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Smoking, alcohol and risk of sarcopenia: a Mendelian randomisation study

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ABSTRACT

Objective Observational studies have found that cigarette smoking increased the prevalence and incidence of sarcopenia, whereas alcohol consumption appeared to decrease the risk. These findings, however, may be susceptible to either confounding bias or reverse causation. We conducted a Mendelian randomisation (MR) study to appraise the causal relation of cigarette smoking and alcohol consumption to the risk of sarcopenia.

Methods Genetic instruments associated with cigarette smoking (cigarettes per day) and alcohol consumption (drinks per week) were retrieved from the publicly available genome-wide association data. Individual-level, electronic medical record-linked data on sarcopenia, grip strength and appendicular lean mass were obtained from the UK Biobank. We performed two-sample univariable and multivariable MR analyses to examine the relation of genetically determined cigarette smoking and alcohol consumption to the risk of sarcopenia and its indices.

Results One SD increase of genetically determined cigarette smoking was associated with an increased risk of sarcopenia (OR=2.51, 95% CI: 1.26 to 5.01, p=0.001), decreased grip strength (β=−0.63 kg, 95% CI: −1.13 to −0.13, p=0.01) and less appendicular lean mass (β=−0.22 kg, 95% CI: −0.44 to −0.01, p=0.04). Although one SD increase of genetically determined alcohol consumption was associated with decreased grip strength (β=−1.15 kg, 95% CI: −2.09 to −0.10, p=0.02), no statistically significant causal association was observed between genetically determined alcohol consumption and either sarcopenia (OR=0.96, 95% CI: 0.35 to 2.62, p=0.94) or appendicular lean mass (β=−0.23 kg, 95% CI: −0.91 to 0.45, p=0.51).

Conclusions Our findings showed that genetically determined cigarette smoking, but not alcohol consumption, was causally associated with the risk of sarcopenia.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study uses Mendelian randomisation (MR), a robust approach to minimise confounding and reverse causality biases inherent in observational studies.
⇒ Genetic instruments for cigarette smoking and alcohol consumption were derived from large-scale genome-wide association studies, ensuring the precision of exposure measurements.
⇒ Although multiple MR methods were used to mitigate pleiotropic confounding, residual bias could not be entirely ruled out, a known limitation of MR.
⇒ The small number of sarcopenia cases in the UK Biobank dataset may limit the statistical power for detecting weak associations, particularly for alcohol consumption.
⇒ Although efforts were made to exclude overlapping participants, the potential for overfitting in two-sample MR analysis remains due to sample overlap between exposure and outcome datasets.

INTRODUCTION

Sarcopenia, characterised by acceleration of muscle mass loss and function degradation, is known as a progressive and generalised skeletal muscle disorder.[1] Sarcopenia affects 10–27% of people aged ≥60 years[2] and often results in poor health outcomes, including frailty, disability and mortality.[3] Considering the population ageing and public health as well as the financial burden of sarcopenia on society, there is an urgent need to identify modifiable causal factors and develop effective preventive strategies targeting these factors to prevent this disease.

Numerous studies have examined the association of cigarette smoking and alcohol consumption, the two most common lifestyle factors, with the risk of sarcopenia. Results from a meta-analysis based on 29 observational studies concluded that cigarette smoking was associated with a higher likelihood of sarcopenia.[4] It is worth noting that most of the included studies (28 out of 29) were cross-sectional, making it challenging to establish causality. A recent longitudinal study found that smokers were at an increased risk of developing sarcopenia[5]; however, such results were susceptible to potential survival bias given that the average age of its study population was around 70 years. The totality of evidence on the association between alcohol consumption and sarcopenia remains inconclusive. Two experimental animal studies revealed that alcohol consumption

would exacerbate the risk of sarcopenia through the mechanism related to impaired skeletal muscle protein metabolism either directly or indirectly.[6 7] However, a meta-analysis of 13 cross-sectional and case-control studies conducted in humans reported that alcohol consumption was associated with a 22% reduction in the odds of sarcopenia.[8] These findings are susceptible to reverse causality, potential confounding bias and measurement error. For example, individuals with sarcopenia might be more inclined to abstain from alcohol because of their poor health (ie, sick quitters).[9] Moreover, unmeasured confounding factors (eg, jobs, dietary patterns and social connections) might affect both alcohol consumption and sarcopenia.[10 11] In addition, the estimated levels of alcohol consumption based on self-reporting might have been affected by recall bias and induced misclassifications of alcohol intake levels.[12] Recently, an updated meta-analysis of 19 studies indicated that alcohol consumption was not significantly associated with sarcopenia risk.[13] However, this meta-analysis included only cross-sectional studies on alcohol and sarcopenia, which still suffer from the aforementioned limitations inherent in observational studies.

Mendelian randomisation (MR) is a technique that refers to the use of genetic variants as proxies for the exposure of interest.[14] This approach offers several advantages over observational studies. First, MR studies can help minimise reverse causality because genetic variants are fixed at conception. Second, MR studies are less influenced by socioeconomic, physiological and common behavioural confounders due to the random allocation of alleles at meiosis. Third, genetic variants are usually precisely measured, making them less susceptible to measurement errors. To date, four MR studies have investigated the associations of cigarette smoking and alcohol consumption with muscle strength or muscle mass.[15–18] Sarcopenia, defined as decreased muscle strength alongside reduced muscle mass, recognises that strength involves factors beyond just muscle size.[19 20] However, no MR study has yet investigated the causal associations of cigarette smoking and alcohol consumption with the risk of sarcopenia as a comprehensive concept. Using data collected from the UK Biobank, we performed multiple MR analyses to examine the causal effect of genetically determined cigarette smoking and alcohol consumption on the risk of sarcopenia, as well as on the levels of two disease-related traits: grip strength and appendicular lean mass.

METHODS

Study design

Two-sample MR was performed using the summary-level genetic data retrieved from genome-wide association studies (GWAS)[21] and the UK Biobank.[22] Summary-level data (ie, standard errors and β coefficients) of the associations between single nucleotide polymorphisms (SNPs) and cigarette smoking and alcohol consumption were extracted from a large-scale published GWAS.[21] The standard errors and corresponding β coefficients of the associations between the smoking-associated or alcohol-associated SNPs and the sarcopenia, grip strength and appendicular lean mass were generated in the UK Biobank.

Genetic instruments

We derived the instrumental variables related to cigarette smoking and alcohol consumption from the largest, predominantly European ancestry genome-wide association meta-analysis containing 29 studies (335 843 individuals with cigarette smoking data and 941 280 individuals with alcohol consumption data).[21] That meta-analysis identified 55 genome-wide significant SNPs ($p<5\times10^{-8}$) associated with cigarette smoking (ie, the cigarettes per day) and 99 SNPs with alcohol consumption. Smoking exposure was defined as the average number of cigarettes smoked per day, reported either as a current smoker (how many cigarettes do you smoke per day?) or a former smoker (how many cigarettes did you smoke per day?). Responses were recorded either as an exact number or categorised into predefined bins. Alcohol consumption was recorded as the number of self-reported drinks of any type of alcoholic beverage per week and was left anchored to 1 and log-transformed (ie, the effect estimate was measured as log-transformed drinks per week).

To guarantee statistical independence, we included genome-wide significant SNPs and applied LD pruning to remove those with pairwise LD $R^2>0.1$. Genetic instruments included 55 SNPs for cigarette smoking and 93 SNPs for alcohol consumption, explaining 1.1% and 0.2%~0.3% of the variation in cigarette smoking and alcohol consumption, respectively. The corresponding F-statistics were 68.2 and 20.2–31.1, respectively, indicating a low potential for weak instrumental bias.[23] The SNPs used as instruments of exposure are presented in online supplemental table 1.

Outcome definitions

Data on sarcopenia, grip strength and appendicular lean mass were retrieved from the UK Biobank, which is a prospective cohort containing data from 500 000 adults aged 40–69 years in the United Kingdom and enrolled between 2006 and 2010. The study protocol was available online and more details were published elsewhere.[22] We excluded participants who had non-white European ancestry (to minimise confounding by ancestry), sex mismatches, excess heterozygosity, missingness or closer than second-degree relatives. Detailed information regarding participant selection is available in online supplemental figure 1. Individual-level phenotypic data on sarcopenia and its related traits, potential confounding factors (ie, age, sex and relatedness) and genotypic data were available in the UK Biobank. Sarcopenia was defined by the 2019 definition provided by the European Working Group on Sarcopenia in Older People 2 (EWGSOP2),[19] which includes criteria for low muscle strength and low muscle mass. In our analysis, we

applied this guideline, setting <27 kg for men and <16 kg for women as low grip strength thresholds, and <7.0 kg/m^2 for men and <5.5 kg/m^2 for women for low muscle mass. Grip strength and appendicular lean mass were measured using a Jamar handheld dynamometer and bioelectrical impedance analysis, respectively.

Statistical analysis

Genome-wide association study for sarcopenia and its related traits

We first conducted GWAS analyses for sarcopenia and its related traits (ie, grip strength and appendicular lean mass) to compute GWAS summary statistics, including β coefficients and standard errors using data from 378 634 individuals of European descent in the UK Biobank. Given the case-control imbalance in sarcopenia (577 cases vs 354 865 controls) and binary outcome structure, we employed the SAIGE (Scalable and Accurate Implementation of Generalized mixed model) software (https://saigegit.github.io/SAIGE-doc/), which uses a saddle-point approximation to handle extreme imbalance and controls for type I error inflation in large-scale biobank data.[24] For continuous traits (grip strength and appendicular lean mass), linear mixed models were implemented via PLINK V.2.0.[25] To minimise potential confounding and population stratification, all analyses were adjusted for age, sex, genotype batch effects and the top 20 genetic principal components.

Primary two-sample MR

First, the causal relations of genetically determined cigarette smoking and alcohol consumption with sarcopenia and its related traits were assessed by employing the inverse-variance weighted (IVW) method with a multiplicative random-effects model. The Wald ratios were generated for the single-SNP estimates. This approach provided the most precise and unbiased estimates assuming that all SNPs were valid instrumental variables or that horizontal pleiotropy was balanced.[26]

Multivariable two-sample MR

Further, multivariable MR analysis was performed to examine the relations between 141 genome-wide significant SNPs for either cigarette smoking or alcohol consumption and the risk of sarcopenia and its related traits (ie, grip strength and appendicular lean mass), since cigarette smoking and alcohol consumption were genetically correlated (r_g=0.07, p<0.05). Then, an extended IVW MR method was applied to estimate the causal effects in multivariable MR analysis, and the conditional F-statistic was used to examine the strength of the instrument.

Sensitivity MR analyses

The presence of horizontal pleiotropy was examined through other MR sensitivity analyses (ie, weighted median, the MR-Egger, and the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) methods), which made different assumptions. The weighted median method can provide consistent estimates as long as no less than 50% of the weight in the analysis originates from valid instrumental variables.[26] The MR-Egger method can detect and correct directional pleiotropy but is of low power.[26] The MR-PRESSO method can help identify and remove outlier variants to correct the potential directional horizontal pleiotropy and address the detected heterogeneity.[27] Therefore, a consistent effect across multiple sensitivity analyses strengthens the causal evidence. Additionally, overlapping participants in the UK Biobank's exposure and outcome datasets might cause overfitting in the causal estimates in a two-sample MR analysis. To assess the robustness of our results, we conducted a sensitivity analysis using summary statistics for cigarette smoking and alcohol consumption from a genome-wide association meta-analysis, which excluded overlapping samples, including those from the UK Biobank and were obtained from the original GWAS authors.[21] We also assessed the statistical power of the MR analyses using an online calculator (https://shiny.cnsgenomics.com/mRnd/).[28]

Secondary analysis

Considering heavy alcohol use may have a more explicit detrimental effect on health outcomes, we also assessed the effect of alcohol dependence on the three outcome variables described above. 20 SNPs ($p<5\times10^{-6}$) associated with alcohol dependence were extracted from a meta-analysis of GWAS in 28 cohorts with 46 568 European ancestry individuals.[29]

Reported results and software

For grip strength and appendicular lean mass, estimates were presented as βs (ie, the difference in means) and the corresponding 95% CIs. For sarcopenia, estimates were presented as ORs with their 95% CI. Both β and OR were calibrated to the effect of one SD increase in the exposures (eg, per one SD increase of cigarettes per day) on an outcome variable.

All statistical tests were two-tailed. Two-sample MR analyses were implemented with the 'MendelianRandomization', 'MVMR' and 'MR-PRESSO' packages in R (V.3.6.3). The associations of genetic variants with sarcopenia and its related traits were conducted via the SAIGE and PLINK (V.2.0) software.

Patient and public involvement

None.

RESULTS

Participants

Given the sample size and the strength of the genetic instruments, our analysis included 378 634 individuals of European descent. The mean age was 56.9 (SD=8.0) years and 46.2% were men. Among the 577 (0.2%) individuals diagnosed with sarcopenia, 74.3% were men. Characteristics of the included individuals are presented in table 1.

Cigarette smoking

Using 55 SNPs ($p<5\times10^{-8}$) independently associated with cigarette smoking in the discovery GWAS (online

Table 1 Participant characteristics at recruitment in UK Biobank

Characteristics	
All subjects at recruitment, n	378 634
Age, mean (SD), years	56.9 (8.0)
Body mass index, mean (SD), kg/m^2	27.4 (4.7)
Men, n (%)	175 017 (46.2)
Grip strength, mean (SD), kg	
Men	25.2 (6.3)
Women	18.4 (2.4)
Appendicular lean mass, mean (SD), kg	
Men	41.9 (8.8)
Women	27.0 (3.9)
Low grip strength, n (%)	19 394 (5.1)
Low muscle mass, n (%)	8124 (2.1)
Sarcopenia, n (%)	577 (0.2)

n, number of participants; SD, standard deviation.

supplemental table 1), the univariable two-sample MR analyses showed that genetic predisposition to cigarette smoking significantly increased the risk of sarcopenia (OR=2.51 per SD increase, equivalent to 1.22 cigarettes/day, 95% CI: 1.26 to 5.01, p<0.001) (table 2). MR analyses had more than 90% power to detect the causal effect of cigarette smoking on sarcopenia at a significance level of α=0.05. The direction of effect was consistent across the sensitivity MR methods (figure 1 and table 2), although the weighted median approach results had a wide 95% CI (0.65 to 4.99). One outlier SNP detected by MR-PRESSO indicated heterogeneity (online supplemental table 2), while MR-Egger intercepts indicated limited evidence of directional pleiotropy (online supplemental table 3). Sensitivity analyses based on GWAS meta-analysis summary statistics, after removal of overlapping samples, yielded consistent results for the effect of cigarette smoking (OR=2.48, 95% CI: 1.53 to 4.02, p<0.001) (online supplemental table 4).

Genetic predisposition to cigarette smoking was significantly associated with decreased grip strength (β=−0.63 kg per one SD increase in cigarettes per day, 95% CI: −1.13 to −0.13, p=0.01) and appendicular lean mass (β=−0.22 kg, 95% CI: −0.44 to −0.01, p=0.04) (table 2). No evidence of directional pleiotropy was detected in the MR-Egger MR analyses (online supplemental table 3). Overall, the magnitude and direction of the estimates for the effects of cigarette smoking on grip strength and appendicular lean mass were consistent across various sensitivity MR methods. When summary statistics for cigarette smoking excluded overlapping samples, effects on grip strength (β=−0.39 kg, 95% CI: −0.80 to 0.01, p=0.06) and appendicular lean mass (β=−0.20 kg, 95% CI: −0.37 to −0.03, p=0.02) were consistent, though slightly smaller (online supplemental table 4).

Alcohol consumption

Univariable MR analyses showed that genetic predisposition to alcohol consumption was associated with decreased grip strength (β=−1.15 kg per one SD increase in log-transformed drinks per week, 95% CI: −2.09 to −0.10, p=0.02). The results were robust from various sensitivity analyses when accounting for horizontal pleiotropy (figure 2 and table 3). Additionally, the robustness of the

Table 2 Two-sample MR estimations showing the effect of cigarette smoking on sarcopenia, grip strength and appendicular lean mass

Outcomes	N SNPs	MR methods	Estimates (95% CI)*	P value
Sarcopenia	55	IVW	2.51 (1.26 to 5.01)†	0.001
		Weighted median	1.80 (0.65 to 4.99)†	0.25
		MR-Egger	2.74 (0.79 to 9.15)†	0.12
		MR-PRESSO	2.51 (1.26 to 5.01)†	0.001
Grip strength	55	IVW	−0.63 (−1.13 to −0.13)	0.01
		Weighted median	−0.37 (−0.85 to 0.10)	0.13
		MR-Egger	−0.23 (−1.13 to 0.67)	0.67
		MR-PRESSO	−0.69 (−1.04 to −0.34)	<0.001
Appendicular lean mass	54‡	IVW	−0.22 (−0.44 to −0.01)	0.04
		Weighted median	−0.32 (−0.56 to −0.08)	0.01
		MR-Egger	−0.26 (−0.47 to −0.05)	0.02
		MR-PRESSO	−0.26 (−0.46 to −0.06)	0.01

*Values are expressed as beta (95% CI) unless stated otherwise.
†Values are expressed as odds ratios (95% CI).
‡MR-PRESSO identified an influential outlier (ie, rs7766641), which was also shown to be a clear outlier in scatter plots. The direction of the causal effect estimate was consistent and significant after removing this outlier.
CI, confidence interval; IVW, inverse-variance weighted; MR, Mendelian randomisation; PRESSO, pleiotropy residual sum and outlier.

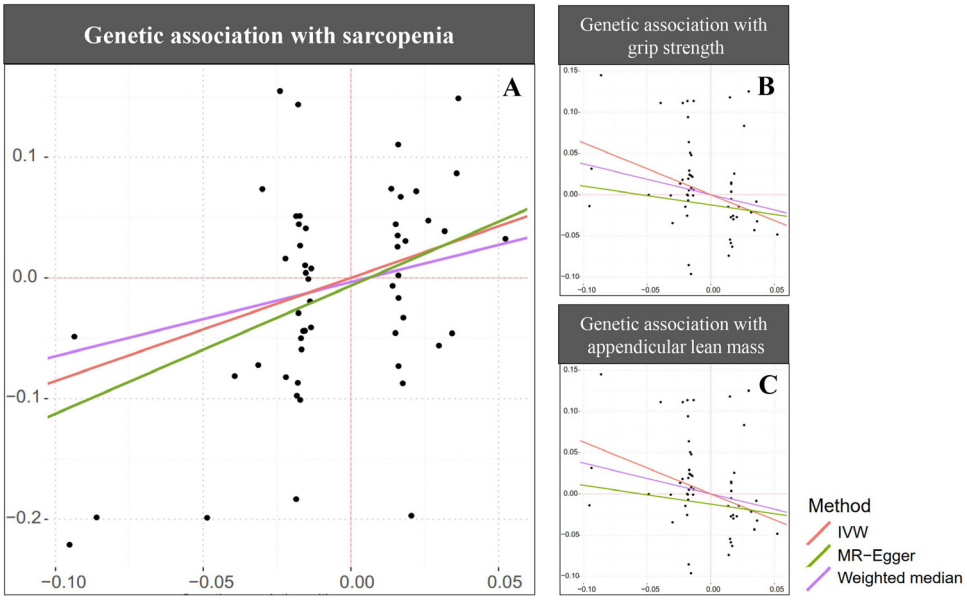

Figure 1 Two-sample Mendelian randomisation (MR) analyses for the genetically determined cigarette smoking on sarcopenia (A), grip strength (B) and appendicular lean mass (C), respectively. IVW, inverse-variance weighted.

results was further confirmed in sensitivity analyses using summary statistics for alcohol consumption obtained without overlapped samples, as detailed in online supplemental table 5. However, no statistically significant causal association was observed between genetically determined alcohol consumption and risk of either sarcopenia (OR=0.96, 95% CI: 0.35 to 2.62, p=0.94) or levels of appendicular lean mass (β=−0.23 kg, 95% CI: −0.91 to 0.45, p=0.51). Our power analysis revealed that the study had limited power (<20 %) to detect the causal effect of alcohol consumption on sarcopenia at a significance level of α=0.05, primarily due to the small sample size for sarcopenia and the relatively low variance explained by the alcohol consumption. There was also no evidence of directional pleiotropy (p>0.05) (online supplemental table 3).

Multivariable MR results

After accounting for alcohol consumption in multivariable MR analysis, genetically determined smoking was still associated with an increased risk of sarcopenia (OR=1.48 per one SD increase in cigarettes per day, 95% CI: 1.17 to 1.88, p=0.001) and decreased grip strength (β=−0.21 kg, 95% CI: −0.42 to 0.00, p=0.06), but showed no association with appendicular lean mass (β=−0.04 kg, 95% CI: −0.18 to 0.10, p=0.60). After accounting for cigarette smoking, genetically determined alcohol consumption still had a significant causal effect on decreased grip strength

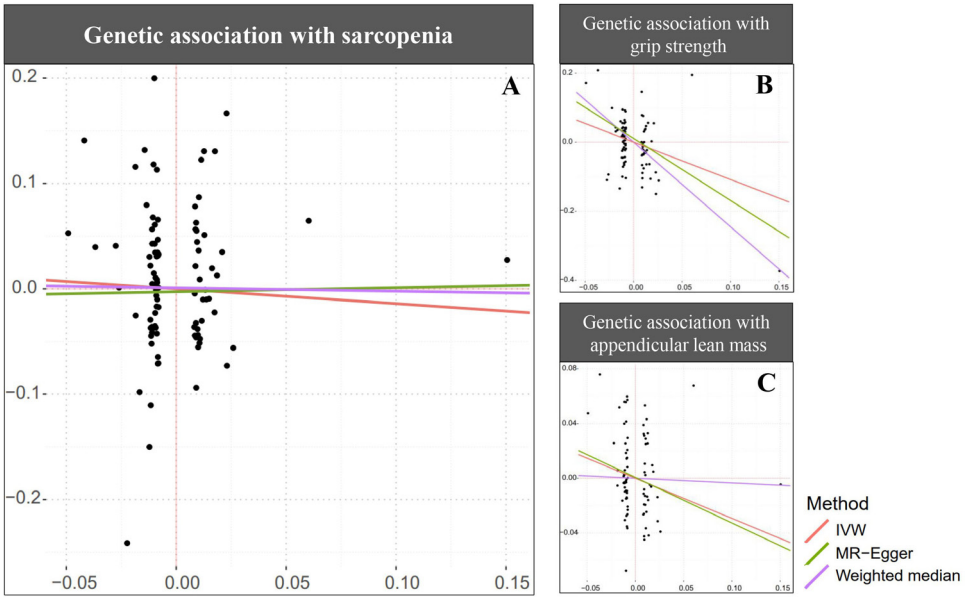

Figure 2 Two-sample Mendelian randomisation (MR) analyses for the genetically determined alcohol consumption on sarcopenia (A), grip strength (B) and appendicular lean mass (C), respectively. IVW, inverse-variance weighted.

Table 3 Two-sample MR estimations showing the effect of alcohol consumption on sarcopenia, grip strength and appendicular lean mass

Outcomes	N SNPs	MR methods	Estimates (95% CI)*	P value
Sarcopenia	93	IVW	0.96 (0.35 to 2.62)†	0.94
		Weighted median	1.16 (0.19 to 7.24)†	0.87
		MR-Egger	1.00 (0.15 to 6.67)†	0.99
		MR-PRESSO	0.96 (0.40 to 2.33)†	0.93
Grip strength	93	IVW	−1.15 (−2.09 to −0.10)	0.02
		Weighted median	−2.45 (−3.40 to −1.50)	<0.001
		MR-Egger	−1.77 (−3.62 to 0.07)	0.06
		MR-PRESSO	−1.42 (−2.23 to −0.59)	<0.001
Appendicular lean mass	93	IVW	−0.23 (−0.91 to 0.45)	0.51
		Weighted median	−0.03 (−0.51 to 0.45)	0.89
		MR-Egger	0.28 (−1.05 to 1.61)	0.68
		MR-PRESSO	−0.24 (−0.63 to 0.15)	0.25

*Values are expressed as beta (95% CI) unless stated otherwise.
†Values are expressed as odds ratios (95% CI).
CI, confidence interval; IVW, inverse-variance weighted; MR, Mendelian randomisation; PRESSO, pleiotropy residual sum and outlier.

(β=−1.02 kg per one SD increase in log-transformed drinks per week, 95% CI: −1.82 to −0.23, p=0.01); however, no such effect was found on sarcopenia and appendicular lean mass (online supplemental table 6).

Alcohol dependence

There was no apparent causal association of genetically determined alcohol dependence with risk of sarcopenia (OR=0.59, 95% CI: 0.10 to 3.42, p=0.56), grip strength (β=0.02 kg, 95% CI: −0.13 to 0.16, p=0.81) and appendicular lean mass (β=0.02 kg, 95% CI: −0.03 to 0.07, p=0.34) (online supplemental table 7 and figure 2). These findings were consistent regardless of which MR methods were performed.

DISCUSSION

Principal results

Using MR analyses, we demonstrated that genetically determined cigarette smoking was causally associated with an increased risk of sarcopenia, decreased grip strength and appendicular muscle mass. Although genetically determined alcohol consumption was associated with decreased grip strength, no such effect was observed on the risk of either sarcopenia or appendicular lean mass. These associations persisted across various sensitivity analyses, indicating the robustness of the study findings.

Comparison with prior work

Our results of cigarette smoking increasing the risk of sarcopenia are consistent with the findings of previous studies.[4 5] Several previous studies have shown that alcohol consumption was associated with a decreased risk of sarcopenia.[8 30 31] However, these findings may be influenced by either potential confounding bias, reverse causation or measurement error. Alcohol consumption, especially moderate level, was associated with high socioeconomic status (ie, unmeasured confounding factor),[10 11] and decreased alcohol consumption may arise as a result of poor health conditions (eg, sarcopenia).[9] In addition, self-reported data on alcohol consumption may introduce recall errors and social desirability bias.[12] Using MR analyses, which are free of reverse causation and have much less risk of potential confounding bias, we found that the results were consistent with those from observational studies. Specifically, genetically determined alcohol consumption showed no apparent protective effect on sarcopenia; instead, increased alcohol consumption could reduce grip strength, and alcohol dependency slightly elevated the risk of sarcopenia, albeit not statistically significant.

Four MR studies have explored the associations of genetically determined cigarette smoking and alcohol consumption with grip strength or appendicular lean mass.[15–18] Among them, two studies reported that cigarette smoking was causally associated with decreased appendicular muscle mass, although not with grip strength.[17 18] One study indicated that cigarette smoking might be associated with a lower risk of low grip strength but not appendicular lean mass.[15] Regarding alcohol consumption, two studies found no significant association between alcohol consumption and grip strength and/or appendicular lean mass.[16 17] One study did find a significant association between alcohol consumption and low grip strength, although it did not impact appendicular lean mass.[15] Several factors may have contributed to these inconclusive findings. First, previous investigators dichotomised the grip strength or appendicular lean mass. Doing so may reduce the statistical power.[32] Second, variations

observed in the choice of exposure indicators varied across these studies, as did the selection of instrumental variables, which can directly influence the outcomes. For example, the null associations between smoking initiation (ie, a binary phenotype for ever-smoking) and grip strength or appendicular lean mass may result from cigarette smoke exposure among never-smokers or misclassification of smoking status (ever-smokers misreported as never smoked regularly), as self-reports often underestimate cotinine levels.[33] Finally, our study investigated the relationship between cigarette smoking and alcohol consumption to the risk of sarcopenia, using the recently proposed definition (ie, EWGSOP2 criteria). The EWGSOP2 recognised that muscle strength does not only depend on lean mass and that the relationship between these quantities is non-linear, thus defining sarcopenia as having both low strength and lean mass.[19] This approach aimed to promote the diagnosis and management of sarcopenia in clinical practice, and, therefore, this definition aimed to identify indisputable cases.

Possible explanations

Several explanations may account for the association between genetically predicted cigarette smoking and the risk of sarcopenia. First, cigarette smoking could impair muscle protein synthesis and increase oxidative stress, myostatin muscle expression and cytokine production in skeletal muscle.[34 35] Second, studies have revealed an association between cigarette smoking and poor oral health and reduced appetite,[36 37] leading to compromised food intake and negative energy balance. Poor nutritional intake can increase the risk of sarcopenia.[1] Finally, cigarette smoking is deemed the primary cause of chronic obstructive pulmonary disease.[38] Previous studies have shown that chronic obstructive pulmonary disease is correlated with a higher risk of sarcopenia attributed to the factors of systemic inflammation, lower body mass index, osteoporosis, physical inactivity, cachexia and skeletal muscle weakness.[39–42]

Chronic alcohol abuse and acute alcohol intoxication are linked to a decrease in muscle protein synthesis, which, in turn, is governed by impaired activity of the protein kinase, the mechanistic target of rapamycin complex-1 (mTORC1).[43 44] However, one study reported that moderate and regular alcohol consumption cannot alter the majority of mTORC1-related signalling events, and thus could not suppress muscle protein synthesis.[45] In addition, excessive alcohol intake causes DNA damage, oxidative stress and inflammation,[46 47] which are important contributors to the pathogenesis of sarcopenia.[1] Nevertheless, moderate and regular alcohol consumption has been associated with lower levels of inflammatory cytokines (eg, interleukin-6 and C-reactive protein),[48] while a reduction of those cytokines may decrease the risk of sarcopenia. Taken together, the effect of alcohol consumption on sarcopenia is multifactorial, and at least no protective effects of alcohol consumption in reducing sarcopenia risk were observed in the present study.

Limitations

Several limitations should be acknowledged. First, despite the use of multiple MR methods to resist confounding due to pleiotropy, we could not fully eliminate residual bias, which is an established weakness of the MR method.[49] Second, only around one-third of participants in the UK Biobank were included in both the exposure dataset and outcome dataset in primary analyses. The overlapped samples in a two-sample MR analysis might result in overfitting in the causal estimates in the direction of the observed associations.[50] When we used the summary statistics for cigarette smoking and alcohol consumption which were obtained from the genome-wide association meta-analysis excluding overlapped samples, the results did not change materially, suggesting that the bias caused by sample overlap was relatively small.[51] Third, the validity of our MR analysis depends on the selected SNPs being true causal variants for smoking and alcohol consumption. Thus, limitations in the source GWAS, including measurement errors, population stratification or sample size constraints,[52] may affect the robustness of our findings. Fourth, smoking and alcohol behaviours and their physiological effects may vary by sex due to hormonal, metabolic and sociocultural factors.[53 54] Although our study could not perform formal sex-stratified analyses, future research should focus on exploring gender-specific mechanisms in smoking-related sarcopenia. Another limitation is that the number of sarcopenia cases was relatively small and the proportion of variance in alcohol consumption explained by genetic variants was small. Although no causal association between alcohol consumption and sarcopenia was observed, we could not completely rule out the possibility due to insufficient statistical power. Future studies with larger sample sizes and stronger genetic instruments are needed to improve statistical power and provide more precise estimates of the causal effect. Finally, due to a mere 5% response rate and healthy volunteer bias in the UK Biobank, whether our findings can be generalised to the broader UK population remains uncertain, despite the large sample size.

Clinical and research implications

Our study adds further evidence to support that genetically determined cigarette smoking has a significantly detrimental effect on health. Approximately 25% of men and 5% of women in the world smoke cigarettes.[55] Since cigarette smoking is a modifiable lifestyle factor, the public and healthcare providers have one more reason to advocate smoking prevention and cessation. Alcohol consumption, especially alcohol abuse, is a cause of more than 200 diseases, for example, liver cirrhosis, cardiovascular diseases and various cancers.[47] Studies have found that alcohol abuse results in 3.3 million deaths worldwide each year.[47] Although previous studies reported the potential protective role of alcohol consumption against sarcopenia,[8 30 31 56] our results do not support these findings. If anything, genetically determined alcohol consumption seems to have a detrimental effect on grip

strength, suggesting that the protective effects of alcohol consumption against sarcopenia may be artefacts of reverse causation or residual confounding. Furthermore, as we acknowledged, the number of sarcopenia cases and the proportion of variance in alcohol consumption explained by genetic variants in the present study were relatively small, which could not completely rule out the possibility that our study may not have adequate power to detect a potential causal association between alcohol consumption and increased sarcopenia risk. If confirmed by further data and more powered studies, such an association suggests another reason to avoid high habitual alcohol consumption and may guide policymakers and public health workers to develop guided communications and interventions for alcohol users against sarcopenia.

CONCLUSION

Genetically determined cigarette smoking was causally related to the risk of sarcopenia, indicating targeted strategies for smoking prevention and cessation should be developed to mitigate the risk of sarcopenia. Further research is required to explore the association between alcohol consumption and sarcopenia risk.

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