Introduction

Frailty describes a syndrome in a growing number of older adults, characterized by deteriorative function of multiple systems and increased vulnerability to endogenous as well as exogenous exposures (1). In the clinical setting, frailty can be defined as a reduction in physical strength and endurance, with or without a decline in cognitive ability. Individuals with frailty experience a higher risk of adverse

Background: Previous epidemiological evidence has suggested that frailty status might be associated with cardiovascular diseases (CVDs). However, the exact causality remains unestablished. In this study, we employed Mendelian randomization and sought to investigate the potential causality in association of frailty index (FI) with cardiovascular outcomes [coronary artery disease (CAD), myocardial infarction (MI), atrial fibrillation (AF), and heart failure (HF)].

Methods: Independent single nucleotide polymorphisms (SNPs) at genome-wide significance for FI were obtained from a recent genome-wide association study (GWAS) meta-analysis of European descent (n=175,226). The association of these SNPs with CVDs was examined in summary statistics from corresponding GWASs of European descent (CAD: 184,305 cases and 60,801 controls; MI: 184,305 cases and 43,676 controls; AF: 1,030,836 cases and 60,620 controls; and HF: 977,323 cases and 47,309 controls). Replication analyses were performed using GWAS datasets from FinnGen.

Results: In the meta-analysis of inverse-variance weighted estimates from different data sources, genetically determined higher FI conferred an odds ratio (OR) of 1.46 [95% confidence interval (CI): 1.13 to 1.87; P=0.003] for CAD, 1.62 (95% CI: 1.21 to 2.17, P=0.001) for MI, and 1.46 (95% CI: 1.24 to 1.72; P=4.89×10^{-6}) for HF. However, FI failed to be potentially influential on AF risk (OR, 1.43; 95% CI: 0.93 to 1.66; P=0.107). Several complementary analyses also received broadly concordant results.

Conclusions: We have provided genetic evidence of a causal association between FI and the risk of CAD, MI, and HF. Further studies are warranted to clarify whether FI is causally related to AF risk.

Keywords: Causal association; cardiovascular diseases (CVDs); frailty index (FI); Mendelian randomization; genome-wide association study (GWAS)
outcomes including falls, disability, and hospitalization (1,2). To assess this complex condition, Searle et al. introduced the frailty index (FI), which is based on the proportion of age-related deficits among a list of 30 physical parameters (3).

Cardiovascular diseases (CVDs) are commonly known as a group of diseases including coronary artery disease (CAD), myocardial infarction (MI), atrial fibrillation (AF), and heart failure (HF). An increased prevalence of CVDs among the aging population has led to elevated morbidity and mortality worldwide (4). Identification of modifiable risk factors including hypertension, diabetes mellitus, and smoking, has facilitated the management of CVDs. Notably, observational studies have suggested a pattern of associations between frailty and CVDs. Frailty is more prevalent in patients with CVDs than in those without it (5,6). A longitudinal cohort study enrolling 4,211 community-dwellers showed that experiencing baseline frailty was correlated with an increased risk of CVDs over an 8-year follow-up (7). Besides, a previous study has further revealed that the FI might have a more pivotal value than traditional CVD risk factors to discriminate CVD events (8). Regarding the causal effect of frailty on CVDs, true relationships may be distorted by reverse causation or residual confounders (9). Well-designed large-scale cohort studies can to some extent overcome these obstacles and shed light into this issue, but at a relatively high cost.

Therefore, exploring the potential causal link could facilitate enhanced management of CVDs. Mendelian randomization (MR) is an application of genetic variants to plausibly infer the causal associations between phenotypic traits (exposures) and health-related outcomes. The upside of this approach lies in leveraging a large sample size from a genome-wide association study (GWAS) and minimizing bias caused by reverse causation and confounding factors. There are 3 basic principles when performing MR analysis. First, the instrumental variables (IVs) should be associated with exposure of interest at a genome-wide significance level; Second, the IVs are irrelevant to any confounders that may affect the exposure or outcome; Third, the IVs do not directly lead to the outcome, except through its association with the exposure (10). This approach has been applied to the fields of genetics, epidemiology, statistics, econometrics, and bioinformatics (11). In the present study, we used instrumental variables (IVs) identified from a recent GWAS meta-analysis for FI, and performed a 2-sample MR to decipher whether genetically determined higher FI causally leads to increased CVDs risk. The robustness of the results was tested by replicating the main analyses using different outcome datasets. We present the following article in accordance with the STREGA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4239/rc).

Methods

Study design

The potential causal effect of genetic liability to FI on CVDs was assessed using a 2-sample MR study based on summary statistics from published GWAS meta-analyses and the FinnGen consortium (https://www.finngen.fi/en). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data sources

Summary-level GWAS data related to CAD/MI, AF, and HF were drawn from the Coronary Artery Disease Genome-wide Replication and Meta-analysis plus The Coronary Artery Disease Genetics (CARDioGRAMplusC4D) consortium (12), a GWAS meta-analysis conducted by Nielsen et al. (13), and the Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) consortium (14), respectively. Replication analyses were performed using data from FinnGen consortium (15). Detailed information for these outcome datasets (sample size, ethnicity, case definition, adjustment, etc.) is listed in the Table S1. No ethical permission or informed consent was necessary given that this MR study was based on publicly available summary statistics.

IVs selection

A total of 14 FI-related single nucleotide polymorphisms (SNPs) were provided by a large GWAS meta-analysis compromising European participants from UK Biobank (n=164,610) and TwinGene (n=10,616) (16). The FI was defined based on the accumulation of deficits as described previously (3). All these SNPs reached a genome-wide association (P<5x10^-8) upon adjustment for age, gender, and 10 principal components, and were not in linkage disequilibrium with each other (r^2<0.001 across a 10,000 kb window) according to the European 1000 genomes panel (17). The details of the associations of genetic variants with the exposure and outcomes are displayed in Table S2. The phenotypic variance explained by
these SNPs ($R^2$) was calculated using the method described by Shim et al. (18). To attain the first assumption of MR design, SNPs with $F$ statistics [$F = R^2(n - k - 1)/k (1 - R^2)$] higher than 10 were considered valid IVs. The rs9275160 was not available in the CARDIoGRAMplusC4D dataset; no suitable proxy was found by searching an online website tool (https://snips.helmholtz-muenchen.de/snipsa3/).

**Statistical analysis**

Effect estimates of each SNP on outcomes were pooled using multiplicative random-effects inverse-variance weighted (IVW) as the primary statistical method (19). The IVW method confers convincing results when all 3 MR assumptions are satisfied. However, it was susceptible to horizontal pleiotropy. Therefore, a set of complementary analyses were used, including the simple median, the weighted median (20), MR-Egger regression (21), and MR pleiotropy residual sum and outlier (MR-PRESSO) (22) methods. These approaches make distinct assumptions on the presence of invalid IVs, and were applied to test the robustness of the results. Heterogeneity was evaluated using Cochrane’s Q test and $I^2$ index. Significant heterogeneity was considered when \(P_{\text{Cochrane}}<0.05 \) and \(I^2>50\%\) for IVW estimates (23). The MR-Egger regression can evaluate horizontal pleiotropy bias by employing its intercept as an indicator \((P_{\text{intercept}}<0.05 \text{ suggests pleiotropy})\) (24). In addition, potential pleiotropic outlying IVs were detected by MR-PRESSO approach (22).

The effect size for each SNP was scaled to genetically determined 1 total point increase in FI. The IVW results based on GWAS datasets and the FinnGen consortium were combined using meta-analysis in a fixed-effect model if no heterogeneity was found, otherwise, a random-effect model was applied. Post hoc statistical power was calculated using sample size and proportion of cases of outcome datasets, Type-I error rate (0.05), odds ratio (OR), and percentage of variation explained by IVs (Table S3) (25). Considering the multiple tests, associations with a Bonferroni-corrected $P$ value of <0.0125 were considered significant. All analyses were performed using R packages TwoSampleMR (26) and MR-PRESSO (22) within software R (version 4.1.0; The R Foundation for Statistical Computing, Vienna, Austria).

**Results**

For all IVs considered, the $F$ statistics ranged from 28.5 to 113.6, suggesting that these IVs exhibited sufficient strength for the present MR. All together they explained ~0.3% of phenotypic variation of FI (Table S2).

The IVW analyses showed that a genetically determined 1 point increment in FI conferred an OR of 1.47 [95% confidence interval (CI): 1.10 to 1.96; \(P=0.009\)] for CAD, 1.62 [95% CI: 1.15 to 2.29, \(P=0.006\)] for MI, 1.15 (95% CI: 0.92 to 1.44, \(P=0.222\)) for AF, and 1.42 (95% CI: 1.19 to 1.71; \(P=1.34\times10^{-6}\)) for HF in the GWAS datasets (Figure 1). The causal associations remained broadly consistent in the analyses based on the FinnGen consortium (Figure 1).

The meta-analysis combining different data sources was in further support of the causal effect of FI on CAD (OR, 1.46; 95% CI: 1.13 to 1.87; \(P=0.003\)), MI (OR, 1.62; 95% CI: 1.21 to 2.17; \(P=0.001\)), and HF (OR, 1.46; 95% CI: 1.24 to 1.72; \(P=4.89\times10^{-6}\)) (Figure 1). However, the results showed that the association for AF may not be causal (OR, 1.43; 95% CI: 0.93 to 1.66; \(P=0.107\)) (Figure 1).

We had sufficient power (>90%) in detecting the OR in all cases (except for AF) by applying both GWAS meta-analyses and FinnGen consortium (Table S3). Complementary analyses including weighted median, simple median, and MR-PRESSO methods were in accord with prior results, albeit with a smaller magnitude with wide CIs in several analyses (Figure 2). Cochrane’s Q test and $I^2$ index suggested a modest heterogeneity for FI-CAD and FI-MI associations in the FinnGen consortium, whereby no evidence was found for horizontal pleiotropy based on the $P$ value for MR Egger intercept (Table S4). In addition, MR-PRESSO detected no pleiotropic outlying SNPs for all results considered (except for CAD in the FinnGen consortium: rs4146140) (Table S4). There was no observed substantial difference when we recalculated MR estimates by excluding this SNP (Figure 2).

**Discussion**

The present MR study yielded strong evidence indicating causal relationships between genetically predicted FI and risk of CAD, MI, and HF, with sufficient statistical power. The results were broadly consistent in replication analyses and several complementary analyses. In consideration of heterogeneous results from the different data sources and insufficient power, having a higher FI may not put a person at a higher risk of AF.

The genetic determinants of FI include gene loci associated with traits such as BMI, CVDs, smoking, HLA proteins, depression and neuroticism (16). Higher educational attainment and lower BMI are associated with
decreased FI. Besides, mental health plays a pivotal role in the biological mechanisms of frailty (16). The degree of frailty is expected to increase along with aging, and FI has been considered an indicator of biological age that could even outperform DNA methylation age (27). However, frailty acts as a modifiable variable that could be adjusted by controlling the risk factors (1). Investigators in recent years have successfully decoded the underlying associations between frailty and other diseases and health-related outcomes. The causal association between FI and risk of CAD, MI, and HF found in this MR study was in line with observations from several traditional epidemiology studies (7, 28, 29). Notably, the clinical data also showed that frailty was an essential independent predictor of prognosis for patients with acute coronary syndrome (30, 31). Despite adjusting for some clinical and biochemical variables, current conclusions from observational studies also call for further validation due to limited sample size and biases such as residual confounders and reverse causality. In the present MR study, we managed to provide genetic evidence for the causal relationships between FI and CVDs outcomes. Our conclusion strengthens the conceptual framework that FI increases the risk of CAD, MI, and HF, and that effort to prevent FI may have substantial cardiovascular benefits.

Life style changes, such as regular exercise and appropriate food intake have been considered to curb the progression of frailty (1). Importantly, identification of frailty using FI could aid clinicians in providing better primary, secondary, and tertiary prevention of these CVDs. Besides, frailty index performs better than traditional cardiovascular risk factors in predicting the risk of CVD events (8). Frailty index, together with traditional cardiovascular risk factors, will provide greater prognostic value when clinicians identify those with higher CVDs risks.

Previous studies have suggested some molecular and cellular pathways through which frailty leads to CVDs. First, frail patients often present with higher levels of oxidative stress (32), resulting in an accumulation of cellular damage that impairs endothelium function and further triggers the onset of atherosclerotic CVD (33). Second, the Cardiovascular Health Study reported that frailty status was characterized by elevated inflammatory marker (C-reactive protein) and blood clotting markers (factor VIII and D dimer) (34). High inflammation levels and a hypercoagulable state perpetuate CVDs (35, 36). Furthermore, cross-sectional studies have demonstrated that frail people are placed at a higher risk of IGF-1 and sex hormone deficiency (37), which are positively related
to higher CVDs risk (38,39). A recent cross-sectional study found a pattern of association between frailty and high waist circumference and high body fat mass, and low skeletal muscle mass (40). Meanwhile, these body composition changes have been recognized as risk factors as predictors of CVD outcomes (41,42). Therefore, body composition changes may present one of the biologic mechanisms of how frailty leads to higher CVDs risks.

The frailty state was more pronounced among those developed with AF (43). A longitudinal study from Ireland showed that the frailty phenotype in people with AF may be useful in detecting early deterioration and accelerated aging (44). Besides, patients with AF and FI had a greater tendency to experience stroke, bleeding, and mortality (45). However, prevalent frailty status may not significantly affect AF incidence as reported by the

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**Figure 2** Complementary analyses of genetically determined FI with CVDs risk. *, MR-PRESSO instrumental variable outlier detected: rs4146140. FI, frailty index; CVDs, cardiovascular diseases; CARDioGRAMplusC4D, Coronary ARtery Disease Genome-wide Replication and Meta-analysis plus The Coronary Artery Disease Genetics; HERMES, Heart Failure Molecular Epidemiology for Therapeutic Targets; MR-PRESSO, MR-pleiotropy residual sum and outlier; OR, odds ratio; CI, confidence interval.
Framingham Heart Study Offspring cohort study (hazard ratio, 1.22; 95% CI: 0.95 to 1.55) (46), which corroborated the results from the present MR study. This may be due to the fact that the mechanism of AF is to some extent different from that of atherosclerotic CVDs. Nonetheless, it is still plausible that frailty may increase the risk of AF given the limited sample size and insufficient statistical power of this MR study. Further well-designed clinical trials are needed to shed light on this important issue.

GWAS is an observational study which is sought to find genetic variants associated with a trait at genome-wide scale. GWASs provide genome-wide significant variants that can be utilized as instrumental variables in the MR studies (11). The biggest advantage of GWAS is its increased scale and scope in the past decades. Thereby, investigators are enabled to perform MR studies more efficiently (11). The MR framework, by applying hitherto largest GWAS meta-analyses, is one of the major strengths of this study. Using genetic variants randomly assorted and constant after conception, MR analysis minimized the influence of the reverse causation and confounding factors. We had sufficient statistical power to assess the causal association of FI with CAD, MI, and HF. Importantly, the MR estimates were broadly in accordance with across replication analyses using the FinnGen dataset and complementary analyses by other MR methods with no overt horizontal pleiotropy. Taken together, the MR estimates by multiple means reinforced the causal effect of FI on CVDs.

There were several limitations to our study. Firstly, study samples were confined to European cohorts, which may limit the generalizability of conclusions to different populations. Secondly, we had limited statistical power for the FI-AF association in both Nielsen et al. GWAS dataset and the FinnGen dataset. This may be ascribed to the small sample size as well as the low percentage of phenotypic variance explained by IVs. Therefore, we should take prudent steps when properly interpreting the corresponding results. Third, moderate heterogeneity was detected in several analyses. However, here we used IVW in multiplicative random effects, which are known to be applicable in the case of heterogeneity (47).

Conclusions
This MR study ascertained a contribution to the causal associations between genetically predicted FI and the risk of CAD, MI, and HF. However, FI may not be causative in AF incidence. Programs aimed at curbing frailty may be of benefit in the prevention of atherosclerotic CVDs and HF.

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Footnote
Reporting Checklist: The authors have completed the STREGA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4239/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4239/coif). All authors report that this work was supported by grants from the National Natural Science Foundation of China (Nos. 82170331, U21A20337, and 82003372); and the Key Research and Development Plan of Zhejiang Province (No. 2020C03017). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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