# Tobacco and alcohol consumption and the risk of frailty and falling: a Mendelian randomisation study

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## ABSTRACT

**Background** Epidemiological data have suggested that tobacco and alcohol consumption were associated with the risk of frailty and falling, but it is yet unclear whether these associations are of a causal nature. Thus, we conducted two-sample Mendelian randomisation analysis using genetic instruments to determine the causal associations of tobacco and alcohol consumption on frailty and falls.

**Methods** Independent instrumental variables strongly (p<5E−09) associated with tobacco and alcohol consumption were obtained from the genome-wide association study (GWAS) and Sequencing Consortium of Alcohol and Nicotine use (up to 2 669 029 participants). Summary statistics of the frailty index (FI, N=175 226) and falling risk (N=451 179) were from the two latest published GWAS datasets on FI and falling risk.

**Results** Using the inverse-variance weighted method, our results showed that genetically determined initiation of smoking was significantly associated with an increased FI (β=0.34, 95% CI=0.29 to 0.40, p=5.48E−33) and risk of falling (OR=1.39, 95% CI=1.30 to 1.50, p=1.01E−20). In addition, the age of initiation of smoking and cigarettes consumption per day was negatively and positively associated with both FI and falls, respectively. Current smokers were prone to having a higher FI and falling risk than individuals who quit smoking. There was no significant causal association between alcohol use and the risk of frailty and falling. Similar results were obtained using other statistical approaches with good stability.

**Conclusions** Our findings demonstrate that tobacco use, but not alcohol drinking, significantly increases the risk of frailty and falling. Future studies are warranted to clarify the underlying physiopathological mechanisms.

## INTRODUCTION

Frailty and falls are two common geriatric syndromes affecting the physiological function of multiple systems, which are tightly associated with disability, mobility, hospitalisation and mortality in geriatric populations.[1–3] Previous studies suggested that frailty was also associated with an increased risk of falling.[4 5] Using the physical frailty measures and the frailty index (FI), the largest meta-analysis of frailty in 1 755 497 individuals showed that the prevalence of frailty was around 12% and 24% among people more than 50 years old, respectively.[6] A recent review showed that the cost of healthcare for frailty ranged from US$8620 to US$29 910 per patient each year.[7] These data demonstrate that frailty is a major public health issue among the elders, causing a huge socioeconomic burden worldwide.

Previous observational studies suggested that smoking and alcohol consumption were associated with the risk of frailty and falls.[8–10] A community-dwelling-based study in England showed that current smokers had a higher risk to develop frailty over 4 years among a population aged ≥60 years.[11] However, other studies suggested that there was no significant association between smoking and frailty and falls among elders.[12 13] It is worth noting that the results of observational studies are often distorted by confounding factors and reverse causality. As both smoking and alcohol drinking are modifiable lifestyle factors, cessation or postponing the age of initiation of smoking and alcohol intake may be beneficial for preventing frailty and falls. Thus, it invokes the need for clarifying whether tobacco and alcohol use was causally associated with the risk of frailty and falls.

The Mendelian randomisation (MR) analysis, treating genetic variants as instrumental variables (IVs) to minimise the bias introduced by confounding factors and reverse causality, is now an advanced epidemiological strategy commonly applied to assess the causal association between exposures and corresponding outcomes.[14] Therefore, we here performed a two-sample MR analysis to investigate the causal association between

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### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Observational studies have suggested that tobacco and alcohol consumption are associated with the risk of frailty and falling, but the results are inconsistent owing to confounding and reverse causation.

### WHAT THIS STUDY ADDS

⇒ The present Mendelian randomisation study shows that tobacco consumption is significantly associated with an increased risk of frailty and falling, but no significant causal relationship is found between alcohol drinking and frailty and falls.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our data remind people that smoking, but not alcohol intake, increases the susceptibility to frailty and falling, while cessation or delaying the age of initiation of smoking could reduce the risk of frailty and falling.
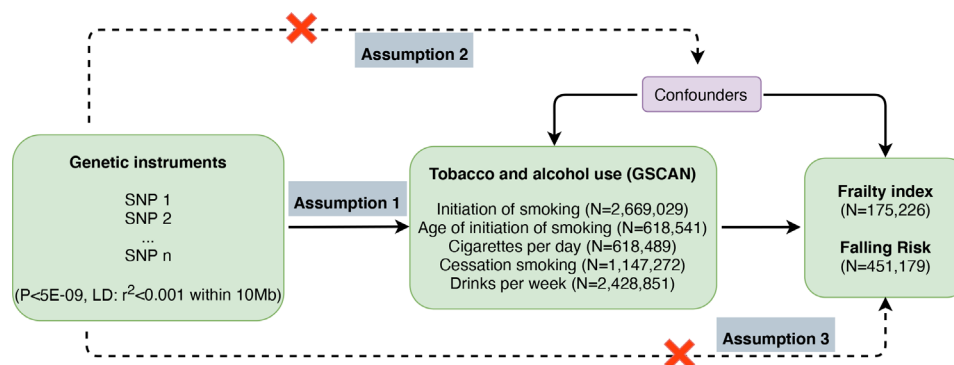
**Figure 1** Study design and three corresponding assumptions of this Mendelian randomisation study. The red cross indicates that genetic variants are not associated with confounding factors and outcomes. Assumption 1: IVs are strongly associated with tobacco and alcohol use; Assumption 2: IVs are not associated with confounding factors; Assumption 3: IVs affect the risk of frailty and falls via tobacco and alcohol consumption directly. GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use; IV, instrumental variables; LD, linkage disequilibrium; N, number; SNP, single-nucleotide polymorphism.

genetically determined tobacco and alcohol consumption and the risk of frailty and falling.

## METHODS
### Study design and data source
Single-nucleotide polymorphisms (SNPs) were used as IVs in this MR study. Three assumptions should be satisfied in MR analysis: (1) IVs should be strongly associated with tobacco and alcohol use; (2) IVs should not be associated with any confounding factors and (3) IVs should affect the risk of frailty and falls via the tobacco and alcohol consumption directly, but not indirectly through alternative factors (figure 1).

The summary-level data on tobacco and alcohol use were obtained from the latest large-scale meta-analysis of GWAS performed by GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) with sample sizes of up to 2.6 million individuals of European descent from 59 cohorts.[15] Tobacco use was further divided into four smoking phenotypes, including initiation of smoking (N=2 669 029), the age of initiation of smoking (N=618 541), cigarettes per day (N=618 489) and smoking cessation (N=1 147 272). The detailed definition of different traits of tobacco use was fully described in online supplemental information). Alcohol use was defined as the average number of drinks a participant reported drinking per week (N=2 428 851). Frailty is commonly defined using either the frailty phenotype or the FI.[16] In this MR study, frailty was measured based on the FI, which was calculated according to the accumulation of 44–49 self-reported health deficits during the life course.[16 17] Summary

statistics of FI were obtained from the latest GWAS meta-analysis of UK Biobank participants and Swedish TwinGene participants of European descent (N=175 226).[16] Summary statistics of falling risk were obtained from the latest genome-wide association analysis conducted by the GEnetic Factors for OSteoporosis Consortium, including 89 076 cases and 362 103 controls of European descent.[18] The detailed information on study design, such as a collection of samples, diagnostic criteria, quality control and imputation method, has been well described in the original publication (table 1).

### IVs selection and MR analysis
According to the definition of genome-wide significant variants in the GWAS study by GSCAN, SNPs with a p<5E–09 were selected as potential IVs for tobacco and alcohol consumption. Independent IVs were obtained after being clumped based on the 1000 Genomes Project linkage disequilibrium (LD) structure ($r^2 < 0.001$ within 10 Mb). When an SNP was absent in the summary statistics of the corresponding outcome phenotype, an overlapping proxy SNP in LD ($r^2 = 0.8$) was used. SNPs strongly (p<5E–08) associated with the outcome (FI or falling risk) were also excluded from the IVs before MR analysis. To strengthen the reliability of MR analysis, SNPs with minor allele frequency less than 0.3 were also removed. Inverse variance weighted (IVW), providing a robust causal evaluation under a lack of directional pleiotropy,[19] was applied as the default approach to calculate causal estimates (β and OR) between tobacco and alcohol consumption and FI and falling risk. Multiple testing

**Table 1** All the GWAS summary data were used in this Mendelian randomisation study

| Phenotype | Consortium/author | Year | Sample size (N) | SNP(N) | PMID | URL (data download) |
|---|---|---|---|---|---|---|
| Tobacco use | | | | | | |
| Initiation of smoking | GSCAN | 2022 | 2 669 029 | 13 595 219 | 36 477 530 | https://conservancy.umn.edu/handle/11299/241912 |
| Age of initiation of smoking | GSCAN | 2022 | 618 541 | 13 732 312 | 36 477 530 | https://conservancy.umn.edu/handle/11299/241912 |
| Cigarettes per day | GSCAN | 2022 | 618 489 | 13 763 312 | 36 477 530 | https://conservancy.umn.edu/handle/11299/241912 |
| Cessation smoking | GSCAN | 2022 | 1 147 272 | 13 642 427 | 36 477 530 | https://conservancy.umn.edu/handle/11299/241912 |
| Drinks per week | GSCAN | 2022 | 2 428 851 | 13 268 540 | 36 477 530 | https://conservancy.umn.edu/handle/11299/241912 |
| Frailty index | Atkins et al | 2021 | 175 226 | 7 589 717 | 34 431 594 | https://figshare.com/ndownloader/files/28842861 |
| Falling risk | GEFOS | 2020 | 451 179 | 7 720 247 | 32 999 390 | http://www.gefos.org/ |

GEFOS, GEnetic Factors for OSteoporosis Consortium; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use; GWAS, genome-wide association study; N, number; SNP, single-nucleotide polymorphism.

adjustments were made using the Bonferroni method, and statistical significance was indicated by a p<0.01 (0.05/5 exposures).

## Sensitivity and power analysis

To address the stability of the MR results, three sensitivity analyses, including MR-Egger, weighted median and MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test, were also employed.[20] The MR-PRESSO and MR-Egger methods were able to detect and correct directional horizontal pleiotropy in calculating the causal estimates.[21] The MR-PRESSO approach could identify outliers and provide a causal estimate without the outliers.[20] Cochran's Q statistic was used to quantify the heterogeneity in the MR analysis. Leave-one-out permutation analysis was performed by excluding a single SNP each time to evaluate the influence of any single SNP on the overall MR estimates. Meanwhile, the MR Steiger directionality test was applied to confirm that the causal direction is oriented from exposure to outcome. The $R^2$ explaining the variance of the exposure and the F-statistic of each SNP was calculated as we previously described.[22] An F value of more than 10 indicated a good strength of the IV and a small bias caused by sample overlap.[23] In addition, to further address the impact of sample overlap on the estimates, we employed a recently published method, MR for causal inference accounting for pleiotropy and sample structure (MR-APSS), which took the sample overlap into account, to recalculate the MR estimates with default parameters.[24] All

statistical analyses were performed by using the TwoSampleMR package (V.0.5.6), MR-PRESSO package (V.1.0.0) and MR-APSS package (V.0.0.0.9) in R software (V.4.1.3).[25]

## RESULTS

### Causal associations between tobacco and alcohol consumption and frailty and falls

A detailed list of all harmonised IVs for each exposure–outcome group was archived in online supplemental table S1. Using the IVW method, genetically determined initiation of smoking was associated with an increased FI (β=0.34, 95% CI=0.29 to 0.40, p=5.48E–33) and risk of falling (OR=1.39, 95% CI=1.30 to 1.50, p=1.01E–20). In addition, the age of initiation of smoking was negatively associated with the FI (β=−0.27, 95% CI=−0.46 to −0.09, p=4.17E–03) and falls (OR=0.76, 95% CI=0.64 to 0.90, p=1.30E–03), while cigarettes consumption per day was positively associated with FI (β=0.20, 95% CI=0.13 to 0.26, p=3.41E–10) and falls (OR=1.14, 95% CI=1.05 to 1.24, p=2.17E–03) (figure 2). Meanwhile, current smokers had a higher FI (β=0.31, 95% CI=0.19 to 0.44, p=1.44E–06) and falling risk (OR=1.33, 95% CI=1.13 to 1.56, p=6.08E–04) than individuals who quit smoking. There was no statistically significant causal association between drinks per week and falling risk (figure 2), but a suggestive causal relationship was observed between drinks per week and FI (β=−0.09,
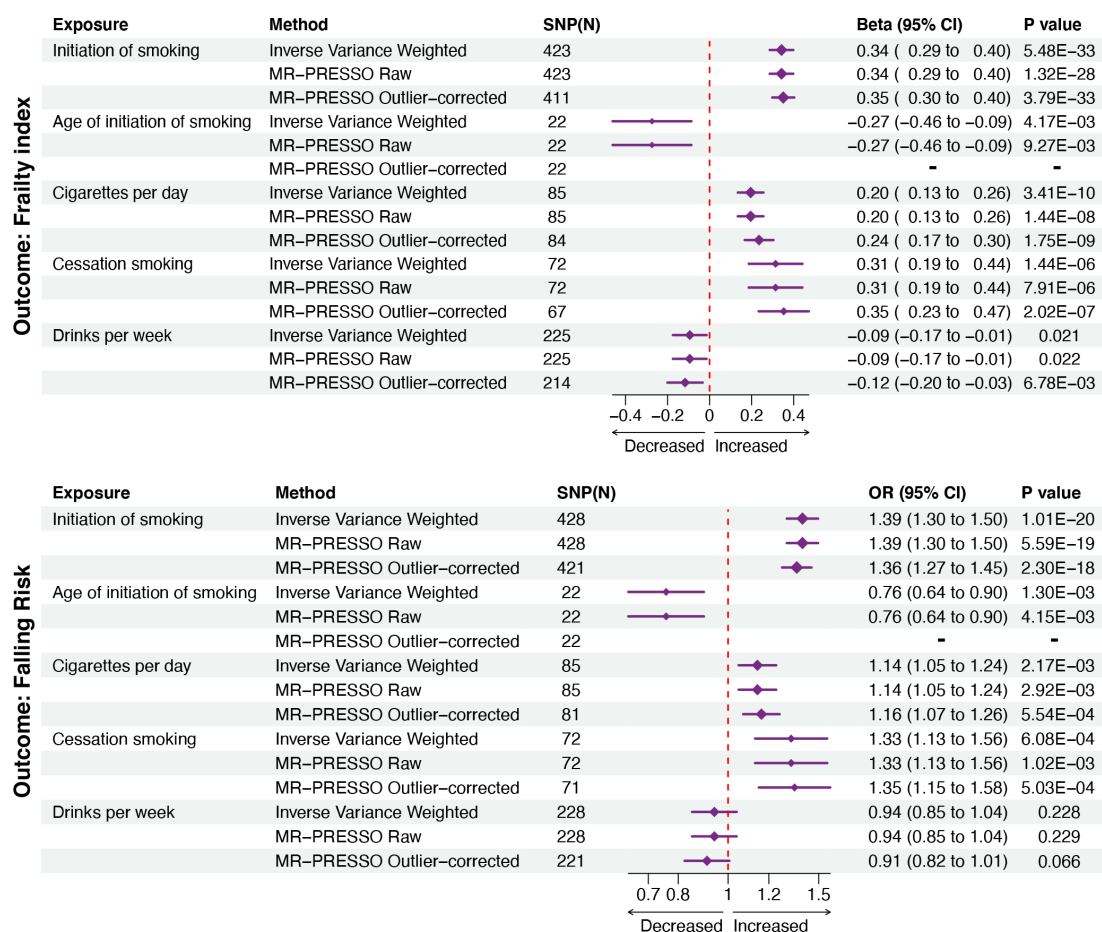


**Figure 2** Causal associations of tobacco and alcohol use on frailty index and falls. Using the IVW method, genetic predisposition to tobacco use, including initiation of smoking and the age of initiation of smoking was associated with the frailty index and falls. MR-PRESSO test was used to evaluate the causal associations before and after the removal of outliers if presented. IVW, inverse variance weighted; MR-PRESSO, MR-Pleiotropy RESidual Sum and Outlier; N, number; SNP, single-nucleotide polymorphism.

**Table 2** Association of genetically predicted tobacco and alcohol use and frailty index and falling risk in sensitivity analysis

| Exposure | MR method | Causal estimate on frailty index | | | Causal estimate on falling risk | | |
|---|---|---|---|---|---|---|---|
| | | Beta (95% CI) | P value | Heterogeneity/ pleiotropy | OR (95% CI) | P value | Heterogeneity/pleiotropy |
| Initiation of smoking | MR-APSS | 0.39 (0.29, 0.49) | 5.11E−15 | Cochran Q: 916.98 | 1.18 (1.12, 1.25) | 1.66E−08 | Cochran Q: 801.04 |
| | MR-Egger | 0.26 (0.09, 0.44) | 3.29E−03 | MR-Egger intercept (P): 0.348 | 1.42 (1.14, 1.75) | 1.44e−03 | MR-Egger intercept (P): 0.880 |
| | Weighted median | 0.32 (0.25, 0.38) | 7.32E−21 | Distortion test (P): 0.765 | 1.39 (1.27, 1.51) | 2.56E−13 | Distortion test (P): 0.420 |
| Age of initiation of smoking | MR-APSS | −0.36 (−0.65, 0.08) | 0.013 | Cochran Q: 55.35 | 0.90 (0.77, 1.04) | 0.169 | Cochran Q: 24.40 |
| | MR-Egger | 0.17 (−0.69, 1.02) | 0.709 | MR-Egger intercept (P): 0.315 | 1.13 (0.52, 2.44) | 0.758 | MR-Egger intercept (P): 0.308 |
| | Weighted median | −0.19 (−0.37, 0.01) | 0.043 | Distortion test (P): NA | 0.73 (0.59, 0.90) | 3.38E−03 | Distortion test (P): NA |
| Cigarettes per day | MR-APSS | 0.17 (0.04, 0.29) | 9.07E−03 | Cochran Q: 161.73 | 1.08 (1.01, 1.16) | 0.035 | Cochran Q: 172.37 |
| | MR-Egger | 0.03 (−0.08, 0.14) | 0.610 | MR-Egger intercept (P): 0.001 | 0.93 (0.80, 1.08) | 0.349 | MR-Egger intercept (P): 0.003 |
| | Weighted median | 0.08 (0.01, 0.15) | 0.030 | Distortion test (P): 0.201 | 0.97 (0.88, 1.07) | 0.543 | Distortion test (P): 0.649 |
| Cessation smoking | MR-APSS | 0.30 (0.08, 0.53) | 8.45E−03 | Cochran Q: 185.42 | 1.08 (0.96, 1.24) | 0.184 | Cochran Q: 177.92 |
| | MR-Egger | −0.24 (−0.56, 0.08) | 0.145 | MR-Egger intercept (P): 001 | 0.83 (0.54, 1.26) | 0.379 | MR-Egger intercept (P): 0.021 |
| | Weighted median | 0.21 (0.07, 0.34) | 2.65E−03 | Distortion test (P): 0.499 | 1.10 (0.91, 1.32) | 0.313 | Distortion test (P): 0.867 |
| Drinks per week | MR-APSS | 0.01 (−0.13, 0.16) | 0.856 | Cochran Q: 542.23 | 1.01 (0.93, 1.10) | 0.743 | Cochran Q: 474.69 |
| | MR-Egger | 0.08 (−0.07, 0.22) | 0.317 | MR-Egger intercept (P): 0.008 | 1.07 (0.89, 1.29) | 0.479 | MR-Egger intercept (P): 0.113 |
| | Weighted median | 0.03 (−0.06, 0.12) | 0.487 | Distortion test (P): 0.563 | 1.15 (1.01, 1.30) | 0.030 | Distortion test (P): 0.541 |

MR, Mendelian randomisation; MR-APSS, MR for causal inference accounting for pleiotropy and sample structure; NA, not applicable; SNPs, single-nucleotide polymorphisms.

95% CI=−0.17 to −0.01, p=0.021). The MR Steiger directionality test showed that the causal direction of tobacco use on FI and falling risk was valid (online supplemental table S2).

**Sensitivity and power analysis**
Except for the age of initiation of smoking phenotype, there were several outliers (1–12 SNPs) identified by the MR-PRESSO test in evaluating the association between tobacco and alcohol consumption and FI and falls. The causal estimates obtained from the MR-PRESSO and MR-PRESSO corrected approaches showed consistent results (figure 2), and the distortion test indicated no significant difference between MR estimates before and after removing outliers (table 2). In addition, similar causal associations were also found in a sensitivity analysis using the weighted median approach after the removal of outliers, but not in the MR-Egger regression test (online supplemental table S3). After accounting for potential sample overlap using the MR-APSS approach, the initiation of smoking, cigarettes per day and smoking cessation remained significantly linked with the risk of frailty (p<0.01), while the association between drinks per week and frailty disappeared (table 2). Except for the initiation of smoking trait, the MR-APSS approach eliminated the causal relationship between alcohol and tobacco use and falling risk (table 2). The F statistics values across this MR study ranged from 34.22 to 1837.36 (online supplemental table S1), suggesting good stability of the causal estimates and minimal bias introduced by sample overlap. The results of the leave-one-out analysis showed that there was no single SNP driving the bias of the overall causal estimates (online supplemental figures S1–S5). The intercept from the MR-Egger regression test showed there was no obvious pleiotropy for the initiation of smoking, age of initiation of smoking and drinks per week (table 2, online supplemental table S3).

**DISCUSSION**
Although various observational studies have been performed to explore the association between tobacco and alcohol consumption and frailty and falls, there is still no definite conclusion.[9 26] Thus, the present MR study was performed to evaluate the causal associations of tobacco and alcohol intake on the risk of frailty. Our results demonstrated that genetically predicted tobacco use was causally associated with an increased risk of frailty and falling while delaying the age of initiation of smoking might reduce the risk of frailty and falling. However, no significant causal relationship was found between alcohol consumption and FI and falling.

Most but not all previous studies have suggested a positive association between smoking and frailty.[26] Similarly, the present MR study showed that initiation of smoking causally increased the risk of frailty. Although the heaviness of smoking (cigarettes/day) was also found to be positively associated with FI, this result should be explained very cautiously due to the potential pleiotropy of IVs. Our MR data showed that current smokers were more likely to have a higher FI than those who have quit smoking, which is in line with the results from previous studies.[8] A 4-year longitudinal study performed by Kojima *et*

*al* showed that compared with non-smokers, current smokers were more likely to develop frailty among community-dwelling older people (≥60 years old) in England.[11] Yet interestingly, we found that the age of initiation of smoking was negatively associated with FI. Previous studies suggested that early initiation of regular smoking predicted various physiological impairments, poorer self-rated health and increased susceptibility to illness independent of the duration of smoking,[27 28] which were implicated in the development of frailty. On the contrary, accumulating evidence has demonstrated that smoking cessation can substantially reduce the above health risks, even in those people quitting smoking in old age.[29] These data suggested that smoking cessation and postponement of smoking onset may be beneficial for preventing or delaying the development of frailty. Our MR data indicated that tobacco consumption was associated with an elevated risk of falling. A previous study on skiers showed that the odds of falls in smokers were significantly higher than that in non-smokers.[10] However, data from Looker suggested that there was no obvious association between smoking and falls among adults aged 50 years and older in USA.[13] Unexpectedly, a recent meta-analysis of 11 observational studies including 42 429 participants showed that smoking is associated with a decreased risk of falling in postmenopausal women (relative risk=0.78).[30] A potential explanation for the protective role in falls may be that smokers often suffered from cardiopulmonary diseases, which could lead to dysmotility or less activity and indirectly reduce the risk of falling.[31] Further studies are warranted to assess the pathological mechanisms underlying the inconsistent results between observational studies and this MR study.

The current MR investigation consistently demonstrated that initiation of smoking was linked to an increased risk of frailty and falls using several methods, but the underlying mechanism that contributed to the above association remains largely undetermined. Previous studies suggested that chronic inflammation, oxidative stress and DNA methylation induced by various toxic chemicals from cigarettes were associated with the risk of frailty.[11 32] However, smoking leads to declines in a wide range of human organs and tissues, which might mediate the association between smoking and frailty.[1 8] For example, previous studies showed that smoking is strongly linked with different cardiovascular diseases, respiratory diseases and metabolic diseases,[8] which have been suggested to be associated with the risk of frailty.[8 33] Although the MR-Egger intercept did not support potential pleiotropy for the association between initiation of smoking or age of initiation of smoking and frailty, there was obvious pleiotropy for cigarettes per day and smoking cessation. Therefore, we could not fully exclude the possibility that the causal association between smoking and frailty might be mediated by the potential alternative pathways mentioned above.

The effects of alcohol consumption on human health have always been hotly debated over the past decades without a consistent conclusion. Most of the previous studies have suggested that moderate alcohol use was associated with a decreased risk of frailty.[34–36] One study showed that the Mediterranean drinking pattern, but not regular drinking, confers reduced frailty risk (OR=0.68) compared with non-drinkers in older adults.[37] Kojima *et al* found that there was no relationship between high levels of alcohol consumption and frailty, but individuals with low alcohol consumption were likely to have a decreased risk of frailty compared with non-drinkers.[38] However, another study showed that high alcohol consumption in midlife was associated with an increased risk of both frailty (OR=1.61) and prefrailty (OR=1.42).[9] A meta-analysis of 44 051 participants (≥55 years) indicated that compared with those without alcohol consumption,

people with heavier alcohol consumption predicted a lower incidence of frailty with nominal statistical significance (p=0.05).[39] The potential explanations contributing to the discrepant results could be the differences in alcohol consumption quantification, demographic characteristics and types of alcohol, 'sick quitter' effects, and other confounding factors.[39] The present MR study showed a suggestive relationship between alcohol use and frailty (p=0.021), but not statistically significant after multiple testing adjustments (p>0.01). Thus, future GWAS research with larger sample sizes is warranted to verify the causal association between alcohol use and frailty, which is important for controlling alcohol consumption.

Some limitations should also be addressed here due to the behind assumptions of MR. First, although the causal estimates between tobacco use and FI and falls remained after removing outliers identified in the MR-PRESSO test, it is hard to avoid all the biases introduced by other potential outliers.[20] Second, there was heterogeneity found in the Cochran Q test, except for the association between the age of initiation of smoking and FI and falls. Third, despite removing potential outliers, pleiotropy remained in evaluating the causal relationship between cigarette consumption per day or cessation of smoking and FI and falls, which should be interpreted very cautiously in practice. Fourth, the results of the MR-APSS approach after accounting for potential sample overlap eliminated the causal relationship between alcohol and tobacco use and falling risk except for the initiation of smoking. However, it is worth noting that the full summary statistics of alcohol and tobacco consumption used for the MR-APSS test were based on samples other than 23andMe,[15] which make up the majority of the GWAS's samples on alcohol and tobacco consumption. Finally, since this MR study was performed using GWAS summary statistics of European descent, whether the causal link between tobacco use and frailty and falls remained in other ethnicities needed to be further investigated.

## CONCLUSIONS

In conclusion, our results of this MR study demonstrate that individuals with tobacco use have an increased risk of frailty and falling, and there is no causal relationship between alcohol use and frailty and falls. On the contrary, the age of smoking initiation was negatively associated with the FI and falling risk. Our findings remind people that cessation or delaying the age of initiation of smoking could reduce the risk of frailty and falling. To clarify the underlying mechanism contributing to the causal impact of smoking on frailty and falls may help guide frailty prevention and therapy.

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