Physical Activity and Memory Performance: A Mendelian Randomization Study

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Abstract

Background

Physical activity has been associated with better memory performance by epidemiological studies. However, the conclusion was still controversial, and whether the association was causal is elusive.

Methods

To evaluate the role of physical activity in memory performance from a genetic perspective, we first estimated their genetic correlation, and then conducted two-sample and multivariable Mendelian randomization analyses.

Results

Significant positive genetic correlation was identified between moderate to vigorous physical activity and prospective memory (PM) and episodic memory (EM). Genetically determined higher physical activity was significantly associated with better performance of both PM and EM after the Bonferroni correction. Such association was further verified using summary statistics from another study on overall physical activity. The results were robust under all sensitivity analyses.

Conclusions

Current results suggested physical activity could improve memory performance. These findings help better understand the role of physical activity in memory, and provide some lifestyle recommendations.

Introduction

As people get older, memory impairment is an unavoidable concern which could bring about problems such as restrictions to lifestyle activities and negative emotions, thus reducing the quality of life[1, 2]. The prevalence of age-associated memory impairment was ~ 40% in individuals over 65 years old[1], and such risk was increasing dramatically as people live longer. However, most studies focused on dementia or cognitive impairment so far, while fewer researches were conducted on memory loss. Identifying risk factors for memory performance could help better understand the pathogenesis, and provide care and therapeutic strategies for individuals and clinicians.

Multiple factors were suggested to influence the memory function, like genetics and environmental factors such as alcohol consumption and smoking[3]. Physical activity, which could improve overall body health, has been suggested to be beneficial in memory performance as well. A previous epidemiological study found that physical activity was positively associated with a composite measure of visual episodic memory in older adults[3, 4]. Meanwhile, resistance exercise was shown to enhance prospective memory as well[5]. However, such a conclusion was still contradictory. For example, an analysis of longitudinal associations over 12 years in 29,740 participants reported that more frequent light physical exercise was related to more age-related decline in episodic memory[6]. Nevertheless, such observational studies might be biased by unavoidable confounding factors, and cannot determine causation. Therefore, whether physical activity has a beneficial role in memory performance is still elusive.

In this context, we performed a two-sample Mendelian randomization (MR) analysis to explore the causal role of physical activity on the performance of two kinds of memories including prospective memory (PM) and episodic memory (EM). The MR approach is not susceptible to reverse causation or confounding factors which may distort interpretations of

conventional observational studies. As a result, we found that moderate to vigorous physical activity was causally associated with better performance of both PM and EM.

Methods

Datasets

Exposure data were from a recent GWAS on physical activity among 377,234 participants from the UK Biobank[7]. Physical activity during work and leisure time was ascertained through a touchscreen questionnaire similar to the International Physical Activity Questionnaire. Four physical activity phenotypes from this study were analyzed, including self-reported moderate-to-vigorous physical activity (MVPA), self-reported vigorous physical activity (VPA), overall acceleration average (AccAve), and 2–3 days/week or more in doing strenuous sports or other exercises for a duration of 15–30 minutes or greater (SSOE) (**Supplementary Table 1**). As a replication, we further analyzed summary data from another GWAS on overall physical activity[8] (**Supplementary Table 1**). The overall activity level was measured by average vector magnitude for each 30-s epoch using wrist worn accelerometers, which was the recommended variable for activity analysis. The detailed design like quality control procedures and statistical analyses could be found in the original publication. Single nucleotide polymorphisms (SNP) that passed the genome-wide significance threshold ($P < 5E-08$) were chosen as instrument variables, which were then clumped based on the 1,000 Genomes Project linkage disequilibrium (LD) structure. Index SNPs ($R^2 < 0.001$ with any other associated SNP within 10 Mb) with the minimum P value were kept. Furthermore, we used the PhenoScanner v2 tool to check for variants associated with other phenotypes ($P < 5E-08$) which might affect the memory performance independent of physical activity.

We obtained GWAS summary statistics for prospective memory ($N = 152,605$) based on the UK Biobank data. In the prospective memory test, participants were allowed up to 2 attempts to correctly recall the color/shape shown to them earlier in the touchscreen section (data field: 20018). The detailed design like quality control procedures and statistical analyses could be found in <http://www.nealelab.is/uk-biobank/>. Summary statistics of episodic memory ($N = 331,679$) was from the recent GWAS on cognitive traits based on data from the UK Biobank[9]. Episodic memory was measured using a ‘pairs-matching task’. In this self-administered task, participants are shown a randomly arranged 4×3 grid of 12 ‘cards’, with six pairs of matching symbols. The symbols were then hidden and the participant was instructed to select the locations of the pairs that matched, in the fewest possible number of attempts. Harmonization was undertaken to rule out strand mismatches and ensure alignment of SNP effect sizes.

Genetic correlation

We estimated the genetic correlation between physical activity and memory performance using LDSC and GNOVA with default parameters. The LDSC method quantifies the contribution of each SNP by examining the relationship between GWAS summary statistics and LD. GNOVA estimates genetic covariance with the genetic variants summary data shared between two GWAS, and then calculates the genetic correlation based on genetic covariance and variant-based heritabilities. Compared with LDSC, GNOVA provides greater statistical power as well as higher estimation accuracy. We ran GNOVA on all the SNPs in both phenotypes together with reference data derived from the 1000 Genomes Project European population. A P value below 0.01 (0.05/5) was considered statistically significant after the Bonferroni correction.

Mendelian randomization analysis

We hypothesized that physical activity as a protective factor could causally improve the memory performance, and the following assumptions were satisfied: the genetic variants used as instrumental variables are associated with physical activity; the genetic variants are not associated with any confounders; the genetic variants are associated with memory through physical activity (namely horizontal pleiotropy should not be present).

To evaluate the causative effect of physical activity on memory performance, we performed a two-sample MR analysis using the random effects inverse variance weighted (IVW) method, which is most widely used in MR studies and could provide robust causal estimates under the absence of directional pleiotropy. A P value below 0.01 (0.05/5) was considered statistically significant after the Bonferroni correction. In addition, we conducted comprehensive sensitivity analyses to estimate potential violations of the model assumptions in the MR analysis. We conducted Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) analysis and leave-one-out analysis to detect outlier instrument variables. Outlier instrument variables identified by the MR-PRESSO analysis were removed step-by-step to reduce the effect of horizontal pleiotropy. Cochran's Q test was executed to check heterogeneity across the individual causal effects. MR-Egger regression was performed to evaluate the directional pleiotropy of instrument variables. Reverse causal inference with Steiger analysis was conducted to explore whether memory performance has a causal impact on physical activity. To evaluate the strongness of each instrument variable, we computed the F-statistic of each SNP. The statistical power was calculated using an online tool at <http://cnsgenomics.com/shiny/mRnd/>. The statistical analyses were conducted using R package TwoSampleMR 0.5.5.

Results

We first estimated the genetic correlation between physical activity and memory function. We detected a significant and positive genetic correlation between MVPA, VPA, AccAve, overall activity and PM using both the LDSC and GNOVA methods. Similarly, significant genetic correlation was identified between MVPA, VPA, AccAve and EM (Fig. 1).

Then we analyzed the role of physical activity in memory function using the two-sample MR approach. Results showed that each standard deviation increase in MVPA, VPA and AccAve was significantly associated with better performance of PM and EM (Fig. 1). In the replication phase, overall activity was significantly associated with better performance of PM, and was identified nominally associated with better performance of PM. In contrast, no association was identified between SSOE and PM and EM, suggesting too strenuous physical activity does not improve memory performance (Fig. 1).

Next, we performed extensive sensitivity analyses to validate the causal association between physical activity and memory performance. There was some evidence of heterogeneity in the SNP effects of SSOE for PM and EM (Table 1). However, no potential instrument outlier was detected at the nominal significance level of 0.05 by the MR-PRESSO analysis, and MR-Egger intercepts indicated no evidence of directional pleiotropy (Table 1). No heterogeneity of effects was detected by Cochran's Q test (Table 1). The F statistics of all the instrument variables were above 10 (ranging from 29 to 82), indicating the absence of weakness in the selected instruments. No apparent horizontal pleiotropy was observed as the intercept of MR-Egger was not significantly deviated from zero (Table 1). Meanwhile, no potential instrument outlier was detected at the nominal significance level of 0.05 by the MR-PRESSO analysis (Table 1). The Steiger test suggested correct directionality (Table 1). The leave-one-out results suggest that the causal effect was not driven by a single instrumental variable (**Supplementary Figs. 1–5**). Given the type 1 error of 0.05, we had sufficient power (>80%) to detect the association between MVPA, VPA and PM, EM (Table 1).

Table 1
Heterogeneity and horizontal pleiotropy analyses between physical activity and memory performance.

exposure trait	outcome trait	Heterogeneity			Horizontal pleiotropy			MR-PRESSO P value	Steiger test		Power
		IVW Q	Q df	P value	Egger intercept	SE	P value		correct direction	P value	
AccAve	PM	3.12	7	0.874	7.8E-04	0.004	0.837	0.853	TRUE	3.08E-08	0.05
	EM	3.47	3	0.325	-2.5E-03	0.011	0.840	0.36	TRUE	6.13E-10	0.05
MVPA	PM	18.00	18	0.455	7.5E-04	0.002	0.759	0.476	TRUE	1.49E-15	0.97
	EM	23.21	12	0.026	-1.9E-02	0.007	0.020	0.05	TRUE	1.02E-35	0.83
VPA	PM	8.36	6	0.213	1.9E-02	0.007	0.037	0.25	TRUE	3.15E-05	1
	EM	10.22	5	0.069	2.0E-03	0.015	0.897	0.103	TRUE	1.56E-19	1
SSOE	PM	23.21	12	0.026	-3.8E-03	0.004	0.351	0.02	TRUE	2.28E-11	0.69
	EM	17.05	8	0.030	-7.2E-03	0.007	0.337	0.574	TRUE	6.11E-28	0.62
overall activity	PM	1.49	4	0.828	-7.7E-03	0.007	0.379	0.845	TRUE	1.40E-16	0.69
	EM	2.97	2	0.227	-1.2E-02	0.016	0.584	0.575	TRUE	7.12E-16	0.4
IVW, Inverse variance weighted; Q, Cochran's Q test estimate; df, Cochran's Q test degrees of freedom; SE, standard error; AccAve, overall acceleration average; PA, physical activity; MVPA, moderate-to-vigorous PA; VPA, vigorous PA; SSOE, strenuous sports or other exercises; OA, overall activity; PM, prospective memory; EM, episodic memory.											

Lastly, we used the PhenoScanner tool to check if the SNPs used in the MR analysis were associated with other phenotypes. As a result, several instrumental variables were associated with body mass index (BMI) which was suggested to affect the memory function[10] (**Supplementary Table 2**). Therefore, we further performed multivariable MR to elucidate the causal relationship between physical activity and memory function adjusting potential pleiotropy due to BMI. The summary data on BMI were obtained from GWAS published by the Genetic Investigation of ANthropometric Traits (GIANT) consortium[11]. As a result, a significant association was still identified between AccAve, MVPA, VPA, overall activity and PM in the multivariable MR analyses adjusting from BMI. Nominal association was identified between AccAve, overall activity and EM, and borderline association was identified between MVPA, VPA and EM (**Supplementary Table 3**). Therefore, moderate to vigorous physical activity was still beneficial for the memory performance in the multivariable MR analyses adjusting from BMI.

Discussion

Previous epidemiological studies have suggested physical activity was beneficial for the performance of memory. However, such a conclusion was still controversial. Meanwhile, unmeasured confounding factors in clinical studies could potentially bias the association evidence, and causation could not be determined. In this context, we investigated the causative role of physical activity in memory performance using the MR approach. The results demonstrated that moderate to vigorous physical activity was causally associated with better performance of both PM and EM. These

findings provided a better understanding of the role of physical activity in memory, and provide some lifestyle recommendations.

Multiple evidence has suggested that physical exercise could benefit brain function and cognition[12]. Using the MR approach, our results demonstrated that physical activity was beneficial for memory performance as well. The beneficial effect may be a result of shared biological and psychological pathways linking physical activity and memory. The previous study has shown that exercise could increase the number of new neurons in the adult hippocampus and increase the size of hippocampus[13–15], while the hippocampus is crucial for long-term episodic memory[16]. In particular, exercise has been shown to enhance hippocampus-dependent spatial memory in rodents in paradigms including the Morris water maze, the Y-maze, and the radial arm maze[17]. Meanwhile, physical exercise could significantly elevate endogenous norepinephrine and thus facilitate memory consolidation[18]. In addition, physical activity has also been shown to stimulate neuronal activity in brain areas like prefrontal cortex and cerebellum which might influence memory performance[19]. Taken together, this plausible evidence suggested that moderate to vigorous physical activity may favorably influence memory[20, 21]. In contrast, SSOE did not show association with memory performance, suggesting too strenuous physical activity was not beneficial for memory performance. Similarly, a randomized controlled trial found that one-year high-intensity interval training (HIIT) did not significantly improve fitness, cognitive performance or mental health[22]. In addition, a previous 6-month randomized controlled trial found that regular aerobic exercise appears to boost the size of the hippocampus, while resistance training, balance and muscle toning exercises did not have the same results[23]. Therefore, the type, intensity and duration of the exercise were important for the beneficial role of physical activity in the memory performance.

There were also some limitations worth mentioning in the current study. First, only a limited number of valid instrumental variables were significant in the current physical activity GWAS, which was susceptible to bias. Therefore, the potential causal associations in the current study should be interpreted with caution, and further replications in well-power studies were still warranted. Second, though several physical activities with different intensities were examined, current GWAS did not differentiate between types of physical activity, like swimming, and running. Considering that different types of physical activity might have different benefits and involve different parts of the body, further investigation into subtypes of physical activities might provide additional insights.

Conclusions

Based on results from the genetic correlation and MR analyses, we demonstrated that moderate to vigorous physical activity could causally improve the performance of PM and EM. These results could help better understand the role of physical activity in memory performance and will facilitate therapeutic drugs in future clinical trials.

Abbreviations

PM, prospective memory; EM, episodic memory; GWAS, genome-wide association study; MR, Mendelian randomization; MVPA, moderate-to-vigorous physical activity; VPA, self-reported vigorous physical activity; AccAve, overall acceleration average; SSOE, 2-3 days/week or more in doing strenuous sports or other exercises for a duration of 15-30 minutes or greater; SNP, single nucleotide polymorphism; LD, linkage disequilibrium; IVW, inverse variance weighted; BMI, body mass index.

Declarations

Ethics approval and consent to participate

The study was approved by the West China Hospital of Sichuan University. No participants were involved.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and material

Summary statistics of physical activity in the discovery phase could be found in GWAS Catalog (<https://www.ebi.ac.uk/gwas/>). Summary statistics of physical activity in the replication phase was available at <https://ora.ox.ac.uk/objects/uuid:ff479f44-bf35-48b9-9e67-e690a2937b22>. Summary statistics of prospective memory could be downloaded from ieu open gwas project (<https://gwas.mrcieu.ac.uk/>, ID: ukb-b-4282). Summary statistics of episodic memory could be found in the original publication. The datasets generated during the analysis were in the supplementary materials.

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Authors' contributions

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique

L.C.: 1A, 1C, 2A, 2B, 2C, 3A; L.J.: 2B, 3A, 3B; J.Q.: 3B, 4A; Y.T.: 3B; X.Y.: 3B; S.H.: 1B, 2C, 3B

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Figures

Figure 1

Genetic correlation between physical activity and memory performance. (A, B) Genetic correlation estimated using the GNOVA method. (C, D) Genetic correlation estimated using the LDSC method. Error bars indicate 95% confidence intervals. AccAve, overall acceleration average; MVPA, self-reported moderate-to-vigorous physical activity; VPA, self-reported vigorous physical activity; SSOE, 2-3 days/week or more in doing strenuous sports or other exercises for a duration of 15-30 minutes or greater; OA, overall activity.

Figure 2

Forest plot showing results from the Mendelian randomization analysis to evaluate potential causal association between physical activity and memory performance. Estimates are per 1 standard deviation increase in the trait. AccAve, overall acceleration average; MVPA, self-reported moderate-to-vigorous physical activity; VPA, self-reported vigorous physical activity; SSOE, 2-3 days/week or more in doing strenuous sports or other exercises for a duration of 15-30 minutes or greater; OA, overall activity.

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