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Dissecting the causal relationship between moderate to vigorous physical activity levels and cognitive performance: a bidirectional two-sample Mendelian randomization study

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Introduction: Recent studies increasingly suggest that moderate-to-vigorous physical activity (MVPA) impacts cognitive risk. However, the bidirectional nature of this relationship warrants further exploration. To address this, we employed a Mendelian randomization (MR) approach, analyzing two distinct samples.

Methods: These analyses utilized published genome-wide association study (GWAS) summary statistics for MVPA ($n = 377,234$) and cognitive performance ($n = 257,841$). Our primary method was the inverse variance weighted (IVW) model with random effects, aiming to deduce potential causal links. Additionally, we employed supplementary methods, including MR Egger regression, Weighted median, Weighted mode, and Simple mode. For sensitivity analysis, tools like the MR Egger test, Cochran's Q, MR PRESSO, and leave-one-out (LOO) were utilized.

Results: Our findings indicate a decrease in cognitive risk with increased MVPA (Odds Ratio [OR] = 0.577, 95% Confidence Interval [CI]: 0.460–0.723, $p = 1.930 \times 10^{-6}$). Furthermore, enhanced cognitive levels corresponded to a reduced risk of inadequate MVPA (OR = 0.866, 95% CI: 0.839–0.895, $p = 1.200 \times 10^{-18}$).

Discussion: In summary, our study demonstrates that MVPA lowers cognitive risk, while poor cognitive health may impede participation in MVPA. Overall, these findings provide valuable insights for developing personalized prevention and intervention strategies in health and sports sciences.

KEYWORDS

moderate to vigorous physical activity levels, cognitive performance, Mendelian randomization, health science, causal relationship

1 Introduction

Cognitive abilities encompass fluid ability (Gf) and crystallized ability (Gc). Gf includes skills like psychomotor speed, memory, and abstract reasoning, while Gc covers literacy, arithmetic, and professional knowledge and skills (Lövdén et al., 2020). These abilities are crucial predictors of educational and occupational success, socio-economic status, health, and longevity (Danesin et al., 2022). Cognitive decline can impair work capacity, social interactions, and daily living activities (Green, 1996). This is particularly concerning when cognitive deficits progress to clinically diagnosed dementia, such as Alzheimer's disease or vascular dementia. Influential factors include age (Crivelli et al., 2022), educational level, socio-economic status (Ma et al., 2015), and physical fitness (Ritchie et al., 2016). The cognitive simulation hypothesis posits that physically demanding activities that also require significant cognitive engagement can notably enhance cognitive functions, including problem-solving, memory, and executive functions (Jackson et al., 2016).

Moderate-to-vigorous physical activity (MVPA) is defined as any exercise that yields ≥ 3.0 metabolic equivalents (METs). Regular participation in physical activity beneficially influences physical health, life quality, cognition, and mental health (Biddle et al., 2019). The World Health Organization's recommendation on physical activity for health is to engage in at least 150 min of moderate-intensity or 75 min of high-intensity physical activity every week, or any equivalent combination of the two (WHO, 2010). Lack of physical activity (i.e., not engaging in ≥ 150 min/week of moderate to vigorous physical activity) is significantly associated with cognitive impairment (Falck et al., 2020). High-intensity and frequent physical activity may be the most effective exercise type for improving mild cognitive impairment and overall cognitive ability in adults (Lista and Sorrentino, 2010).

Currently, the results of epidemiological studies indicate that physical activity can enhance cognitive function in both young and older individuals (Lista and Sorrentino, 2010), attention processes (Kramer et al., 1999), and executive function (Chieffi et al., 2017). Furthermore, physical activity can prevent age-related cognitive decline (Niemann et al., 2014), reduce the risk of dementia (Colberg et al., 2008), and mitigate the extent of executive function deterioration (Hollamby et al., 2017). However, subsequent studies, such as those examining high-intensity interval training (HIIT) style vigorous physical activity (VPA), found no significant improvements in cognitive functions like executive function (EF), relational memory, and processing speed (Wassenaar et al., 2021). Even in studies focusing solely on VPA, no discernible benefits were observed (Haverkamp et al., 2020). This raises questions about the existence of a causal link between PA and cognitive performance. Additionally, in patients with cognitive impairments, such as those with schizophrenia, a common feature is an unhealthy lifestyle characterized by inadequate physical activity (Wichniak et al., 2011) and poor physical health (Mitchell and Malone, 2006). Thus, the potential bidirectional causal relationship between cognitive performance and physical activity remains unclear. Traditional observational research is limited by inherent flaws, including the inability to fully rule out reverse causality and confounding factors

(Sekula et al., 2016). MR, in contrast, offers a robust approach to addressing these issues.

MR is an epidemiological technique that employs single nucleotide polymorphisms (SNPs) associated with an exposure (e.g., MVPA) as instrumental variables (IVs) to deduce potential causal relationships between the exposure and outcomes (Davey Smith and Hemani, 2014). Due to the principle of random assortment and combination in allele distribution, theoretically, the causal effect should be free from confounding factors and reverse causation (Davies et al., 2018). IVs can be derived from the published summary statistics of genome-wide association studies (GWAS), commonly used in two-sample MR studies (Porcu et al., 2019). This study aims to explore the bidirectional causal effects between MVPA and cognitive performance.

2 Materials and methods

2.1 Experimental design

Our MR analysis of the two samples utilized published genome-wide association study (GWAS) summary statistics and received ethical approval from the original study. The data sources for this study are detailed in [Supplementary Table 1](#). We selected major SNPs associated with moderate to vigorous physical activity (MVPA) and cognitive performance as genetic instrumental variables (IVs) to conduct bidirectional two-sample MR. To minimize racial mismatches, our analysis was confined to participants of European descent.

Our selection of qualified genetic instruments involved a thorough quality control process. Initially, we included SNPs closely related to exposure factors at a significance threshold of 10^{-8} . We then employed an $R^2 < 0.001$ and a window size of 10,000 kb for clustering. In cases where the target SNP was unavailable in the result dataset, a proxy SNP with an $R^2 > 0.8$ was used as a substitute. Furthermore, the minor allele frequency of the SNP in the GWAS findings was set at a default value of 0.3. Finally, we aligned exposure and outcome data to exclude palindromic SNPs and ensure that the effective allele was consistent across both datasets (Hartwig et al., 2016). The statistical power of the SNP is calculated using an online tool, and the website is <https://shiny.cnsgenomics.com/mRnd/> (Brion et al., 2013). Therefore, our research design is outlined as follows: (1) Identification of exposure-related SNPs under a genome-wide significance threshold; (2) Independence of the SNP from potential confounding factors; (3) Influence of the SNP on the outcome exclusively through exposure.

2.2 Data sources

For MVPA, we used publicly available GWAS data (Guthold et al., 2018) from a cohort of 377,234 participants. Using genetic variables related to MVPA as tools, 19 SNPs were identified as significantly associated with MVPA ($P < 5 \times 10^{-8}$) and met the IV criteria ([Supplementary Table 2](#)). In our study, F statistic > 29.984 for each SNP ([Supplementary Table 3](#)).

The cognitive performance data was sourced from a GWAS (Lee et al., 2018) involving 257,841 participants. Here, 147 SNPs were identified as significantly related to cognitive performance ($P < 5 \times 10^{-8}$), with 139 of these SNPs meeting the IV criteria (Supplementary Table 4). And F statistic > 29.793 for each SNP (Supplementary Table 5).

2.3 Statistical analysis

In this study, all analyses were conducted using the TwoSampleMR package (version 0.5.8) and MR-PRESSO (version 1.0) in R software (version 4.3.2). The original data and code files are stored in the Open Science Framework.¹ Our primary method for MR was the IVW regression. This approach is widely used for the main analyses in various studies. The IVW model synthesizes the Wald ratios of each single nucleotide polymorphism (SNP) to yield a combined causal estimate (Chen et al., 2022). The IVW model's results are presented as odds ratios (ORs) with corresponding 95% Confidence Intervals (CIs). Additionally, we employed complementary methods, including MR Egger regression, the weighted median, the simple model, and the weighted model, to assess the causal impact of exposure on outcomes. The MR Egger approach relaxes the “no pleiotropy” assumption and allows for a non-zero intercept (Hemani et al., 2018a). The weighted median method considers the median effect of all available SNPs, assuming that at least half of the SNPs are valid instruments.

2.4 Sensitivity analysis

We performed a series of sensitivity analyses to evaluate the robustness and validity of our causal estimates. Cochran's Q statistic was used to assess the heterogeneity among individual effect estimates for each genetic variation. A non-significant Q value may indicate the absence of pleiotropy to some extent (Hemani et al., 2018b). The MR-PRESSO test detects pleiotropy and reassesses the association via IVW after excluding pleiotropic SNPs (Verbanck et al., 2018). The MR Egger intercept test evaluates the directional pleiotropy, a key consideration in IVW estimates (Bowden et al., 2015). Funnel plots were also employed to assess directional horizontal pleiotropy, with a symmetrical distribution suggesting the absence of directional pleiotropy. Lastly, the leave-one-out (LOO) method was used to determine if the aggregated estimates are disproportionately influenced by any single genetic variation (Liu et al., 2021).

2.5 Explanatory measures

Cognitive ability refers to the brain's capacity to process, store, and retrieve information. As a comprehensive cognitive measure, it encompasses both general and specific abilities in various domains, such as working memory, attention, visual and spatial processing,

information processing speed, and executive function (Zimmer et al., 2016). Cognitive performance represents the abilities and behavioral characteristics exhibited by individuals during cognitive processes, such as language, perception, and arithmetic tests. In this study, the measurement criteria for cognitive performance were the respondents' scores on a language cognition test, combined with scores from a cognitive test in the Wisconsin Longitudinal Study (WLS). Cognitive risk refers to the likelihood of an individual experiencing a decline, impairment, or disorder in cognitive ability and performance. MVPA level denotes moderate to high levels of VPA (75–300 min/week) or MPA (150–600 min/week) or any equivalent combination of the two (Lee et al., 2022).

3 Results

3.1 The causal effect of MVPA on cognitive performance

The MR analysis revealed that MVPA acts as a protective factor against cognitive risk (Figure 1). A logarithmic odds ratio (OR) increase in MVPA correlated with a 42.3% decrease in cognitive risk (IVW OR = 0.577, 95% CI: 0.460–0.723, $p = 1.930 \times 10^{-6}$) (Table 1 and Supplementary Figure 1), a statistically significant difference.

Cochran's Q statistics were employed to evaluate heterogeneity, which could be attributed to variations in experimental platforms. However, as our IVW model is a random-effects model, this heterogeneity does not compromise our results. The MR Egger test assessed directional pleiotropy ($p = 0.846$), finding no significant directional pleiotropy in all results. The funnel plot also indicated a low risk of directional pleiotropy in our IVW estimates (Supplementary Figure 2). The stability of the results was confirmed through single SNP exclusion analysis (Supplementary Figure 3).

3.2 Causality of cognitive performance on MVPA

Conversely, when cognitive genetic predisposition was considered as the exposure, MR analysis showed a decrease in MVPA deficiency risk with improved cognitive performance (Figure 2). This suggests a protective causal relationship between cognitive performance and MVPA (IVW OR = 0.866, 95% CI: 0.839–0.895, $p = 1.200 \times 10^{-18}$) (Table 2 and Supplementary Figure 4), which was statistically significant.

Cochran's Q statistics assessed heterogeneity. MR-PRESSO identified 8 pleiotropic SNPs out of 147, yet reanalysis after outlier removal did not materially alter results. All MR Egger intercept tests indicated no horizontal pleiotropy ($p > 0.05$, intercept close to zero). The funnel plot was approximately symmetrical on both sides, suggesting no evident bias (Supplementary Figure 5). Leave-one-out (LOO) analysis confirmed that no single SNP significantly altered the causal effect of MVPA on cognitive performance (Supplementary Figure 6).

¹ https://osf.io/bhp4c/?view_only=75466f8f48fe4d0494cedd31a18c0422

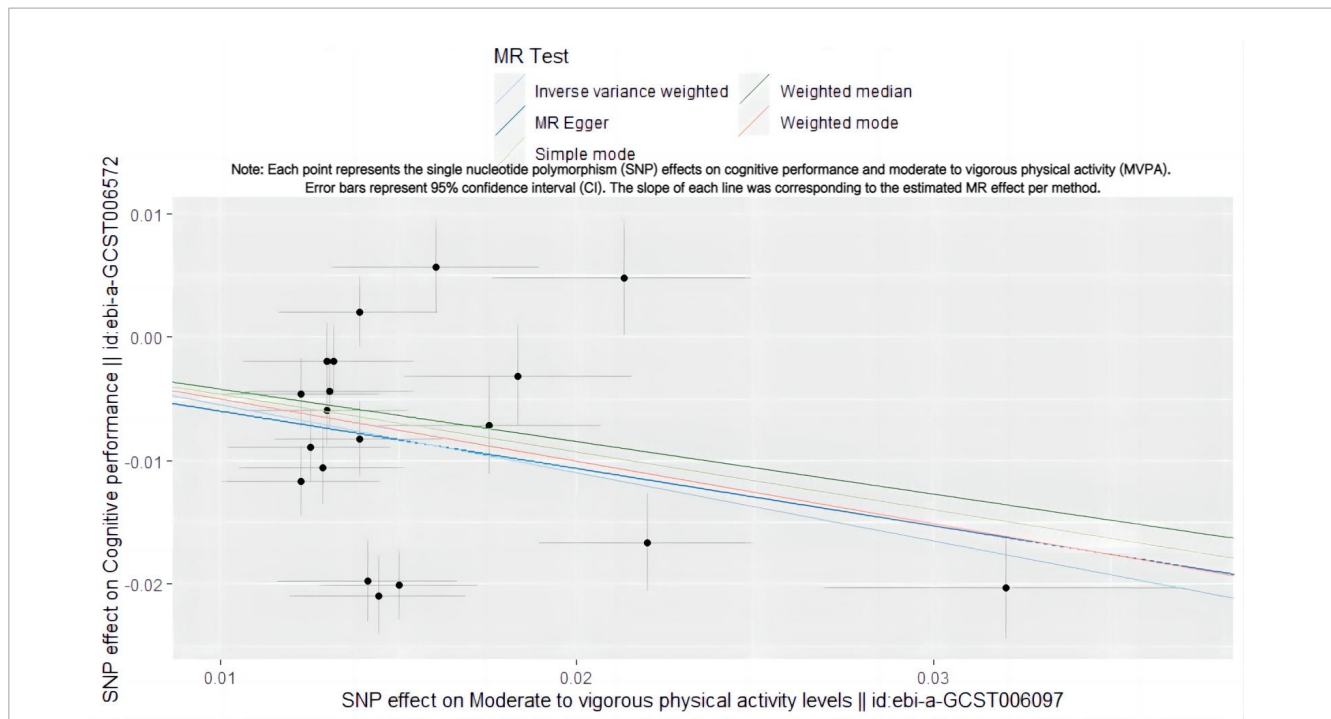


FIGURE 1 Scatter plot illustrating the SNP effect of MVPA on cognitive performance. Each point represents the single nucleotide polymorphism (SNP) effects on cognitive performance and moderate to vigorous physical activity (MVPA). Error bars represent 95% confidence interval (CI). The slope of each line was corresponding to the estimated MR effect per method.

TABLE 1 Mendelian randomization results of MVPA on cognitive performance.

Method	SNPs	Or	or_lci95	or_uci95	P	Q statistic P-value**	MR-Egger pleiotropy test P-value	F-statistical
MR Egger	19	0.629462971	0.254570637	1.556438858	0.330309809			
Weighted median	19	0.654153	0.549593616	0.778604655	1.78546E-06			
Inverse variance weighted	19	0.576571056	0.459614748	0.723288763	1.92969E-06	5.52985E-14	0.846433645	3811.44
Simple mode	19	0.627169785	0.434202836	0.90589445	0.022927511			
Weighted mode	19	0.604286764	0.437512315	0.834633633	0.006786851			

When Cochran's Q statistics $P \leq 0.05$, random-effect modal IVW MR analysis was used. IVW, inverse variance weighted method; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval. **Statistically significant.

4 Discussion

In our MR study, a significant potential causal relationship between MVPA and cognitive performance was identified. We observed that MVPA has a protective effect. Conversely, the MR results suggest a causal link between cognitive impairment and insufficient MVPA. The robustness of these results is supported by comprehensive sensitivity analyses and multiple validity evaluations.

Our research aligns with previous studies, affirming that adequate MVPA significantly reduces cognitive risk. This protective causal effect can be attributed to MVPA's association with enhanced cognitive functions, as supported by Savilla et al. (2008). One plausible explanation is that improved cognitive performance correlates with increased volume in critical brain regions like the

prefrontal cortex (involved in working memory), the temporal cortex (engaged in perception and semantic representation), and the medial orbitofrontal cortex (Cheng et al., 2021). Higher levels of MVPA are linked to increased cortical thickness in the left superior frontal gyrus and the right temporal pole. Thinning of the frontal and temporal cortices is associated with aging and dementia (Salat et al., 2004); hence, higher MVPA is crucial for maintaining the cortical thickness in areas vulnerable to cognitive decline (Cheng et al., 2021). Additionally, MVPA correlates with greater total gray matter volume, enhancing insulin sensitivity and cognitive function through exercise training. This suggests that substantial MVPA can protect brain health (Falck et al., 2020). Moreover, MVPA improves aerobic fitness and cardiovascular health, which in turn benefits higher-order cognitive functions like executive function. This improvement

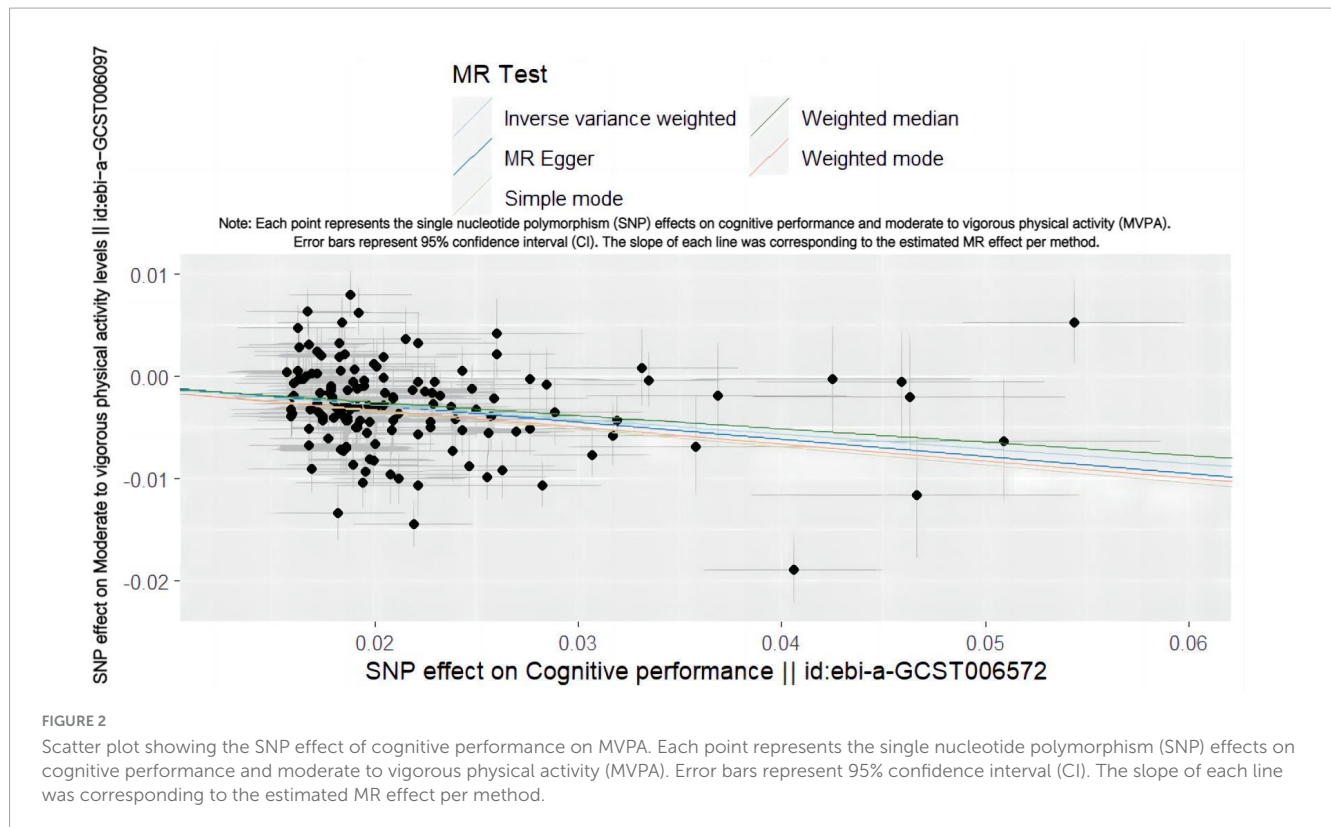


TABLE 2 Mendelian randomization results of cognitive performance on MVPA.

Method	SNPs	Or	or_lci95	or_uci95	P	Q statistic P-value**	MR-Egger pleiotropy test P-value	F-statistical
MR Egger	139	0.846149349	0.735624541	0.973280091	0.020769038			
Weighted median	139	0.878192805	0.851094832	0.906153548	4.56396E-16			
Inverse variance weighted	139	0.866448892	0.839266264	0.894511927	1.19983E-18	1.3276E-22	0.733644572	2605.45
Simple mode	139	0.839176399	0.751766257	0.936749984	0.002172954			
Weighted mode	139	0.846616721	0.768373235	0.932827745	0.000989994			

When Cochran’s Q statistics $P \leq 0.05$, random-effect modal IVW MR analysis was used. IVW, inverse variance weighted method; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval. **Statistically significant.

may be mediated by neurophysiological changes in prefrontal cortex oxygenation related to aerobic fitness levels (James et al., 2023). In aging populations, continual MVPA can mitigate brain aging changes and stimulate repair processes, thereby reducing cognitive decline risks (Köhncke et al., 2018; Dominguez et al., 2021). For individuals with lower cognitive abilities, MVPA improves cognitive performance, including executive function, language, working memory, and processing speed, as observed in schizophrenia patients (Kimhy et al., 2014). A potential mechanism is the upregulation of brain-derived neurotrophic factor (BDNF) during exercise, which preliminary evidence suggests may mediate cognitive improvements in schizophrenia (Firth et al., 2017). Additionally, MVPA is a beneficial intervention for Parkinson’s patients, potentially due to its role in inducing neuroprotection, preventing cell death, and regulating mitochondrial function and neuroinflammation by promoting autophagy and neuronal

regeneration (Liao et al., 2022). Through two-way MR, we discovered that individuals with lower cognitive levels may be less inclined to engage in MVPA. This observation aligns with existing research suggesting that reduced cognitive capacity can hinder participation in MVPA. For instance, patients with mental illnesses often show poor adherence to exercise interventions, tending toward lower levels of physical activity and reduced engagement in intense exercise, while sedentary behaviors significantly increase. This could be attributed to factors such as lack of motivation, cognitive decline, psycho-pathological symptoms, and medication side effects, which make achieving optimal physical activity levels challenging (Vila-Barrios et al., 2023). Additionally, early prodromal symptoms in Parkinson’s disease patients, including hypoesthesia, decreased perception, and sleep disorders, which may manifest up to 20 years before diagnosis, could diminish their inclination toward physical activity. This decrease in activity may

be linked to early dopamine loss, resulting in reduced participation in physical activities (Baumeister et al., 2021).

Furthermore, in this study, we can extend the discussion to the relationship between exercise reserve and cognition. Exercise reserve refers to an individual's abilities or resources in physical activity or exercise that help maintain or improve physical activity levels when needed, such as cardiorespiratory function, muscle strength, flexibility, and balance. Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure, while exercise is a subset of planned, structured, and repetitive physical activity with the ultimate or intermediate objective of improving or maintaining physical fitness (Caspersen et al., 1985). The role of exercise reserve includes improving physical health, enhancing cognitive function, delaying the aging process, and ultimately improving quality of life. Specifically, there is a close relationship between exercise reserve and physical activity. On one hand, physical activity is the primary means to enhance and maintain exercise reserve. For example, physical activities involving large muscle groups are associated with arm and lower limb activities, which can increase muscle strength, balance, and mobility (Weinstein et al., 2023). On the other hand, a good exercise reserve helps individuals reduce exercise fatigue and lower the risk of injury during physical activity. Exercise fatigue refers to the inability to maintain the required force during sustained muscle contraction (Holtzer et al., 2011). Consistent with this study, there is also a close relationship between exercise reserve and cognition. Firstly, research findings have shown that increasing total daily activity levels and exercise capacity can independently improve cognitive abilities and reduce dementia (Buchman et al., 2019). For instance, a recent report indicated that combining aerobic and resistance training improved overall cognition and subdomains such as attention, visuospatial function, and executive function (Marzolini et al., 2013). Physical activity can reduce the risk of cognitive impairment in independently living older adults, primarily vascular dementia (Verdelho et al., 2012). Conversely, high levels of cognitive function can enhance people's mastery and understanding of exercise, especially skilled motor performance and fine motor performance (e.g., handwriting and manual dexterity tasks) (Liou et al., 2020). In contrast, a lack of exercise and prolonged sedentary behavior may lead to cognitive decline and even increase the risk of chronic diseases. For example, individuals with autism often exhibit decreased levels of physical activity. Fewer opportunities for physical activity are more likely to affect their verbal communication, social adaptation, and behavioral difficulties (Pan and Frey, 2006) and lead to some chronic diseases, such as obesity, which is common in individuals with autism (Tyler et al., 2011).

From an individual perspective, we strongly advocate for all adults to engage in at least 150 min per week of MVPA to maintain brain health (Falck et al., 2017) and lessen the risk of age-related cognitive disorders. Cognition-enhancing MVPAs include activities such as running, jumping, rope skipping, active cycling, ice hockey, playing ball games, karate, table tennis, mixed martial arts, and team sports (Peiris et al., 2022). Healthy older adults can derive cognitive benefits from increasing their MVPA, even at moderate intensities (e.g., approximately 110 steps/minute). For individuals with cognitive disorders, physical activity interventions can aid in improving short-term memory, working memory, and processing speed (Chen et al., 2016). On

a national level, we recommend the implementation of effective policies to encourage non-motorized commuting, such as walking and cycling, by enhancing infrastructure and road safety. Creating more opportunities for sports activities in public open spaces, parks, workplaces, and local communities can motivate residents to participate in active recreation and sports activities in their free time.

5 Advantages and limitations

This study extracts genetic instruments from the largest and most recent GWAS of MVPA and cognitive performance. Employing a univariate MR design, a series of sensitivity analyses are conducted to control for pleiotropy bias and validate the robustness of the MR results. Our research using genetic instruments reveals a potential bidirectional causal relationship between MVPA and cognitive performance.

However, it is important to acknowledge certain limitations. The GWAS summary data utilized in this study encompasses only individuals of European descent. Consequently, the applicability of our findings to other populations requires further validation. Additionally, due to the limited information in the aggregated data, we are unable to ascertain if gender influences our results.

6 Conclusion

We discovered that MVPA can mitigate cognitive risk, yet a low cognitive level also contributes to inadequate MVPA. This reciprocal causal relationship between MVPA deficiency and cognitive risk may indicate a detrimental cycle, posing an additional risk factor for increased cognitive impairment. These findings offer valuable insights for the formulation of policies aimed at preventing and intervening in cognitive risks. Our research provides evidence to assist individuals in selecting the appropriate quantity and intensity of physical activity throughout their lives to preserve their overall health.

Data availability statement

The original contributions presented in this study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

QF: Writing – review & editing. JZ: Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsyg.2024.1368241/full#supplementary-material>

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