to 1.62)	0.23
	Naive T-cell telomere length	19	0.55 (0.16 to 1.89)	0.34
	Memory T-cell telomere length	19	0.42 (0.14 to 1.26)	0.12
	B-cell telomere length	19	0.53 (0.15 to 1.84)	0.32
	NK-cell telomere length	19	0.43 (0.14 to 1.30)	0.13
Cereal intake	Granulocyte telomere length	22	0.79 (0.30 to 2.10)	0.64
	Lymphocyte telomere length	22	0.52 (0.20 to 1.38)	0.19
	Naive T-cell telomere length	22	0.67 (0.25 to 1.77)	0.42
	Memory T-cell telomere length	22	0.63 (0.24 to 1.67)	0.35
	B-cell telomere length	22	0.58 (0.22 to 1.53)	0.27
	NK-cell telomere length	22	0.45 (0.17 to 1.24)	0.12
Coffee intake	Granulocyte telomere length	20	1.17 (0.50 to 2.73)	0.71
	Lymphocyte telomere length	20	0.90 (0.39 to 2.10)	0.81
	Naive T-cell telomere length	20	1.00 (0.43 to 2.32)	0.99
	Memory T-cell telomere length	20	0.73 (0.31 to 1.70)	0.46
	B-cell telomere length	20	0.67 (0.29 to 1.56)	0.35
	NK-cell telomere length	20	0.74 (0.32 to 1.72)	0.48
Cooked vegetable intake	Granulocyte telomere length	9	0.32 (0.04 to 2.61)	0.29
	Lymphocyte telomere length	9	0.62 (0.08 to 5.04)	0.65
	Naive T-cell telomere length	9	0.40 (0.05 to 3.26)	0.39
	Memory T-cell telomere length	9	1.35 (0.17 to 10.9)	0.78
	B-cell telomere length	9	0.33 (0.04 to 2.67)	0.30
	NK-cell telomere length	9	0.98 (0.12 to 7.94)	0.98
Dried fruit intake	Granulocyte telomere length	23	4.31 (1.29 to 14.4)	0.02
	Lymphocyte telomere length	23	4.22 (1.21 to 14.7)	0.02
	Naive T-cell telomere length	23	5.49 (1.58 to 19.0)	0.01
	Memory T-cell telomere length	23	2.89 (0.95 to 8.76)	0.06
	B-cell telomere length	23	2.87 (0.92 to 8.97)	0.07
	NK-cell telomere length	23	2.53 (0.78 to 8.16)	0.12
Fresh fruit intake	Granulocyte telomere length	33	1.85 (0.40 to 8.63)	0.17
	Lymphocyte telomere length	35	1.66 (0.44 to 6.32)	0.46
	Naive T-cell telomere length	35	2.52 (0.66 to 9.60)	0.18
	Memory T-cell telomere length	35	0.79 (0.21 to 2.98)	0.73
	B-cell telomere length	35	1.92 (0.51 to 7.24)	0.33
	NK-cell telomere length	34	0.80 (0.23 to 2.71)	0.72
Lamb intake	Granulocyte telomere length	21	2.40 (0.54 to 10.5)	0.25
	Lymphocyte telomere length	21	1.48 (0.42 to 5.24)	0.54
	Naive T-cell telomere length	21	1.24 (0.35 to 4.38)	0.74
	Memory T-cell telomere length	21	1.51 (0.37 to 6.11)	0.56
	B-cell telomere length	21	1.44 (0.35 to 5.82)	0.61
	NK-cell telomere length	21	2.43 (0.56 to 10.5)	0.24
Non-oily fish intake	Granulocyte telomere length	7	1.74 (0.26 to 11.8)	0.57
	Lymphocyte telomere length	7	2.14 (0.31 to 14.5)	0.44
	Naive T-cell telomere length	7	1.88 (0.28 to 12.8)	0.52
	Memory T-cell telomere length	7	1.84 (0.27 to 12.5)	0.53
	B-cell telomere length	7	1.57 (0.23 to 10.6)	0.65
	NK-cell telomere length	7	1.76 (0.26 to 11.9)	0.56
Oily fish intake	Granulocyte telomere length	40	1.64 (0.81 to 3.34)	0.17
	Lymphocyte telomere length	40	1.68 (0.81 to 3.50)	0.16
	Naive T-cell telomere length	40	1.66 (0.80 to 3.45)	0.17
	Memory T-cell telomere length	39	2.55 (1.16 to 5.58)	0.02
	B-cell telomere length	40	1.64 (0.77 to 3.46)	0.20
	NK-cell telomere length	40	1.23 (0.61 to 2.49)	0.56
Pork intake	Granulocyte telomere length	9	1.61 (0.18 to 14.5)	0.67
	Lymphocyte telomere length	9	0.84 (0.09 to 8.30)	0.88
	Naive T-cell telomere length	9	2.15 (0.24 to 19.3)	0.50
	Memory T-cell telomere length	9	0.80 (0.08 to 8.02)	0.85
	B-cell telomere length	9	2.76 (0.21 to 36.8)	0.44
	NK-cell telomere length	9	1.12 (0.10 to 13.0)	0.93
Processed meat intake	Granulocyte telomere length	15	1.33 (0.41 to 4.29)	0.64
	Lymphocyte telomere length	16	1.17 (0.37 to 3.69)	0.78
	Naive T-cell telomere length	16	1.66 (0.54 to 5.10)	0.38
	Memory T-cell telomere length	15	2.35 (0.64 to 8.62)	0.20
	B-cell telomere length	16	1.38 (0.38 to 5.09)	0.62
	NK-cell telomere length	16	1.14 (0.37 to 3.50)	0.82
Salad intake	Granulocyte telomere length	13	1.71 (0.28 to 10.4)	0.56
	Lymphocyte telomere length	13	0.57 (0.10 to 3.23)	0.52
	Naive T-cell telomere length	13	1.13 (0.20 to 6.45)	0.89
	Memory T-cell telomere length	11	0.41 (0.06 to 3.10)	0.39
	B-cell telomere length	13	1.52 (0.27 to 8.65)	0.64
	NK-cell telomere length	11	2.94 (0.39 to 22.4)	0.30
Tea intake	Granulocyte telomere length	28	1.34 (0.67 to 2.69)	0.41
	Lymphocyte telomere length	28	1.34 (0.71 to 2.55)	0.37
	Naive T-cell telomere length	28	1.29 (0.70 to 2.41)	0.42
	Memory T-cell telomere length	28	1.18 (0.63 to 2.22)	0.61
	B-cell telomere length	28	1.15 (0.62 to 2.12)	0.66
	NK-cell telomere length	28	1.26 (0.62 to 2.54)	0.52
water intake	Granulocyte telomere length	31	0.53 (0.25 to 1.13)	0.10
	Lymphocyte telomere length	30	0.61 (0.28 to 1.34)	0.22
	Naive T-cell telomere length	31	0.51 (0.24 to 1.08)	0.08
	Memory T-cell telomere length	31	0.69 (0.33 to 1.47)	0.34
	B-cell telomere length	31	0.69 (0.33 to 1.47)	0.34
	NK-cell telomere length	31	0.86 (0.40 to 1.82)	0.69

Figure 2. Estimation of the causal relationship between telomere length and dietary factors using the IVW method

oily fish intake and memory T-cell telomere length (Supplementary Figure 2). A fixed-effects model was used for these variables. In the pleiotropy test, the p-values ranged from 0.06 to 0.99 and were all greater than 0.05. This indicated the absence of pleiotropy. In addition, In MR-PRESSO test, the *p*-values ranged from 0.07 to 0.99, indicating no pleiotropy, except for the relationship between bread intake and NK-cell telomere length (<0.001). Detailed information was provided in Table 1. In addition, the leave-one-out test revealed that no strong single SNP drives the MR estimation between dried fruit intake and granulocyte telomere length, lymphocyte telomere length, naive T-cell telomere length, as well as between oily fish intake and memory T-cell telomere length (Figure 4).

DISCUSSION

Telomeres are affected by each replication cycle, accelerated by oxidative stress.[19] Foods rich in antioxidants and anti-inflammatory properties played a role in maintaining TL.[20] However, there were controversy viewpoints regarding which specific types of foods impact TL. For instance, a study suggested that individuals with higher intake of vegetables and fruits had longer telomeres,[21] while another found no association between vegetable
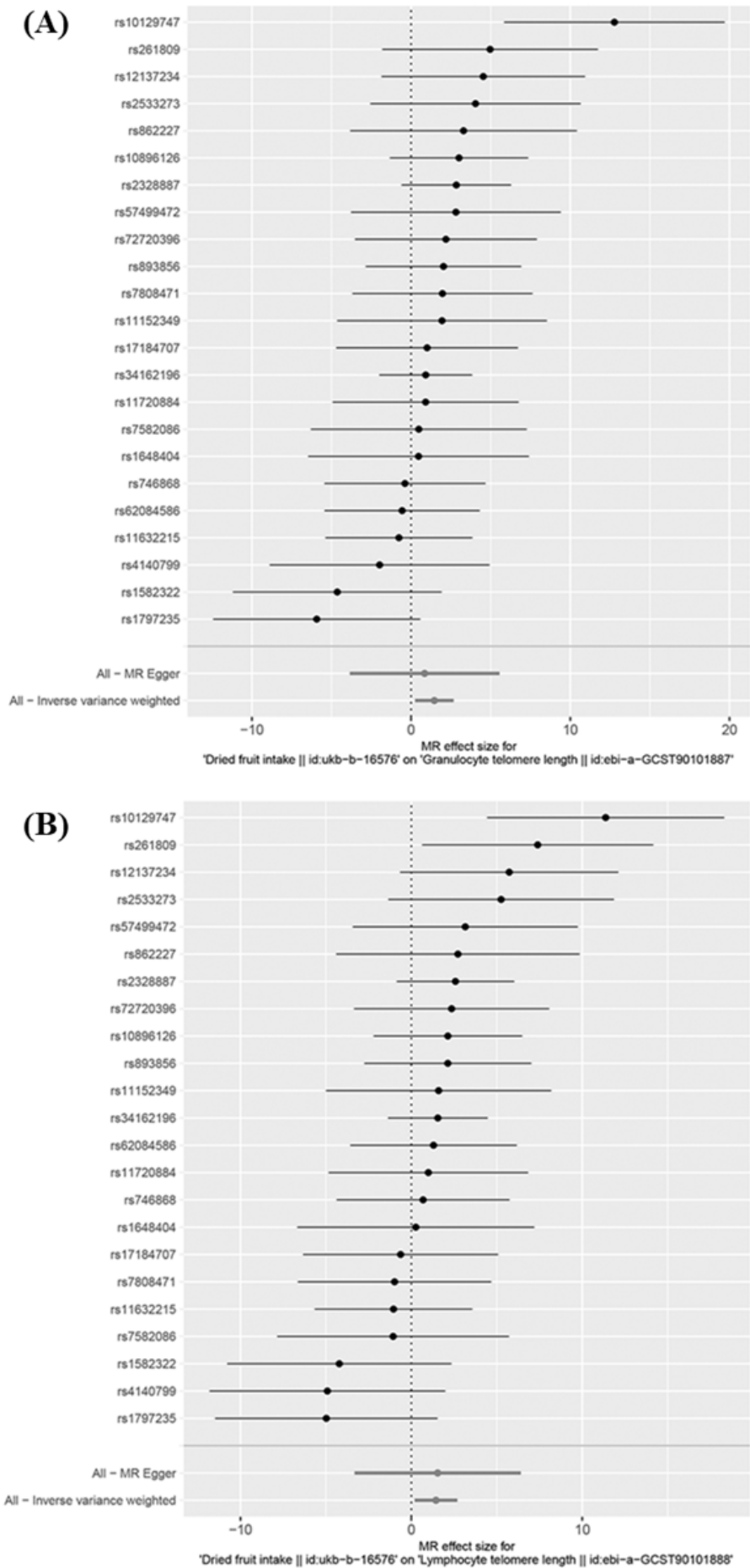
Figure 3. Forest plot: the dot and bar indicate the causal estimate for A: Dried fruit intake and granulocyte telomere length. B: Dried fruit intake and lymphocyte telomere length. C: Dried fruit intake and naive T-cell telomere length. D: Oily fish intake and memory T-cell telomere length
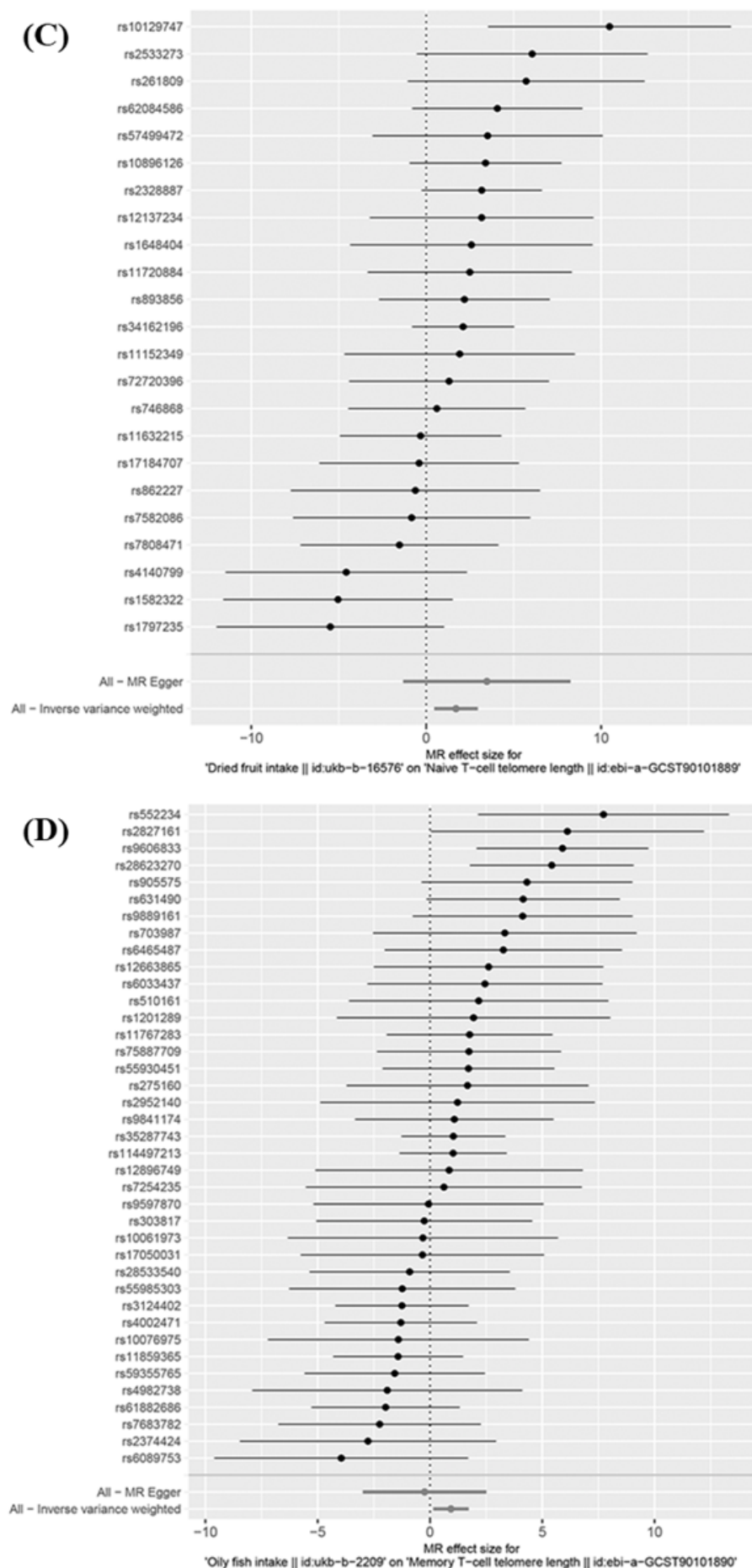
Figure 3. (cont.) Forest plot: the dot and bar indicate the causal estimate for A: Dried fruit intake and granulocyte telomere length. B: Dried fruit intake and lymphocyte telomere length. C: Dried fruit intake and naive T-cell telomere length. D: Oily fish intake and memory T-cell telomere length

Table 1. The results of Heterogeneity test, Pleiotropy test and MR-PRESSO test[†]

Exposure and outcome	Heterogeneity test		Pleiotropy test		MR-PRESSO
	Q[†]	p[†]	Intercept	p	p
Alcohol intake frequency					
Granulocyte telomere length	51.9	0.79	-0.010	0.50	0.87
Lymphocyte telomere length	56.7	0.63	-0.008	0.57	0.68
Naive T-cell telomere length	57.0	0.62	-0.009	0.52	0.65
Memory T-cell telomere length	64.2	0.36	-0.007	0.63	0.40
B-cell telomere length	53.4	0.75	-0.011	0.47	0.81
NK-cell telomere length	53.6	0.74	0.009	0.53	0.79
Alcoholic drinks per week					
Granulocyte telomere length	17.9	0.71	-0.043	0.07	0.75
Lymphocyte telomere length	20.9	0.53	-0.028	0.22	0.54
Naive T-cell telomere length	18.6	0.67	-0.024	0.30	0.71
Memory T-cell telomere length	19.2	0.63	-0.035	0.14	0.64
B-cell telomere length	16.8	0.77	-0.028	0.23	0.81
NK-cell telomere length	15.1	0.86	-0.021	0.36	0.87
Average weekly beer plus cider intake					
Granulocyte telomere length	6.85	0.65	-0.028	0.60	0.72
Lymphocyte telomere length	8.30	0.50	-0.027	0.61	0.66
Naive T-cell telomere length	9.23	0.42	-0.044	0.43	0.56
Memory T-cell telomere length	2.23	0.97	-0.028	0.63	0.98
B-cell telomere length	5.22	0.82	-0.016	0.76	0.92
NK-cell telomere length	6.22	0.72	0.020	0.71	0.79
Average weekly red wine intake					
Granulocyte telomere length	5.45	0.61	0.038	0.67	0.64
Lymphocyte telomere length	6.82	0.45	0.029	0.76	0.47
Naive T-cell telomere length	8.44	0.30	0.049	0.64	0.29
Memory T-cell telomere length	8.34	0.30	0.007	0.94	0.31
B-cell telomere length	7.59	0.37	0.054	0.59	0.39
NK-cell telomere length	12.7	0.08	0.120	0.35	0.09
Beef intake					
Granulocyte telomere length	13.3	0.15	-0.003	0.97	0.16
Lymphocyte telomere length	11.0	0.36	0.050	0.48	0.38
Naive T-cell telomere length	6.49	0.77	0.050	0.46	0.76
Memory T-cell telomere length	8.25	0.60	0.037	0.58	0.60
B-cell telomere length	10.3	0.42	0.084	0.22	0.46
NK-cell telomere length	15.9	0.10	0.027	0.75	0.10
Bread intake					
Granulocyte telomere length	25.3	0.12	0.066	0.13	0.11
Lymphocyte telomere length	22.2	0.22	0.046	0.28	0.16
Naive T-cell telomere length	22.3	0.22	0.078	0.06	0.09
Memory T-cell telomere length	14.3	0.71	0.019	0.61	0.73
B-cell telomere length	22.9	0.20	0.059	0.17	0.07
NK-cell telomere length	17.0	0.52	0.029	0.45	<0.001
Cereal intake					
Granulocyte telomere length	15.9	0.78	0.002	0.95	0.72
Lymphocyte telomere length	11.4	0.95	-0.024	0.48	0.98
Naive T-cell telomere length	14.6	0.84	-0.014	0.68	0.92
Memory T-cell telomere length	17.1	0.71	0.003	0.92	0.68
B-cell telomere length	13.6	0.89	-0.018	0.59	0.82
NK-cell telomere length	22.5	0.37	-0.023	0.51	0.53
Coffee intake					
Granulocyte telomere length	9.90	0.96	-0.006	0.64	0.94
Lymphocyte telomere length	10.8	0.93	0.003	0.85	0.93
Naive T-cell telomere length	17.1	0.59	0.006	0.67	0.60
Memory T-cell telomere length	14.1	0.78	0.0003	0.98	0.78
B-cell telomere length	13.4	0.82	0.008	0.55	0.75
NK-cell telomere length	9.84	0.96	0.010	0.45	0.97

[†]Results were obtained through the R studio TwoSampleMR package.
[‡]Results were obtained through the Inverse variance weighted method.

Table 1. The results of Heterogeneity test, Pleiotropy test and MR-PRESSO test[†] (cont.)

Exposure and outcome	Heterogeneity test		Pleiotropy test		MR-PRESSO
	Q[‡]	p[‡]	Intercept	p	p
Cooked vegetable intake					
Granulocyte telomere length	6.47	0.59	0.025	0.85	0.60
Lymphocyte telomere length	1.66	0.99	-0.009	0.94	0.99
Naive T-cell telomere length	3.31	0.91	0.073	0.58	0.90
Memory T-cell telomere length	2.18	0.97	-0.043	0.74	0.97
B-cell telomere length	0.95	0.99	0.003	0.98	0.99
NK-cell telomere length	4.70	0.79	-0.020	0.88	0.77
Dried fruit intake					
Granulocyte telomere length	26.1	0.25	0.008	0.79	0.29
Lymphocyte telomere length	27.8	0.18	-0.001	0.97	0.23
Naive T-cell telomere length	27.6	0.19	-0.022	0.46	0.26
Memory T-cell telomere length	17.1	0.76	-0.008	0.76	0.79
B-cell telomere length	23.2	0.39	-0.024	0.40	0.42
NK-cell telomere length	24.5	0.32	-0.005	0.85	0.35
Fresh fruit intake					
Granulocyte telomere length	44.8	0.07	0.019	0.49	0.12
Lymphocyte telomere length	43.3	0.13	-0.018	0.38	0.16
Naive T-cell telomere length	43.4	0.13	-0.018	0.39	0.13
Memory T-cell telomere length	42.5	0.15	-0.014	0.51	0.19
B-cell telomere length	42.6	0.15	-0.009	0.68	0.17
NK-cell telomere length	34.6	0.39	-0.011	0.57	0.48
Lamb/mutton intake					
Granulocyte telomere length	27.7	0.12	-0.012	0.75	0.12
Lymphocyte telomere length	18.0	0.59	0.010	0.75	0.63
Naive T-cell telomere length	18.2	0.57	-0.001	0.99	0.62
Memory T-cell telomere length	24.5	0.22	0.020	0.57	0.24
B-cell telomere length	24.6	0.22	-0.010	0.77	0.18
NK-cell telomere length	27.3	0.13	-0.001	0.97	0.15
Non-oily fish intake					
Granulocyte telomere length	0.98	0.99	0.002	0.97	0.99
Lymphocyte telomere length	0.70	0.99	-0.026	0.65	0.99
Naive T-cell telomere length	0.50	0.99	-0.021	0.71	0.99
Memory T-cell telomere length	1.42	0.96	-0.046	0.42	0.96
B-cell telomere length	0.63	0.99	-0.016	0.77	0.99
NK-cell telomere length	3.52	0.74	-0.016	0.78	0.72
Oily fish intake					
Granulocyte telomere length	43.2	0.30	0.018	0.37	0.30
Lymphocyte telomere length	45.8	0.21	0.014	0.50	0.22
Naive T-cell telomere length	45.3	0.22	0.018	0.38	0.23
Memory T-cell telomere length	50.3	0.09	0.019	0.39	0.09
B-cell telomere length	48.0	0.15	0.014	0.51	0.16
NK-cell telomere length	42.2	0.33	0.008	0.69	0.35
Pork intake					
Granulocyte telomere length	7.55	0.48	0.173	0.11	0.47
Lymphocyte telomere length	8.67	0.37	0.156	0.15	0.42
Naive T-cell telomere length	6.93	0.54	0.157	0.14	0.56
Memory T-cell telomere length	8.81	0.36	0.140	0.19	0.37
B-cell telomere length	11.1	0.19	0.207	0.07	0.22
NK-cell telomere length	9.94	0.27	0.135	0.22	0.30
Processed meat intake					
Granulocyte telomere length	14.6	0.41	-0.003	0.96	0.42
Lymphocyte telomere length	15.6	0.41	0.018	0.74	0.43
Naive T-cell telomere length	14.1	0.52	0.029	0.59	0.53
Memory T-cell telomere length	17.4	0.23	0.029	0.64	0.24
B-cell telomere length	20.2	0.17	0.050	0.42	0.17
NK-cell telomere length	14.2	0.51	-0.022	0.68	0.51

[†]Results were obtained through the R studio TwoSampleMR package.
[‡]Results were obtained through the Inverse variance weighted method.

Table 1. The results of Heterogeneity test, Pleiotropy test and MR-PRESSO test[†] (cont.)

Exposure and outcome	Heterogeneity test		Pleiotropy test		MR-PRESSO
	Q[‡]	p[‡]	Intercept	p	p
Salad/raw vegetable intake					
Granulocyte telomere length	12.9	0.38	0.05	0.27	0.19
Lymphocyte telomere length	9.54	0.66	0.079	0.09	0.16
Naive T-cell telomere length	7.84	0.80	0.054	0.23	0.54
Memory T-cell telomere length	8.97	0.54	0.189	0.07	0.09
B-cell telomere length	9.26	0.68	0.059	0.19	0.35
NK-cell telomere length	9.74	0.46	0.167	0.08	0.27
Tea intake					
Granulocyte telomere length	35.3	0.13	-0.016	0.35	0.17
Lymphocyte telomere length	29.9	0.32	-0.004	0.81	0.39
Naive T-cell telomere length	27.9	0.42	-0.003	0.83	0.47
Memory T-cell telomere length	28.9	0.36	-0.001	0.96	0.45
B-cell telomere length	27.2	0.45	0.010	0.50	0.49
NK-cell telomere length	35.7	0.12	0.002	0.90	0.13
Water intake					
Granulocyte telomere length	24.1	0.77	-0.007	0.70	0.81
Lymphocyte telomere length	31.2	0.35	-0.014	0.45	0.39
Naive T-cell telomere length	30.5	0.44	-0.011	0.54	0.46
Memory T-cell telomere length	26.9	0.63	-0.025	0.15	0.63
B-cell telomere length	25.2	0.71	-0.014	0.41	0.69
NK-cell telomere length	21.4	0.88	-0.007	0.67	0.87

[†]Results were obtained through the R studio TwoSampleMR package.
[‡]Results were obtained through the Inverse variance weighted method.
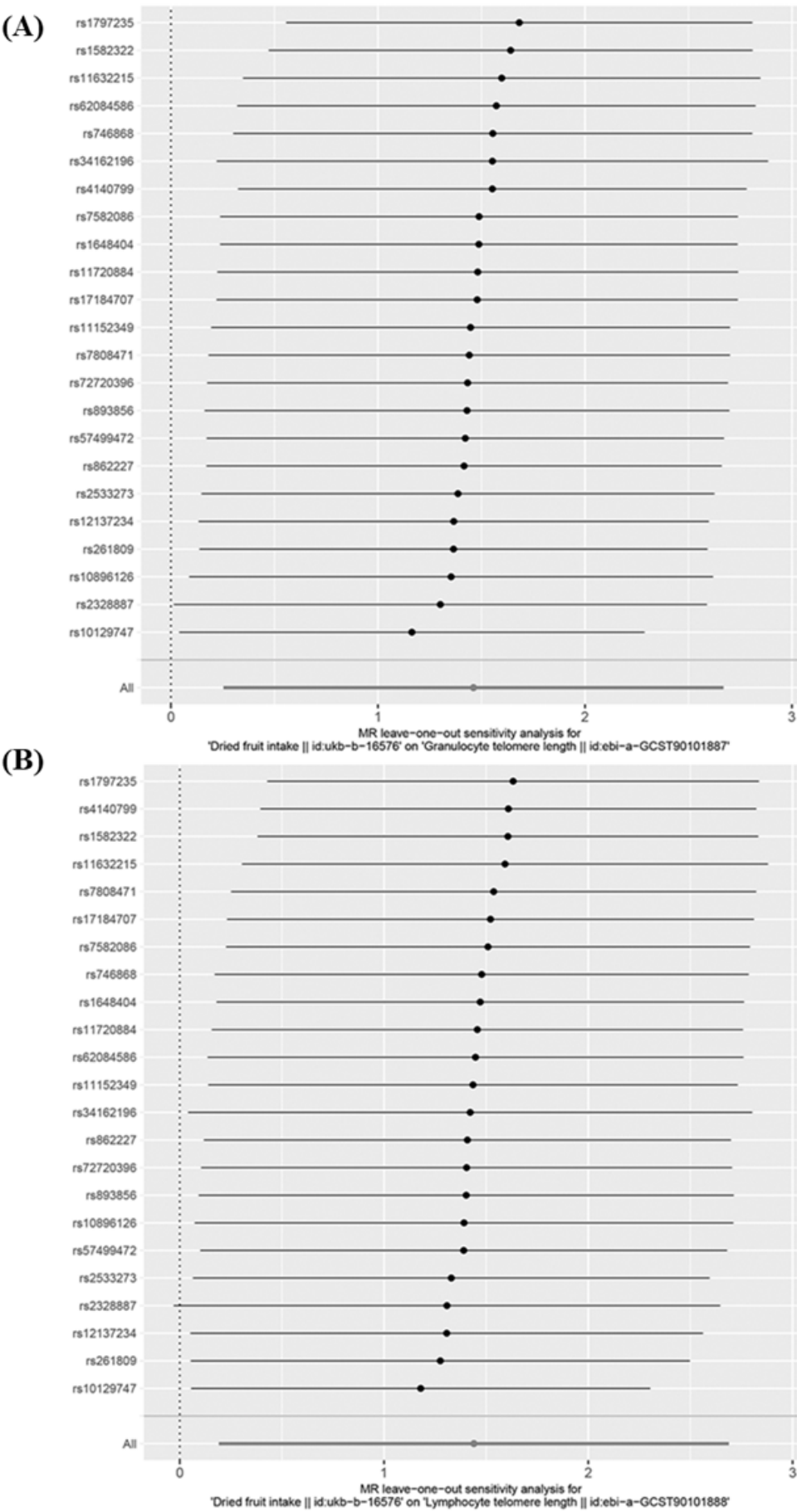
Figure 4. Leave-one-out sensitivity analysis: the dot and bar indicate the estimates and 95% confidence interval when the specific SNP is removed A: Dried fruit intake and granulocyte telomere length. B: Dried fruit intake and lymphocyte telomere length. C: Dried fruit in-take and naive T-cell telomere length. D: Oily fish intake and memory T-cell telomere length
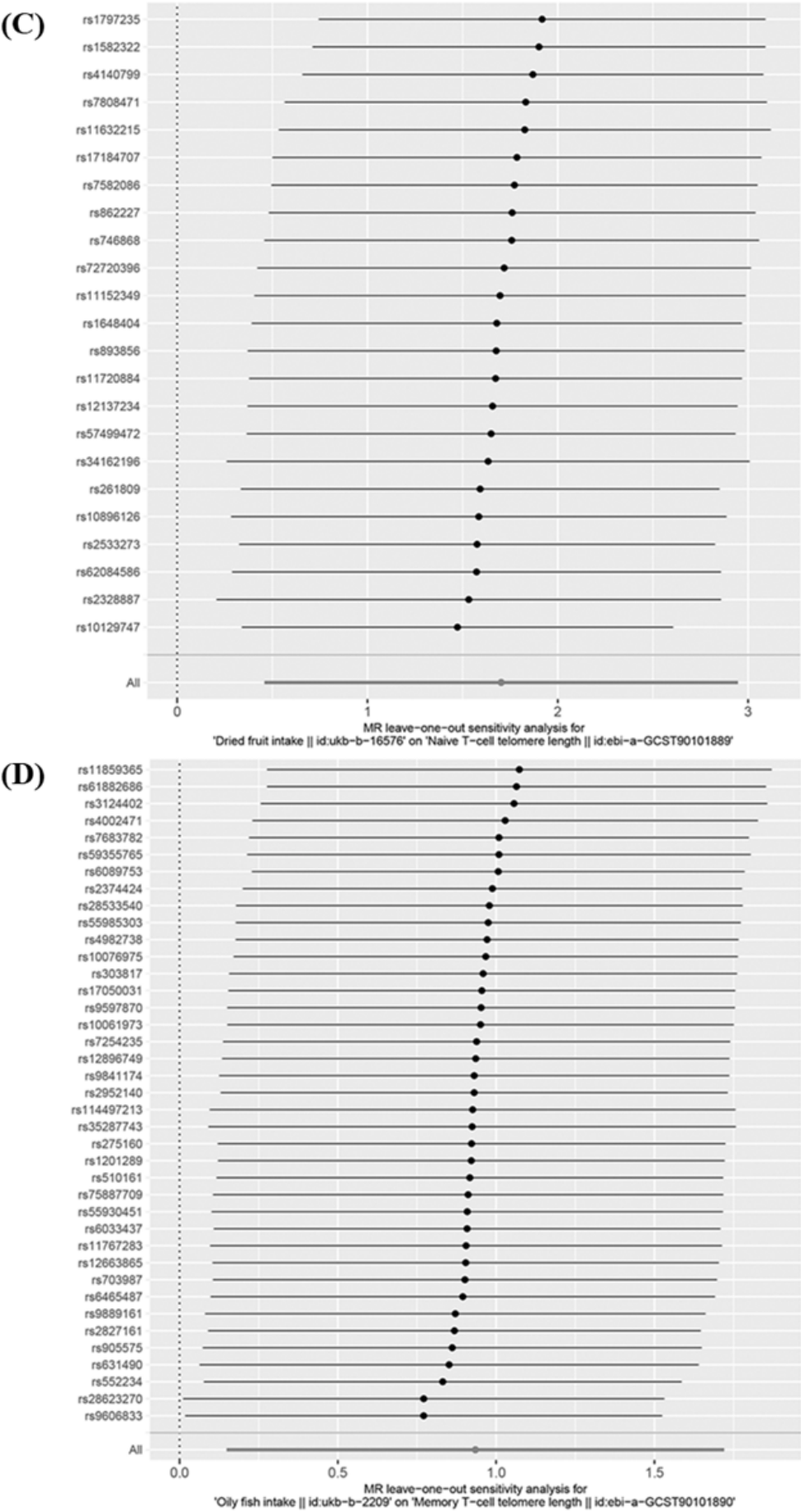
Figure 4. (cont.) Leave-one-out sensitivity analysis: the dot and bar indicate the estimates and 95% confidence interval when the specific SNP is removed A: Dried fruit intake and granulocyte telomere length. B: Dried fruit intake and lymphocyte telomere length. C: Dried fruit intake and naive T-cell telomere length. D: Oily fish intake and memory T-cell telomere length

Graphical abstract.

and fruit intake and TL.[22] Further study is needed to determine which dietary factors specifically influenced TL.

This study identified a positive causal relationship between dried fruit, oily fish and certain types of TLs. Fruits, rich in essential vitamins, minerals, and antioxidants, showed beneficial effects on maintaining TL, and their nutritional components became concentrated during drying.[23] This could be the reason why a causal relationship between dried fruits and TL was found in this study, while fresh fruits did not. Oily fish, rich in omega-3 fatty acids like DHA and EPA,[24] demonstrated longevity benefits in a mouse study.[25] Prospective studies revealed that higher blood omega-3 levels slowed telomere shortening,[26] and plasma DHA/EPA correlated positively with TL.[27] Overall, omega-3 fatty acids were beneficial for maintaining TL, and making a bold inference, oily fish rich in omega-3 fatty acids also likely benefited TL. There are significant tissue-specific differences among different cell types.[28] This may explain why dried fruits and oily fish only affected the telomere length of certain cells. Therefore, in diets for the elderly (beneficial for TL), this study recommended moderate increases in dried fruits and oily fish.

In this study, the use of SNPs with strong correlation strength, along with heterogeneity testing, pleiotropy testing, MR-PRESSO analysis, and leave-one-out testing, helped ensure the accuracy and credibility of the results. All the samples were from individuals of European descent, thus reducing population heterogeneity. Simultaneously, it could display the causal impact of each SNP. These SNPs could be targeted for more in-depth and precise studies, providing ideas and directions for further research. However, limitations existed. The anomaly in the MR-PRESSO test of the relationship between bread intake and NK-cell telomere length might have been caused by outliers. Despite conducting additional data analyses, we were unable to resolve this issue. In addition, due to exposures and outcomes data from public databases, subgroup analyses for factors like age and gender were unfeasible. Lastly, MR analysis revealed the overall exposure impact on outcomes but didn't directly elucidate the biological mechanisms involved. For future studies, conduct larger GWAS, especially those focusing on bread intake and NK-cell telomere length. And use experimental techniques to explore biological mechanisms.

Conclusion

This study found positive associations between dried fruit intake and granulocyte telomere length, lymphocyte telomere length, naive T-cell telomere length, as well as between oily fish intake and memory T-cell telomere length. However, there were no causal relationships identified between TLs and alcohol intake frequency, alcoholic drinks per week, average weekly beer plus cider intake, average weekly red wine intake, beef intake, bread intake, cereal intake, coffee intake, cooked vegetable intake, fresh fruit intake, lamb/mutton intake, non-oily fish intake, pork intake, processed meat intake, salad/raw vegetable intake, tea intake, water intake. This study had significant potential for the field of public health. It provided valuable information for aging prevention, which thereby promoted the overall health and well-being of the population.

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