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Original Article

Causal relationship between hand grip strength and cognition/dementia risk: a Mendelian randomization study

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Abstract: Background: Muscle strength positively correlates with cognitive function, with the bidirectional causal link between hand grip strength and cognition posing a significant but incompletely understood public health challenge. This study aimed to explore the causal relationship between hand grip strength and cognition and its effect on dementia. Methods: A two-sample Mendelian randomization analysis used genome-wide significant single nucleotide polymorphisms (SNPs) ($P < 5\times10^{-8}$, at least $P < 5\times10^{-6}$) linked to hand grip strength (right or left), cognition/dementia risk from the IEU Open GWAS project with 42,484 GWAS summary data sets. The primary analysis employed the inverse variance weighted method, while sensitivity analyses were conducted using the weighted mode and MR-Egger. These analyses aimed to assess the causal relationships between hand grip strength and cognition/dementia risk. Results: The inverse variance weighted (IVW) analysis indicated a directional positive causal effects of hand grip strength on cognition (Left-hand grip strength on cognitive function (OR (95% CI): 1.23 (1.02-1.48), P = 0.026)/performance (OR (95% CI): 1.16 (1.04-1.30), P = 0.009); Right-hand grip strength on cognitive function (OR (95% CI): 1.23 (1.02-1.48), P = 0.031)/performance (OR (95% CI): 1.10 (1.02-1.19), P = 0.018), with almost no reverse causality between cognitive function/performance and hand grip strength. Based on the results above, we then researched the directional causal effects of hand grip strength on neurodegenerative diseases (like dementia) with cognitive decline as the main clinical manifestation. However, the IVW methods yielded no evidence to support a causal effect of left-hand grip strength on dementia (P > 0.05). Conclusions: This MR study indicates a positive directional causal relationship between hand grip strength and cognition, with no observed causal link to dementia. These results hold implications for the development of public health measures and strategies for preventing cognitive decline.

Keywords: Hand grip strength, cognition, dementia, Mendelian randomization

Introduction

The global demographic shift towards aging populations and extended life expectancies has precipitated a surge in age-related cognitive impairment prevalence, imposing mounting socioeconomic burdens on healthcare systems and societal infrastructures worldwide [1, 2]. Given the profound implications of this epidemiological transition, there is a growing consensus among researchers and policymakers that the identification of sensitive biomarkers and preclinical indicators of neurocognitive deterioration must be prioritized. Such advancements in early detection may enable timely intervention during critical windows of neural plasticity, possibly attenuating disease progression and improving outcomes in affected populations.

Grip strength, a cost-effective and straightforward measure of muscle strength [3], has been reported to be linked to aging-related diseases [4, 5]. Substantial epidemiological evidence from longitudinal cohort studies [6, 7] has consistently demonstrated that diminished baseline handgrip strength, as a robust indicator of overall musculoskeletal health, shows signifi-

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cant associations with both accelerated cognitive decline and increased incidence of dementia risk across diverse populations. To wit, among 2618 participants in the National Health and Nutrition Examination Survey 2011-2014, combined grip strength exhibited positive associations with global cognitive function and individual cognitive domains, even after adjusting for demographic, lifestyle, and disease history factors [8]. Such analyses as above aim to define the preventive benefits of hand grip strength measurement and clarify its relationship with cognition. Overall epidemiological conclusions consistently support a strong association between grip strength and cognitive function [9-11]. Notwithstanding robust epidemiologic associations between hand grip strength and cognitive outcome, the establishment of causal inference remains methodologically challenging, primarily due to inherent limitations in traditional observational study designs, including insufficient statistical power from restricted cohort sizes, unmeasured confounding variables, and potential reverse causality bias. While randomized controlled trials (RCTs) are the gold standard for causal inference, their expense, time requirements, and occasional impracticality pose challenges.

Genome-wide association analysis (GWAS) has revolutionized the study of human genetics and our understanding of genetic mechanisms in complex diseases [12-14]. Mendelian randomization (MR) uses GWAS data to examine causal relationships between exposures and outcomes, taking advantage of the law of independent assortment and allele constancy throughout an individual's lifetime, resembling the design of RCTs [15, 16]. Genetic variants as instrumental variables (IVs) are specifically associated with the exposure of interest, thereby minimizing confounding effects through the inherent random allocation of genetic alleles [17]. MR analysis effectively addresses limitations in traditional observational studies, making it a viable method to assess the causal association between grip strength and cognitive function or performance.

In this study, we conducted a bidirectional two-sample MR analysis using extensive GWAS summary statistics to investigate the causal links between hand grip strength and cognition. Subsequently, guided by the causal findings, our future research will focus on examining the causal effects of hand grip strength on dementia through MR analysis. The overarching goal was to explore the relationship between hand grip strength and cognition/dementia risk using various assessment tools in a large-scale, nationally representative population.

Materials and methods

Genetic instrument selection

Our study employed a two-sample MR analysis, using right- or left-hand grip strength as exposures and cognition/dementia as outcomes. Ethical approval was obtained from the original studies. MR relies on three key assumptions [18]: instrumental variables must be correlated with the exposure, unrelated to confounders, and affect the outcome solely through the exposure (no horizontal pleiotropy). The study design and MR assumptions are illustrated in **Figure 1**.

For instrumental variable selection, we implemented several steps: both exposed and outcome populations were derived from the IEU Open GWAS project, using single nucleotide polymorphisms (SNPs) as instrumental variables to minimize confounding. We identified independent SNPs associated with hand grip strength and cognitive function at a significant level, excluding weak instruments; genetic variants (i.e., SNPs) linked to hand grip strength and cognitive function at $P < 5\times10^{-8}$ (at least $P < 5\times10^{-6}$) were selected from a genome-wide association meta-analysis. Linkage disequilibrium across these SNPs was calculated using the 10000 Genomes linkage disequilibrium European panel ($r^2 > 0.001$) as the reference population.

Data sources for hand grip strength

The participants of the GWAS were of European descent. For the exposures, the summary statistics data on hand grip strength were retrieved from the United Kingdom Biobank (UKB), including 461,026 with 9,851,867 SNPs (left-hand grip strength, ukb-b-7478) and 461,089 with 9,851,867 SNPs (right hand grip strength, ukb-b-10215) white British individuals (**Table 1**). In addition, low hand grip strength (ebi-a-GCST90007529) from GWAS Catalog with 256,523 cases with 9,354,214 SNPs was included for validation (Supplementary Table 1).

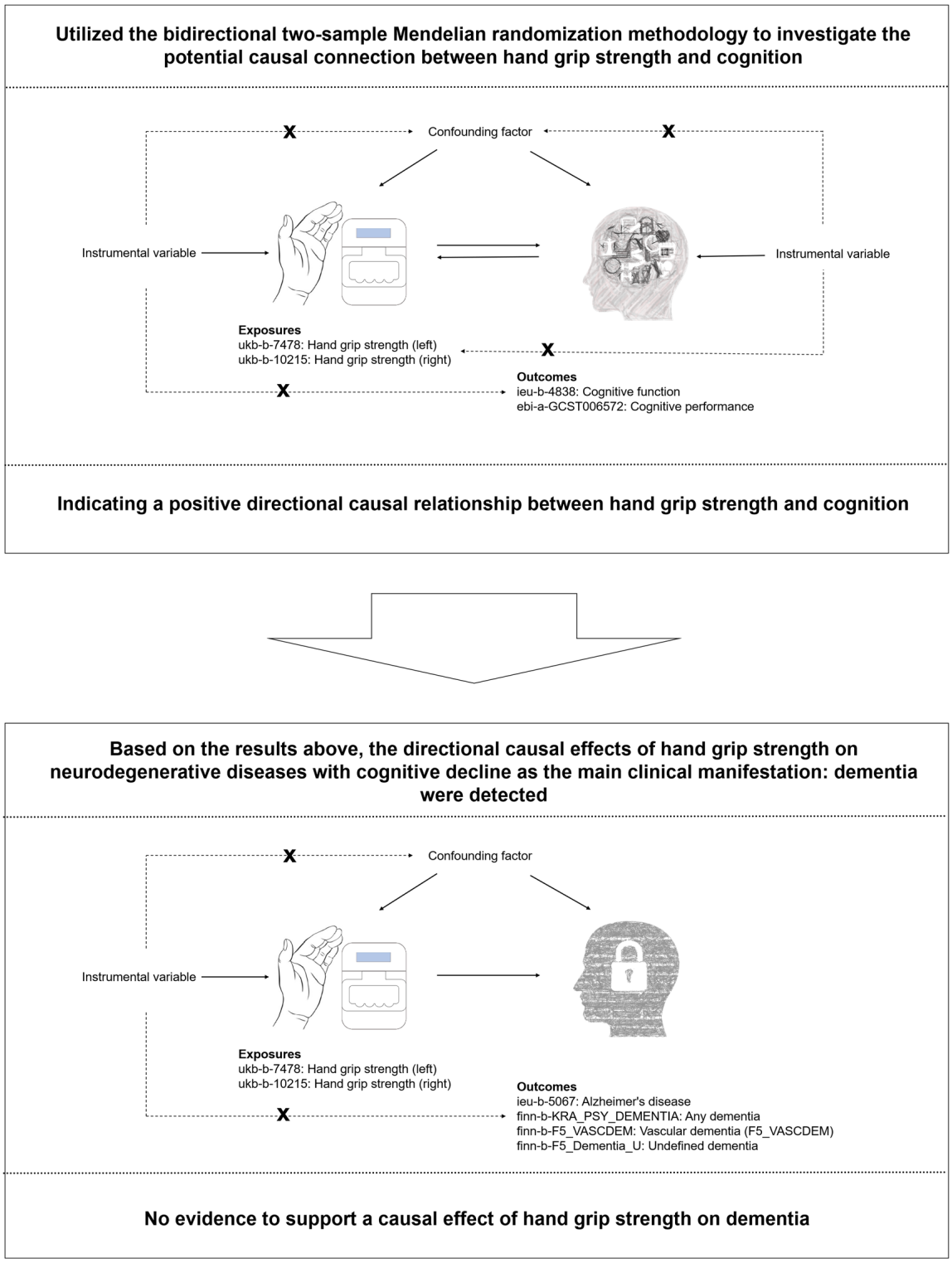


Figure 1. The study design of a two-sample Mendelian randomization analysis for hand grip strength with cognition and dementia: used the bidirectional two-sample Mendelian randomization methodology to investigate a potential causal connection between hand grip strength and cognition indicating a positive directional causal relationship between hand grip strength and cognition. Then, based on the results above, the directional causal effects of hand grip strength on neurodegenerative diseases with dementia as the main clinical manifestation were detected, showing no evidence to support a causal effect of hand grip strength on dementia.

Table 1. Details of the data sources of exposures/outcomes

Exposures/Outcomes	GWAS ID	Year	Consortium	Number of samples	Amount of SNPs	Population
Hand grip strength (left)	ukb-b-7478	2018	MRC-IEU	461,026	9,851,867	European
Hand grip strength (right)	ukb-b-10215	2018	MRC-IEU	461,089	9,851,867	European
Cognitive function	ieu-b-4838	2022	Within family GWAS consortium	22,593	6,719,661	European
Cognitive performance	ebi-a-GCST006572	2018	GWAS Catalog	257,841	10,066,414	European
Any dementia	finn-b-KRA_PSY_DEMENTIA	2021	FinnGen	218,792	16,380,466	European
Undefined dementia	finn-b-F5_Dementia_U	2021	FinnGen	215511	16,380,464	European
Alzheimer's disease	ieu-b-5067	2022	Within family GWAS consortium	488,285	12,321,875	European
Vascular dementia	finn-b-F5_VASCDEM	2021	FinnGen	212389	16,380,457	European

Table 2. Bidirectional causal association between hand grip strength and cognition estimated by Mendelian randomization

Exposure/Outcome	nSNP	IVW		MR Egger		Weighted mode		Heterogeneity *p*		Pleiotropy
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	IVW	MR Egger	*P*
Hand grip strength (left)/Cognitive function	126	1.23 (1.02-1.48)	0.026	0.91 (0.44-1.87)	0.796	1.22 (0.72-2.07)	0.454	0.004	0.004	0.398
Hand grip strength (right)/Cognitive function	136	1.23 (1.02-1.48)	0.031	0.99 (0.49-1.99)	0.980	1.22 (0.71-2.10)	0.469	< 0.001	< 0.001	0.534
Hand grip strength (left)/Cognitive performance	152	1.16 (1.04-1.30)	0.009	1.89 (1.24-2.90)	0.004	1.03 (0.82-1.29)	0.823	< 0.001	< 0.001	0.021
Hand grip strength (right)/Cognitive performance	153	1.10 (1.02-1.19)	0.018	1.22 (0.90-1.66)	0.206	1.06 (0.84-1.33)	0.642	< 0.001	< 0.001	0.502
Cognitive function/Hand grip strength (left)	9	1.01 (0.98-1.04)	0.648	1.01 (0.91-1.11)	0.921	0.98 (0.93-1.02)	0.362	0.004	0.002	0.963
Cognitive function/Hand grip strength (right)	9	1.01 (0.98-1.03)	0.503	1.01 (0.94-1.10)	0.747	1.00 (0.95-1.06)	0.872	0.083	0.053	0.903
Cognitive performance/Hand grip strength (left)	139	1.03 (0.99-1.06)	0.128	1.12 (0.97-1.29)	0.122	0.99 (0.94-1.04)	0.612	< 0.001	< 0.001	0.218
Cognitive performance/Hand grip strength (right)	132	1.02 (0.99-1.05)	0.253	0.96 (0.84-1.09)	0.494	1.04 (0.99-1.09)	0.169	< 0.001	< 0.001	0.341

Data sources of cognition and dementia

For the outcomes, the summary statistics data on cognitive function and performance were retrieved as cognition tests results from the IEU Open GWAS project including 22,593 with 6,719,661 SNPs (ieu-b-4838) and 257,841 with 10,066,414 SNPs (ebi-a-GCST006572) European individuals. The study analyzed cognitive function data from the Cognitive Genomics Consortium (COGENT), involving participants who underwent neurocognitive assessments across eight sessions, covering at least three cognitive domains. Principal component analysis was performed on test scores, with the first unrotated component used to assess cognitive performance. Additionally, UK Biobank participants completed a 2-minute, 13-item language-based numerical reasoning test to evaluate cognitive ability [19, 20]. The datasets for dementia were obtained from the GWAS and FinnGen biobank, including 218,792 any dementia participants with 16,380,466 SNPs (finn-b-KRA_PSY_DEMENTIA), 215,511 undefined dementia participants with 16,380,464 SNPs (finn-b-F5_Dementia_U), 488,285 Alzheimer's disease participants with 12,321,875 SNPs (ieu-b-5067), 212,389 vascular dementia participants with 16,380,457 SNPs (finn-b-F5_VASCDEM) (**Table 1**).

Statistical methods

An inverse variance weighted (IVW) meta-analysis was conducted to estimate the initial causal relationship between exposure and outcome by analyzing each Wald ratio. However, the IVW method can be biased in estimating causality if evidence of horizontal pleiotropy is present, and its robustness depends on the pleiotropy of IVs. The MR-Egger regression, assuming the InSIDE (Instrument Strength Independent of Direct Effect) condition, offers consistent estimations even if not all SNPs are valid IVs, but its accuracy is lower than weighted mode methods and may be influenced by outlying genetic variants. Additionally, MR-Egger regression intercepts were utilized to assess directional pleiotropy, and a 'leave-one-out' sensitivity analysis was performed to evaluate whether causal effects were driven by a single potentially significant SNP. Statistical significance for the association between exposure and outcome was set at $P < 0.05$. All MR and sensitivity analyses were performed using the 'TwoSampleMR' package (version 0.6.8) and 'MRPRESSO' package (version 1.0) within the R statistical computing environment (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Causal association between hand grip strength and cognition

The study used a bidirectional two-sample Mendelian randomization methodology to investigate the potential causal connection between hand grip strength and cognition. Distinct genetic SNPs were discovered for various forms of hand grip strength and cognition, enabling a more comprehensive analysis. The scholars observed horizontal pleiotropy (except for left-hand grip strength on cognitive performance $P = 0.021$, other $P > 0.05$), implying that the genetic variations almost exerted no additional influences on each other through alternative pathways, but with heterogeneity (all $P < 0.05$). Moreover, the IVW analysis indicated a directional positive causal effects of hand grip strength on cognitive function (Left-hand grip strength with 126 SNPs on cognition function: OR (95% CI): 1.23 (1.02-1.48), $P = 0.026$; Right-hand grip strength with 136 SNPs on cognitive function: OR (95% CI): 1.23 (1.02-1.48), $P = 0.031$). However, there were no directional causal effects of cognition function on hand grip strength according to IVW analysis (Cognitive function with 9 SNPs on left-hand grip strength: OR (95% CI): 1.01 (0.98-1.04), $P = 0.648$; Cognitive function with 9 SNPs on right-hand grip strength: OR (95% CI): 1.01 (0.98-1.03), $P = 0.503$).

Still, further examinations specifically concentrated on the bidirectional association between hand grip strength and cognitive performance, also consistently revealed positive causal effects of left- or right-hand grip strength on cognitive performance according to IVW analysis and other statistical approaches (Left-hand grip strength with 152 SNPs on cognition performance: IVW, OR (95% CI): 1.16 (1.04-1.30), $P = 0.009$; MR Egger, OR (95% CI): 1.89 (1.24-2.90), $P = 0.004$; Right-hand grip strength with 153 SNPs on cognition performance: IVW, OR (95% CI): 1.10 (1.02-1.19), $P = 0.018$), with almost no reverse causality between cognitive performance and hand grip strength (Cognitive performance with 139 SNPs on left-hand grip strength: IVW, OR (95% CI): 1.03 (0.99-1.06), $P = 0.128$); (Cognitive performance with 132 SNPs on right-hand grip strength: IVW, OR (95% CI): 1.04 (0.99-1.05), $P = 0.253$) (**Table 2**).

Later investigations focusing on the bidirectional relationship between low hand grip strength and cognition for validation have consistently demonstrated a directional negative causal effect of low hand grip strength on cognitive performance, as evidenced by IVW and MR Egger analysis (45 SNPs as instrumental variables, IVW, OR (95% CI): 0.95 (0.93-0.98), P < 0.001; MR Egger, OR (95% CI): 0.93 (0.86-0.99), P = 0.041), as detailed in Supplementary Table 2.

Furthermore, the leave-one-out analysis demonstrated that the overall outcomes were not influenced by any individual genetic variation in these all examinations (**Figure 2** and Supplementary Figure 1).

Directional causal effects of hand grip strength on dementia

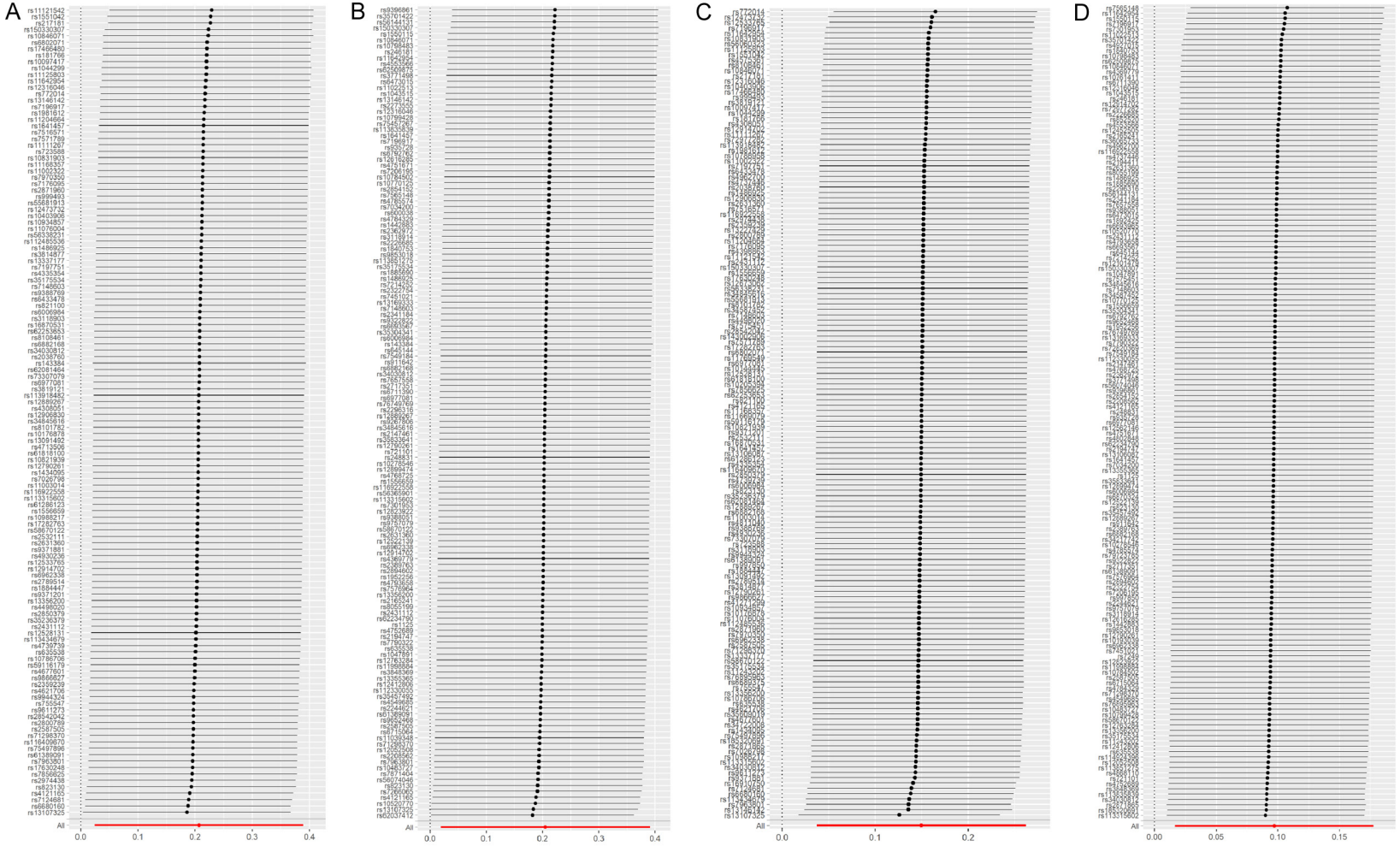
Based on the results above, we tried to research the directional causal effects of hand grip strength on neurodegenerative diseases with cognitive decline as the main clinical manifestation (like dementia). The two-sample MR results between hand grip strength and dementia including any dementia, undefined dementia, vascular dementia, vascular dementia from GWAS data were shown in **Table 3**. We selected 143, 143, 146 and 143 SNPs, or 162, 162, 163 and 162 SNPs as instrumental variables for the causal analyses between left- or right-hand grip strength and any dementia, undefined dementia, vascular dementia, vascular dementia respectively. However, the IVW methods yielded no evidence to support a causal effect of left-hand grip strength on overall dementia (P > 0.05). No evidence of a causal relationship was apparent using the weighted mode and MR-Egger methods. Except the intercepts of the IVM and MR-Egger tests between hand grip strength (left) and undefined dementia were 0.025 and 0.022 respectively and the MR-Egger testing heterogeneity with a 0.047 of *P* value between hand grip strength (right) and vascular dementia. Also, all *P* values for pleiotropy were over 0.05 respectively, suggesting that there was no directional pleiotropy among the SNPs we used.

Moreover, the leave-one-out analysis demonstrated that the overall outcomes were not influenced by any individual genetic variation in these all examinations (**Figure 3**).

Discussion

Hand grip strength, a well-established and reliable biomarker of overall muscular strength, has been extensively used as a key assessment parameter in large-scale epidemiological studies for evaluating musculoskeletal health status and functional capacity [21, 22]. Therefore, understanding the hand grip strength-cognition relationship is crucial in age-related conditions studies. Our investigation utilized GWAS data and MR analysis to explore causal links between left/right hand grip strength and cognition/dementia risk, revealing the probable differences in the postulated direction of association. The results demonstrated a significant positive causal association between hand grip strength (both right and left) and cognition. However, no significant causal relationship was observed between hand grip strength and dementia risk. These findings suggest that hand grip strength measurements may serve as valuable predictive biomarkers for assessing the risk of age-related cognitive decline, while their use in dementia risk prediction appears limited.

Weaker grip strength closely correlates with overall cognition and cognitive impairment, sharing common risk factors and exerting mutual causal effects [23]. The decline in muscle function linked to sarcopenia and reduced aerobic capacity in the elderly [24], directly affects social interactions, daily tasks, cognitive performance, life expectancy and mobility [25]. Fitness training notably influences cognitive processes, particularly executive control [26]. The concurrent decline in cognitive function and muscle strength in the elderly increases the risk of personal injury, poor mobility, and loss of independence [27]. One study in rural Tanzania independently associated factors such as no formal education, low grip strength, female gender, and depression with cognitive decline [28]. Additionally, a Korean Longitudinal Study including 6,435 middle and older adults (33,554 person) showed that low hand grip strength was associated with an increased risk of new-onset cognitive dysfunction over a 6-year follow-up period [29]. Another study including a total of 544 older women aged over 65 years without cognitive impairment from the Korean Longitudinal Study of Aging found that strong handgrip strength was associated with a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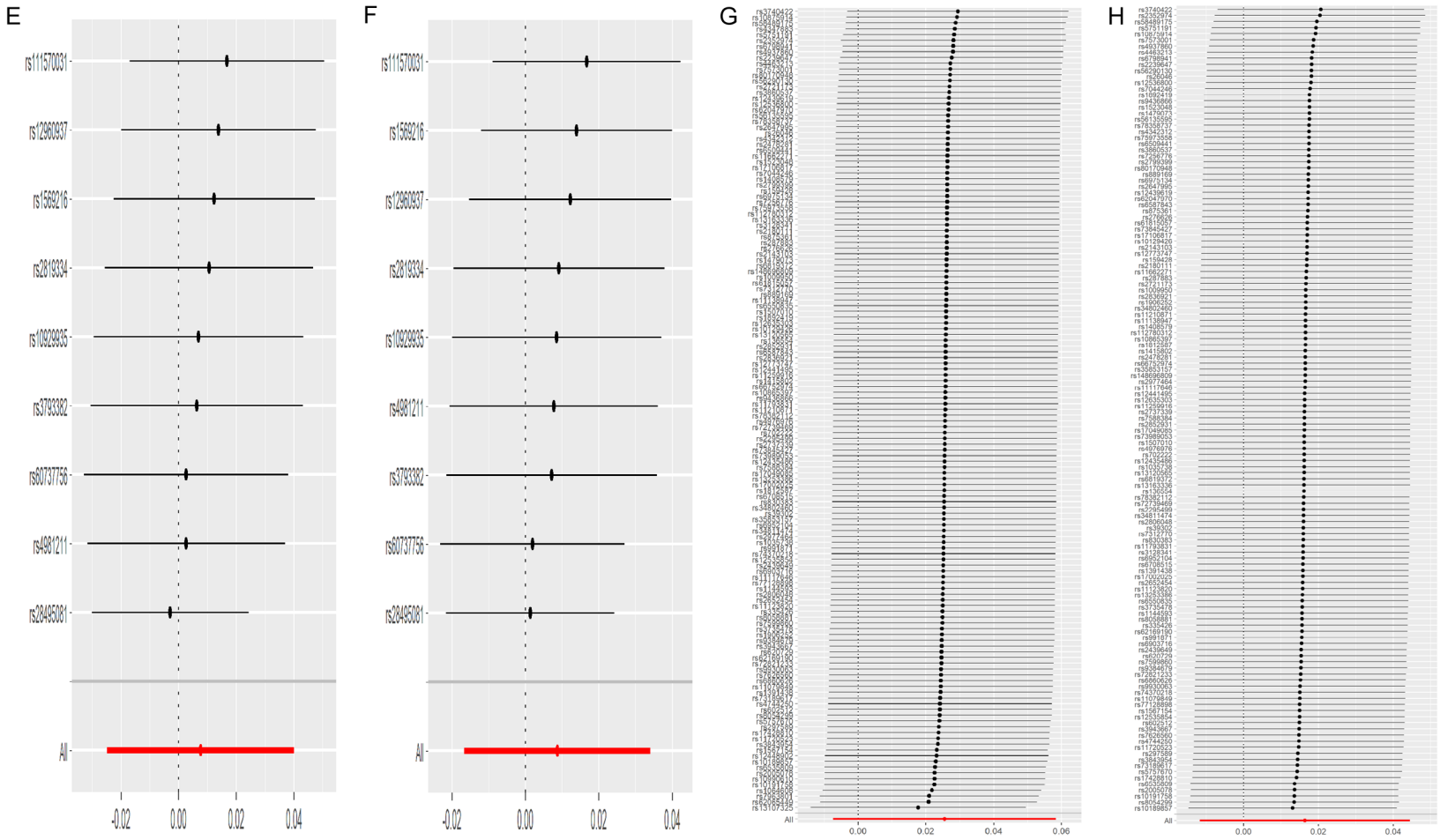

Figure 2. Leave-one-out analysis for bidirectional causal association between hand grip strength and cognition. A. Hand grip strength (left) on cognitive function; B. Hand grip strength (right) on cognitive function; C. Hand grip strength (left) on cognitive performance; D. Hand grip strength (right) on cognitive performance; E. Cognitive function on hand grip strength (left); F. Cognitive function on hand grip strength (right); G. Cognitive performance on hand grip strength (left); H. Cognitive performance on hand grip strength (right).

Table 3. Directional causal association between hand grip strength and dementia estimated by Mendelian randomization

Exposure/Outcome	nSNP	IVW		MR Egger		Weighted mode		Heterogeneity *P*		Pleiotropy *P*
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	IVW	MR Egger	
Hand grip strength (left)/Any dementia	143	0.79 (0.56-1.12)	0.185	0.45 (0.12-1.65)	0.230	0.72 (0.18-2.81)	0.633	0.627	0.623	0.375
Hand grip strength (left)/Undefined dementia	143	0.65 (0.32-1.28)	0.211	0.40 (0.03-5.45)	0.492	0.36 (0.02-6.14)	0.479	0.025	0.022	0.710
Hand grip strength (left)/Alzheimer's disease	146	1.00 (1.00-1.01)	0.236	1.00 (1.00-1.00)	0.068	1.00 (1.00-1.01)	0.424	0.436	0.426	0.462
Hand grip strength (left)/Vascular dementia	143	0.46 (0.21-1.04)	0.063	0.56 (0.03-12.47)	0.718	5.23 (0.28-98.69)	0.272	0.489	0.466	0.897
Hand grip strength (right)/Any dementia	162	0.93 (0.66-1.32)	0.703	0.52 (0.14-1.90)	0.323	1.38 (0.36-5.36)	0.639	0.069	0.069	0.357
Hand grip strength (right)/Undefined dementia	158	0.74 (0.38-1.41)	0.357	0.43 (0.04-4.80)	0.496	0.76 (0.07-8.54)	0.827	0.018	0.016	0.653
Hand grip strength (right)/Alzheimer's disease	163	1.00 (1.00-1.00)	0.457	1.00 (1.00-1.01)	0.101	1.00 (1.00-1.01)	0.506	0.524	0.552	0.136
Hand grip strength (right)/Vascular dementia	162	0.55 (0.24-1.26)	0.155	0.27 (0.01-6.10)	0.414	4.16 (0.25-68.22)	0.319	0.051	0.047	0.649

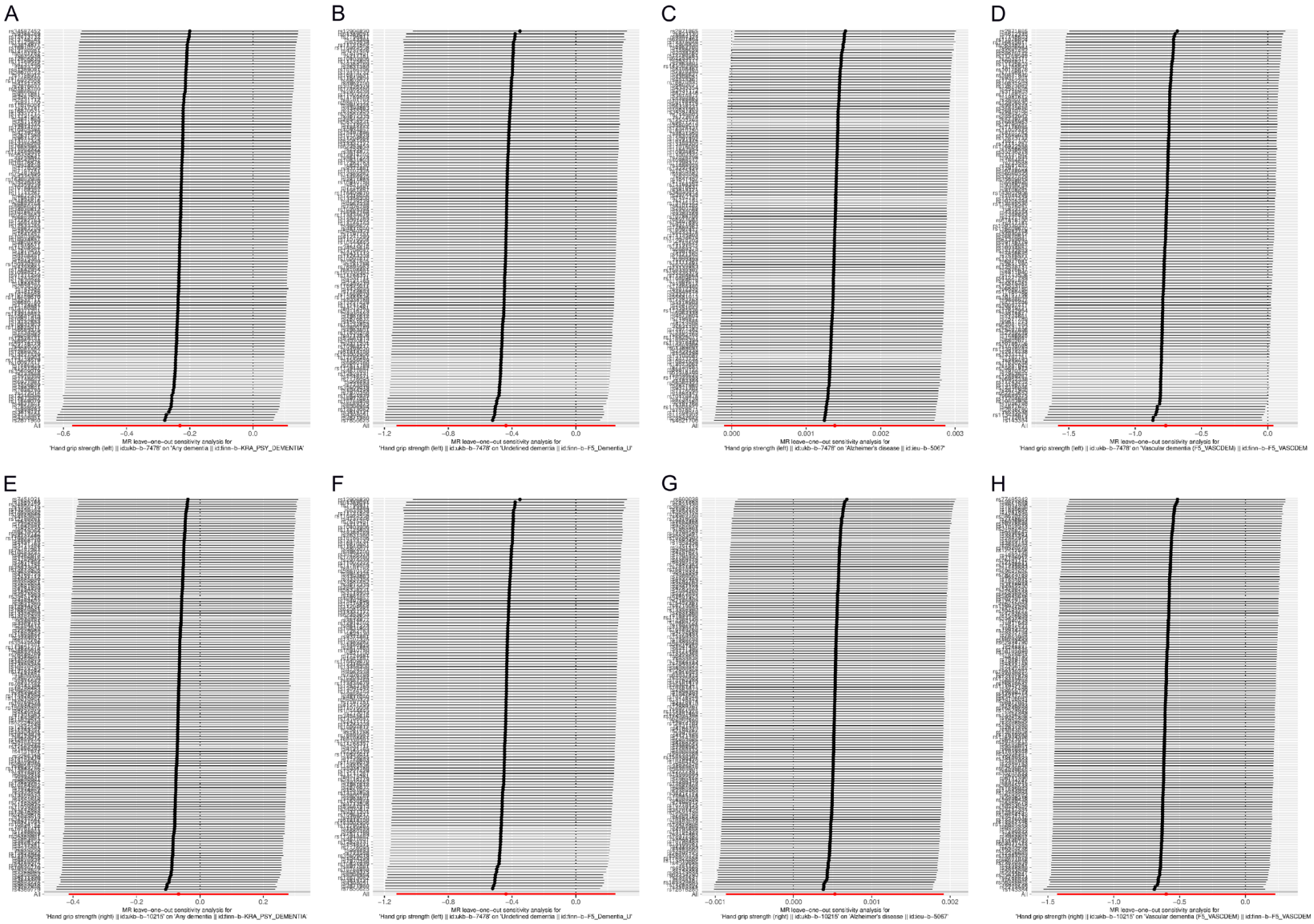

Figure 3. Leave-one-out analysis for the effects of hand grip strength on dementia. A. Hand grip strength (left) on Any dementia; B. Hand grip strength (left) on Undefined dementia; C. Hand grip strength (left) on Alzheimer's disease; D. Hand grip strength (left) on Vascular dementia; E. Hand grip strength (right) on Any dementia; F. Hand grip strength (right) on Undefined dementia; G. Hand grip strength (right) on Alzheimer's disease; H. Hand grip strength (right) on Vascular dementia.

decreased risk of cognitive impairment among obese women [30]. Moreover, a large genome-wide association study was done to discover genetic variation associated with muscular strength, and to evaluate shared genetic etiology with and causal effects of muscular strength on cognition. The results showed shared genetic etiology between grip strength and cognitive health [31]. Causal relationships between low hand grip strength and cognitive performance were further inferred via a two-sample MR analysis approach, which demonstrated that a higher hand grip strength was positively associated with better cognitive performance, and reverse MR assessments did not yield similar findings [32]. Consistent with the conclusion above, our results also suggested that there was indeed a positive directional causal relationship between hand grip strength and cognition, and this MR study has not only explored the causal relationship between both left- and right-hand grip strength and cognitive performance/function, but also it confirmed the generalizability of the conclusions using external validation.

A meta-analysis revealed that lower grip strength was associated with a higher onset of cognitive decline and various subtypes of dementia, encompassing both Alzheimer's Disease and non-Alzheimer's Disease [33]. A prior study confirmed that handgrip strength was independently associated with a lower hazard for both incident dementia and mild cognitive impairment [34]. Grip strength is prognostic for aging-related health outcomes, including a reduced risk of dementia and Alzheimer's Disease [35]. However, one study found that lower hand grip strength beyond age 79 was not a risk factor for subsequent dementia, which was not explained by those with poorer physical fitness having died before the onset of dementia symptoms [36]. Moreover, while lower mobility-related physical performance was associated with dementia risk, grip strength itself was not significantly linked to dementia risk [37]. In this study, we employed MR analysis as a robust methodologic approach to investigate the potential genetic causal relationship between hand grip strength and dementia risk. MR serves as a crucial analytical framework that bridges the gap between traditional observational studies and interventional trials, offering unique insights into causal inference. Notably, our MR analysis did not establish a significant causal association between hand grip strength and dementia risk, suggesting that while hand grip strength may serve as a valuable biomarker for cognitive status, its specific use in dementia risk prediction is questionable.

Although the mechanism remains unclear, the multiple possible pathways included myokine signaling, neurotrophic factor regulation, and systemic inflammatory modulation to explain the association between hand grip strength and cognition. First, loss of skeletal muscle as the core metabolic tissue can significantly promote insulin resistance [38], which influences brain aging via the insulin-IGF-1 pathway [39]. Emerging neuroimaging evidence positions cerebral cortex morphology as a predictive biomarker for cognitive impairment [40], then complementary MR analysis further substantiates that hand grip strength exerts modulatory effects on brain cortical architecture [41]. The pathophysiologic cascade may involve myokine dysregulation, since diminished skeletal muscle mass and functional capacity correlated with attenuated myokine secretion [42]. Of particular interest is brain-derived neurotrophic factor (BDNF), an exercise-responsive neurotrophin that undergoes marked elevation during muscular contraction [43]. This pleiotropic molecule demonstrates unique permeability across the blood-brain barrier, where it orchestrates synaptic plasticity, hippocampal neurogenesis, and memory consolidation, mechanistically linking neuromuscular activity to cognitive enhancement [44, 45]. Expanding this paradigm, recent work identifies irisin-a PGC-1α-dependent myokine-as a potent inducer of BDNF transcription in hippocampal neurons, thereby establishing a molecular bridge between peripheral muscle function and central nervous system adaptability [46]. In addition, oxidative stress and inflammation are directly related to cognitive decline [47], and emerging evidence indicates that skeletal muscle secretes cytokines and peptides including IL-6, IL-8, and IL-15, which are involved in inflammatory processes and loss of muscle strength [48].

MR analysis study has several strengths: First, MR may mitigate confounding factors and reverse causal effects inherent in observational

studies. Second, positioned between interventional trials and observational studies, MR provides insight into public health interventions when RCTs may not be feasible. Third, the large sample size and robustly associated SNPs confer sufficient power to detect causal effects. The other major strength was the bidirectional design, establishing a directional causal association of hand grip strength and cognition. The study employed MR analyses and multiple indicators of hand grip strength, cognition, and dementia, enabling a comprehensive exploration of the hand grip strength-cognition/dementia relationship. Using three different MR methods within the bidirectional framework, each with distinct strengths and assumptions, enhanced the causal interpretation of findings. The general agreement across these analytical approaches, particularly for the muscle strength-cognition relationship, strengthened the study's causal interpretation.

However, the present study had certain limitations. First, the study population comprises individuals of European descent, which may limit the generalizability of MR findings to other ethnicities due to the dependence of MR on ethnicity. Second, although evidence of horizontal pleiotropy was identified in one analysis, the use of MR-Egger regression, while advantageous for detecting and addressing bias from unbalanced pleiotropy, introduces constraints and reduces estimation accuracy. It remains impossible to unequivocally validate all three MR assumptions. Nevertheless, acknowledging these limitations, we opted for MR-Egger regression in the standard MR analysis due to its unique advantages. Third, the bidirectional causal results between hand grip strength and cognition exhibited high heterogeneity, possibly influenced by the selection of different genetic data. In particular, exercise that increases grip strength might also be important in affecting cognitive function, so MR studies on the effect of exercise on cognition are an urgent need.

In conclusion, our MR study indicates a positive bidirectional causal relationship between hand grip strength and cognition, with no observed causal link to dementia. Interpretation of findings should consider study limitations and be supplemented by other cognitive outcomes and complementary methods for robustness. These results hold implications for the development of public health measures and strategies for preventing cognitive decline.

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Disclosure of conflict of interest

None.

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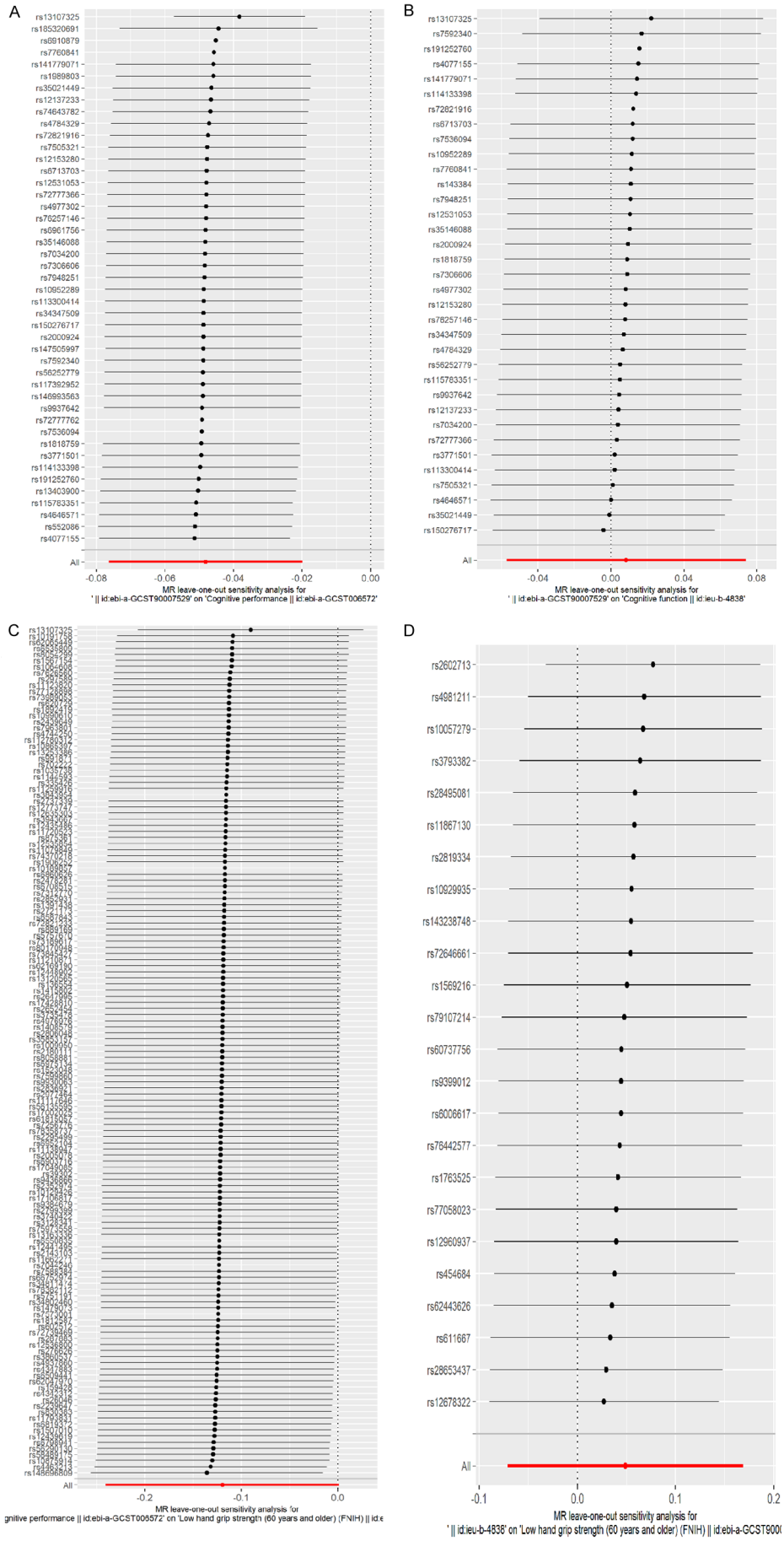
Supplementary Table 1. Details of the data sources of exposures/outcomes for validation

Exposure/Outcome	GWAS ID	Year	Consortium	Number of samples	Amount of SNPs	Population
Low hand grip strength (FNIH)	ebi-a-GCST90007529	2021	GWAS Catalog	256,523	9,354,214	European
Cognitive performance	ebi-a-GCST006572	2018	GWAS Catalog	257,841	10,066,414	European
Cognitive function	ieu-b-4838	2022	Within family GWAS consortium	22,593	6,719,661	European

Supplementary Table 2. Bidirectional causal association between low hand grip strength and cognition estimated by Mendelian randomization for validation

Exposure/Outcome	nSNP	IVW		MR Egger		Weighted mode		Heterogeneity *p*		Pleiotropy
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	IVW	MR Egger	*P*
Low hand grip strength/Cognitive performance	45	0.95 (0.93-0.98)	<0.001	0.93 (0.86-0.99)	0.041	0.98 (0.92-1.04)	0.467	<0.001	<0.001	0.404
Low hand grip strength/Cognitive function	35	1.01 (0.94-1.08)	0.804	1.05 (0.87-1.26)	0.610	0.97 (0.82-1.15)	0.754	0.221	0.195	0.651
Cognitive performance/Low hand grip strength	139	0.89 (0.79-1.00)	0.053	0.67 (0.39-1.13)	0.137	0.98 (0.66-1.45)	0.920	<0.001	<0.001	0.280
Cognitive function/Low hand grip strength	24	1.05 (0.93-1.18)	0.425	1.01 (0.72-1.43)	0.933	1.09 (0.82-1.44)	0.574	0.014	0.010	0.838

Causal associations of hand grip strength with cognition/dementia risk



Supplementary Figure 1. Leave-one-out analysis for bidirectional causal association between low hand grip strength and cognition. A. Low hand grip strength effect on cognitive performance; B. Low hand grip strength effect on cognitive function; C. Effect of cognitive performance on low hand grip strength; D. Effect of cognitive function on low hand grip strength.