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# Vitamin D and Cognitive Performance in Older Adults: A Cross-Sectional and Mendelian Randomization Study

## ABSTRACT

**Background:** Cognitive decline is a prevalent health problem in older adults, and effective treatments remain to be produced. Serum vitamin D, a commonly used biochemical marker, is widely recognized as an indicator of various diseases. Existing research has not fully elucidated the relationship between vitamin D and cognitive function. The aim of this study is to investigate the real relationship between vitamin D and cognitive function and to identify indicators that have a strong predictive effect on cognitive decline.

**Methods:** At first, we used the dataset of the genome-wide association studies studying vitamin D and cognitive performance to conduct Mendelian randomization analysis. Subsequently, we employed linear regression and smooth curve fitting methods to assess the relationship using the National Health and Nutrition Examination Survey data. Finally, we investigated other predictive features of cognitive performance utilizing a machine learning model.

**Results:** We found that a 1-unit increase in vitamin D is associated with a 6.51% reduction ($P < .001$) in the risk of cognitive decline. The correlation between vitamin D and cognitive performance is nonlinear, with the inflection point at 79.9 nmol/L (left: $\beta = 0.043$, $P < .001$; right: $\beta = -0.007$, $P = .420$). In machine learning, the top 5 predictors are vitamin D, weight, height, age, and body mass index.

**Conclusion:** There is a causal relationship between vitamin D and cognitive performance. 79.9 nmol/L could be the optimal dose for vitamin D supplementation in the elderly. Further consideration of other factors in vitamin D interventions is necessary.

**Keywords:** Cognitive performance, vitamin D, dose–response relationship, Mendelian randomization, machine learning

## Introduction

With the increase in life expectancy, the decline in cognitive function associated with age has become one of the major health challenges for the elderly.[1] As the US population ages, cognitive dysfunction has become a significant public health issue.[2] Without proper prevention and treatment, the progression of cognitive decline to dementia becomes irreversible. However, it is disappointing to know that no effective treatment has been developed for dementia so far. Currently, drugs that have therapeutic value are very limited. Studies on other alternative methods have also not achieved convincing evidence. Thus, one of the most helpful methods is to develop a series of practical measures to prevent and reduce the risk of low cognitive performance.

Vitamin D participates in many cellular activities, such as inflammation, oxidative stress, excitotoxicity, and cell apoptosis.[3] Vitamin D levels in the body are often assessed using serum 25(OH)D. Vitamin D intake among a large proportion of adults in the US is lower than the standard Estimated Average Requirements (EARs).[4] Additionally, around one-third of the elderly in America have serum 25(OH)D levels <50 nmol/L.[5] This indicates a widespread daily vitamin D deficiency among older adults.

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Previous research has shown that vitamin D deficiency is associated with cognitive dysfunction and an increased risk of dementia.[6,7] However, several recent studies have concluded that supplementing vitamin D has no significant effect on cognition compared to placebo groups.[8,9] In contrast, another trial involving healthy older adults with initially insufficient levels found significant cognitive improvements with vitamin D supplementation.[10] The potential explanation for these inconsistent results may include accidental and systematic errors, such as varying optimal concentrations of serum 25(OH)D for cognitive function, the dose–response relationship between vitamin D and cognitive performance, and the duration of interventions.

Determining the optimal dose of vitamin D is crucial for assessing its effect on cognition and for future clinical interventions. However, the dose-dependent effects and the optimal dosage are still uncertain. A study by Maddock et al.[11] showed an inverted U-shaped relationship between immediate word recall in middle-aged individuals and vitamin D levels, with both low (25 nmol/L) and high (75 nmol/L) levels linked to poorer cognition. Patetersen's study[10] suggested that a lower dose (mean 85.9 nmol/L, standard deviation (SD) = 16) was more effective in improving immediate recognition tests for nonverbal memory than a higher dose of vitamin D (mean 130 nmol/L, SD = 26). Previous findings[12] suggest that high-dose vitamin D, reaching an average of 130 nmol/L, may not provide additional benefits and could potentially lead to less improvement than a baseline compared to a lower-dose vitamin D group (100 nmol/L). In conclusion, exploring the appropriate vitamin D dosage to improve cognitive function will be beneficial for clinical practice.

In addition to vitamin D, several factors are associated with cognitive performance. Previous studies have shown that age is an important factor affecting cognitive function decline, and the majority of participants exhibit a stable decline trajectory with age.[13,14] Furthermore, obesity in early adulthood and the appearance of the heaviest weight between 18 and 40 years of age are associated with lower cognitive function later in life.[15] According to guidelines in the United States, a variety of physical activities such as muscle strengthening, balance training, and aerobics can reduce the risk of cognitive decline.[16] Another study showed that a body mass index (BMI) < 18.5 kg/m$^2$ is a risk factor for cognitive decline. Only participants with a slow decline in cognitive performance with age and a BMI > 28 kg/m$^2$ showed a protective effect on cognitive function.[14] Therefore, indicators including vitamin D, age, weight, height, BMI, and physical activity may collectively contribute to cognitive performance.

The goal of the study was 3-fold: firstly, we used a 2-sample Mendelian randomization (MR) method to explore whether vitamin D content is causally related to protecting cognitive function. Secondly, we investigated the dose–response relationships between serum vitamin D and cognitive performance in the elderly using data from the National Health and Nutrition Examination Survey (NHANES) conducted between 2011-2012 and 2013-2014. Thirdly, we identified predictors of cognitive performance using the Extreme Gradient Boosting (XGBoost) model. These findings will add to the current understanding of serum vitamin D levels as a predictor of cognitive function while providing new insights into the influencing factors of cognitive function and possible interventions.

## MAIN POINTS

- *Vitamin D has a causal association with the cognitive performance of older adults.*
- *The optimal dose of vitamin D associated with optimal cognitive performance in older adults is approximately 79.9 nmol/L or higher.*
- *Machine learning models provide the most important factors closely related to the cognitive performance of older adults: vitamin D, weight, height, age, body mass index, and other indicators.*

## Material and Methods

Firstly, we extracted information on single-nucleotide polymorphisms (SNPs) based on publicly available summary statistics from the most recent genome-wide association studies (GWASs) publications, associated with vitamin D concentration[17] and cognitive performance.[18] The chosen SNPs, selected at the genome-wide significance threshold of $P < 1 \times 10^{-5}$, met the assumption of being strongly associated with vitamin D concentration (for detailed information on selected SNPs of cognitive performance and vitamin D, see Supplementary Tables 1 and 2).

This study included data from NHANES 2011-2012 and NHANES 2013-2014, which obtain ethics approval from the National Center for Health Statistics (Protocol#2011-17, Continuation of Protocol#2011-17).

Secondly, we analyzed data from the NHANES database in the 2011-2012 and 2013-2014 surveys.[19] Participants who were aged over 60 years, completed the Animal Fluency Test, and had data on serum 25(OH)D were included in the study population. A total of 1139 participants were included in the final analysis. The serum levels of 25(OH)D were presented in nmol/L. Cognitive performance was assessed using the Animal Fluency test.[20] Given the significant impact of age on cognitive ability, we further classified participants by age (60-69 years, 70-79 years, and ≥80 years). The cutoff values for the animal fluency tests were 14, 13, and 12, respectively.[21] Participants were divided into low and normal cognitive performance groups. Confounding factors included gender, age, educational level, season of examination, minutes of sedentary activity, physical activity, weight, height, BMI, and history of hypertension.

Finally, we constructed the XGBoost algorithm model as a predictive model,[22] to analyze the contribution of each variable to the animal fluency test scores. Gradient Boosting Tree (GBT)[23,24] is a decision tree-based ensemble prediction model that utilizes gradient descent to continuously build decision trees in order to minimize the loss function. The final prediction is made using a weighted majority vote of all decision trees.

### Statistical Analysis

All statistical analyses were performed using EmpowerStats (http://www.empowerstats.com) and R statistical software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), using the "car," "gbm," "xgboost," and "mendelianRandomization" packages. Inverse variance weighted (IVW) regression and Egger's regression were used to analyze the single SNPs and multiple SNPs, respectively. Forest and scatter plots combined the results of single and all SNP analyses. A leave-one-out approach was used to examine whether the analyses were driven by any single SNP. *F*-statistics above 10 indicated that the instruments were sufficiently strong. If the *P*-value was less than .050, the MR-PRESSO would affect the accuracy of the MR analysis by eliminating abnormal SNPs.The Kolmogorov–Smirnov test was used to test the normality of variables. Continuous variables were presented with mean ± SD. Categorical variables were presented with n (%). The chi-square test and 2-independent sample *t*-test were used for comparisons between the 2 groups. Multivariable linear regression analyses were used to examine the association of serum 25(OH)D with cognitive performance. Smooth curve fitting was used to examine whether vitamin D is partitioned into intervals. We applied segmented regression to fit each interval. A log-likelihood ratio test comparing a 1-line model to a segmented regression model was used to determine whether a threshold exists. A 2-sided *P*-value of less than .05 was considered statistically significant.

## Results

### Mendelian Randomization Study

The *F*-values for vitamin D and cognitive performance in the Mendelian randomization analysis were 238.92 and 72.97, respectively ($F > 10$). Genetically predicted vitamin D was causally associated with a 6.51% improvement in cognitive performance (OR_IVW = −0.0651, $P = .001$) (see Table 1, Supplementary Figures 1 and 2). Sensitivity analyses confirmed that no single SNP was strongly driving the overall effect of vitamin D on cognitive performance (see Supplementary Figure 3). The MR-Egger test for heterogeneity indicated that there was heterogeneity in the MR analysis results ($P < .050$) (see Supplementary Table 3). MR-Egger regression results also showed evidence of pleiotropy in the MR results (see Supplementary Table 3). The MR-PRESSO test in the Mendelian randomization was applied to demonstrate that genetically predicted vitamin D affects the accuracy of the MR analysis by eliminating abnormal SNPs (see Supplementary Table 4).

### Clinical study in NHANES Analysis

The NHANES 2011-2012 cycle (n = 9338) and the 2013-2014 cycle (n = 19 151) were both utilized in this study. A total of 1139 participants were included in the final analysis. For the flowchart of the exclusion criteria, see Figure 1. There were significant differences in age, weight, height, education, vigorous and moderate work activity, hypertension, and vitamin D distribution during the Animal Fluency test between the low and normal cognitive performance groups, see Table 2.

The results of the multivariable linear regression analyses of associations between vitamin D and cognitive performance are shown in Table 3. In the fully adjusted model (including gender, age, examination season, education, weight, height, BMI, minutes of sedentary activity, vigorous work activity, moderate work activity, walking or bicycle, hypertension, and sleep time), vitamin D had a significant effect with a $\beta = 0.016$ (95% CI: 0.006-0.026, $P = .002$) on the association with cognitive performance. This effect was present in the nonadjusted model and the other 2 different adjustment models.

Restricted cubic spline analyses suggested an L-shaped association of vitamin D with the animal fluency test score (see Figure 2). Adjusted smoothed plots indicated a nonlinear relationship between vitamin D and the Animal Fluency test score, which increased with vitamin D up to the turning point (turning point: vitamin D 79.9 nmol/L) (see Supplementary Table 5).

**Table 1.** Mendelian Randomization (MR) Analysis of Vitamin D and Cognitive Performance (Animal Fluency Test)

| | | Cognitive Performance | | | |
|---|---|---|---|---|---|
| | **Method** | **SNPs (n)** | ***β*** | **SE** | ***P*** |
| Vitamin D | MR Egger | 250 | 0.050 | 0.028 | .078 |
| | Weighted median | 250 | -0.005 | 0.020 | .806 |
| | IVW | 250 | -0.065 | 0.020 | .001 |
| | Weighted mode | 250 | 0.003 | 0.015 | .870 |

IVW, inverse variance weighted; MR, Mendelian randomization; SE, standard error; SNPs, single-nucleotide polymorphisms.

### Machine Learning Select Feature to Predict Cognitive Performance

Using the feature importance scores from the XGBoost model (see Figure 3), the most important factors closely related to cognitive performance were identified. In order of significance, these include serum vitamin D, weight, height, age, BMI, sedentary activity, sleep duration, educational levels, hypertension, examination season, intense work activity, moderate work activity, walking or cycling, and

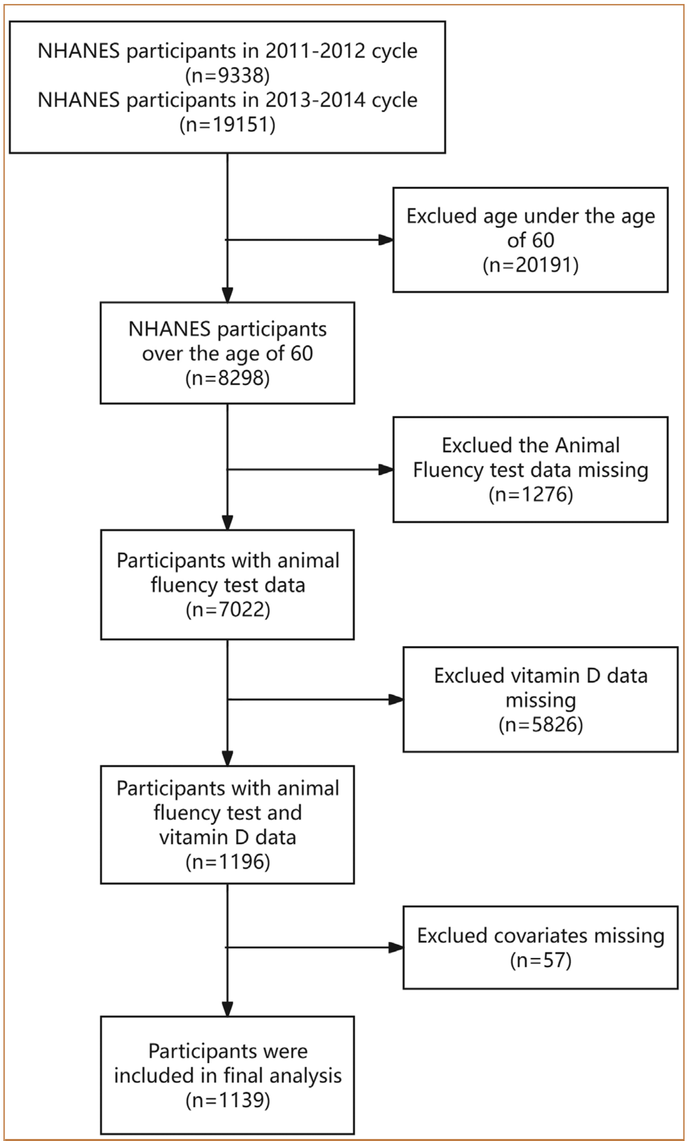

**Figure 1. Flowchart of patient disposition**

**Table 2.** Baseline Characteristics of Participants

| | Animal Fluency Test | | | |
|---|---|---|---|---|
| **Variable** | **Total, Mean ± SD/n (%)** | **Low Cognitive Performance, Mean ± SD/n (%)** | **Normal Cognitive Performance, Mean ± SD/n (%)** | ***P*** |
| n | 1139 | 214 | 925 | |
| Age (years) | 69.3 ± 6.8 | 71.2 ± 7.0 | 68.9 ± 6.7 | <.001[‡,*] |
| 60-69 | 63.9 ± 2.8 | 64.2 ± 3.0 | 63.8 ± 2.7 | .148[‡] |
| 70-79 | 73.8 ± 2.9 | 73.9 ± 2.8 | 73.8 ± 3.0 | .699[‡] |
| ≥80 | 80.0 ± 0.0 | 80.0 ± 0.0 | 80.0 ± 0.0 | .525[‡] |
| Gender | | | | .868[†] |
| Male | 569 (50.0) | 108 (50.5) | 461 (49.8) | |
| Female | 570 (50.0) | 106 (49.5) | 464 (50.2) | |
| Serum vitamin D (nmol/L) | 76.2 ± 31.3 | 71.8 ± 35.3 | 77.2 ± 30.3 | .022[‡,*] |
| Weight (kg) | 80.1 ± 19.7 | 77.6 ± 19.6 | 80.7 ± 19.7 | .042[‡,*] |
| Height (cm) | 165.4 ± 9.8 | 164.2 ± 10.3 | 165.7 ± 9.7 | .041[‡,*] |
| BMI (kg/$m^2$) | 29.2 ± 6.5 | 28.7 ± 6.3 | 29.3 ± 6.6 | .197[‡] |
| Minutes sedentary activity (minutes) | 370.5 ± 191.4 | 371.8 ± 211.6 | 370.2 ± 186.6 | .911[‡] |
| Sleep times (hours) | 7.0 ± 1.4 | 7.1 ± 1.6 | 7.0 ± 1.4 | .268[‡] |
| Examination season | | | | .482[†] |
| November to April | 513 (45.0) | 101 (47.2) | 412 (44.5) | |
| May to October | 626 (55.0) | 113 (52.8) | 513 (55.5) | |
| Education level | | | | <.001[†,*] |
| Less than 9th grade | 127 (11.2) | 39 (18.2) | 88 (9.5) | |
| 9-11th grade | 147 (12.9) | 43 (20.1) | 104 (11.2) | |
| High school graduate /GED or equivalent | 277 (24.3) | 63 (29.4) | 214 (23.1) | |
| Some college or AA degree | 321 (28.2) | 37 (17.3) | 284 (30.7) | |
| College graduate or above | 267 (23.4) | 32 (15.0) | 235 (25.4) | |
| Vigorous work activity | | | | .009[†,*] |
| Yes | 120 (10.5) | 12 (5.6) | 108 (11.7) | |
| No | 1019 (89.5) | 202 (94.4) | 817 (88.3) | |
| Moderate work activity | | | | <.001[†,*] |
| Yes | 343 (30.1) | 43 (20.1) | 300 (32.4) | |
| No | 796 (69.9) | 171 (79.9) | 625 (67.6) | |
| Walk or bicycle | | | | .091[†] |
| Yes | 240 (21.1) | 36 (16.8) | 204 (22.1) | |
| No | 899 (78.9) | 178 (83.2) | 721 (77.9) | |
| Hypertension | | | | .040[†,*] |
| Yes | 707 (62.1) | 146 (68.2) | 561 (60.6) | |
| No | 432 (37.9) | 68 (31.8) | 364 (39.4) | |

BMI, body mass index; SD, Standard Deviation.

[†] Chi-square test.

[‡] *t*-test.

[*] *P* < .05

sex. These 13 features are ranked from the most to the least important in the dataset.

## Discussion

Our study demonstrated that vitamin D has a positive causal association with cognitive performance, with genetically predicted vitamin D being causally associated with a 6.51% improvement in cognitive performance. These findings are consistent with previous studies in Parkinson's disease and Alzheimer's disease.[25,26] However, they are not consistent with results from studies in the normal population.[27] This discrepancy may be due to the age of the study population, suggesting that the relationship between vitamin D and cognitive performance is causal in the elderly, but not in the younger population. After establishing the causal relationship between vitamin D and cognitive performance, we further explored the nonlinear relationship between vitamin D and cognitive performance in the elderly to find the optimal dose for supplementation. International experts have agreed that vitamin D deficiency should be considered a risk factor for poor cognitive performance.[28] Our analysis of NHANES data showed that the association between vitamin D and the Animal Fluency test score was significant, with an L-shaped dose–response

**Table 3.** Association Between Serum Vitamin D and Animal Fluency Test, NHANES 2011–2014 (n = 1139)

| Variable | | $\beta$ (95%CI) | $P$ |
|---|---|---|---|
| Vitamin D (nmol/L) | Model 1 | 0.014 (0.004, 0.025) | .007* |
| | Model 2 | 0.015 (0.005, 0.025) | .004* |
| | Model 3 | 0.018 (0.007, 0.028) | <.001* |
| | Model 4 | 0.016 (0.006, 0.026) | .002* |

Model 1 is a nonadjusted model. Model 2 is adjusted for age, gender, season of examination, and education. Model 3 is adjusted for age, gender, season of examination, education, weight, height, and BMI. Model 4 is adjusted for age, gender, season of examination, education, weight, height, BMI, minutes of sedentary activity, vigorous work activity, moderate work activity, walking or bicycling, hypertension, and sleep time.*$P < .05$.BMI, body mass index; NHANES, National Health and Nutrition Examination Survey.

relationship detected in both crude-adjusted and fully adjusted models. The optimal dose of vitamin D associated with optimal cognitive performance is approximately 79.9 nmol/L. Below this level, cognitive performance increases with the dose, while above it, no significant association is observed, suggesting a plateau. Another study indicated that the association between serum 25(OH)D levels and Animal Fluency test scores in males was statistically significant when serum levels exceeded 61.41 nmol/L.[29] Despite some authorities recommending serum vitamin D levels of 75-80 nmol/L or higher, a recent RCT found that excessive intake of vitamin D had no effect on preventing cognitive impairment.[9] Vitamin D has been shown to have a neuroprotective effect by reducing the risk of oxidative stress, and this effect is concentration dependent.[30,31] Our findings suggest that a serum vitamin D concentration of around 79.9 nmol/L may be optimal for reducing the risk of cognitive impairment in the elderly. Nonetheless, we look forward to prospective cohort studies to confirm our results.

An interesting finding in our study is the coincidence between features identified by the XGBoost-based model and the results of the association analysis, exploring other important factors associated with cognitive performance. This enables us to tailor vitamin D supplementation programs to individual patients' conditions. However, the relationship between these features and the dose–response has not been fully explained. Therefore, investigating the potential mechanisms underlying the role of these variables is necessary. Among them, vitamin D has the greatest effect, suggesting it is a crucial predictor of cognitive function. This result aligns with some clinical studies and is consistent with previous studies showing a nonlinear relationship between serum vitamin D levels and cognitive function.[6,7,32,33] Considering that most older people have low levels of serum vitamin D, we recommend using it as an instructive index for the treatment and care of older adults to prevent cognitive decline.

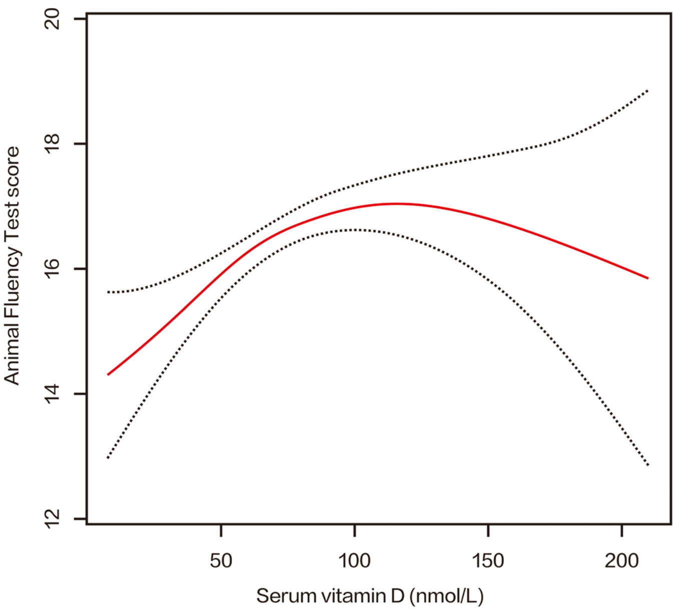

**Figure 2.** Dose–response relationship between Vitamin D and Animal Fluency test score

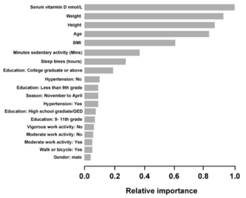

**Figure 3.** Average feature importance for cognitive performance from Animal Fluency test classifiers

This study conducted a comprehensive analysis of the relationship between vitamin D and cognitive performance in the elderly. Initially, we used the Mendelian randomization method to analyze the causal relationship, then explored the nonlinear and dose–response relationships between vitamin D and cognitive performance using a large, nationally representative elderly sample in the United States. Additionally, machine learning technology was employed to explore other factors affecting cognitive performance, providing clues and a scientific basis for personalized vitamin D intervention.

Our study has limitations. Firstly, the lack of association between the respective SNPs and cognitive performance may be due to a weak instrumental bias. However, the F-value indicated that the genetic instruments used were sufficiently strong. Secondly, as a cross-sectional study, it cannot show causal associations. Thirdly, the cognitive test selected did not cover all domains of cognitive function.

Our study shows that vitamin D has a causal association with cognitive performance. The optimal dose of Vitamin D associated with optimal cognitive performance is approximately 79.9 nmol/L or higher. We conclude that machine learning models based on NHANES data can provide an automatic identification mechanism for patients to confirm our association results and identify key contributors to the predictions. This can further explore their impact on electronic health records. Large-scale prospective studies are needed to further elucidate the effect of vitamin D on cognitive performance in the elderly.

*__Availability of Data and Materials:__ The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.*

*__Ethics Committee Approval:__ This study was approved by Ethics Committee of National Center for Health Statistic (Protocol#2011-17, Continuation of Protocol#2011-17; date: October 26, 2011).*

*Informed Consent: Informed consent was obtained from the participants who agreed to take part in the study.*

*Peer-review: Externally peer-reviewed.*

*Author Contributions: Concept – B.Z., P.L.; Design – B.Z., P.L.; Supervision – N.L., P.L.; Resources – N.L.; Materials – N.L., P.L.; Data Collection and/or Processing – N.L., P.L.; Analysis and/or Interpretation – P.L., N.L.; Literature Search – B.Z., P.L.; Writing – N.L., P.L.; Critical Review – B.Z., P.L.*

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**Supplementary Table 1:** https://docs.google.com/spreadsheets/d/1jJIHJIYRBSUOsgW0T7xjuG55hWmRMK3-PYba2hRlrN4/edit?usp=sharing

**Supplementary Table 2:** https://docs.google.com/spreadsheets/d/1ns0rjo70EUxtOXuEGG9SR2QNxpf-g2yniWCG_blrt-E/edit?usp=sharing

**Supplementary Table 3.** Sensitivity Analysis of the Mendelian Randomization (MR) Analysis Results of Vitamin D and Cognitive Performance (Animal Fluency Test).

| **Exposure** | | **Vitamin D** |
|---|---|---|
| **Outcome** | | **Cognitive performance** |
| IVW (heterogeneity) | *P* | 5.8466e−70 |
| | Q | 871.1698 |
| MR Egger (heterogeneity) | *P* | 6.6483e−56 |
| | Q | 777.1958 |
| MR Egger (pleiotropy) | *P* | 1.0654e−07 |
| | Intercept | −0.0033 |

IVW, inverse variance weighted; MR, Mendelian randomization.

**Supplementary Table 4.** MR-Presso Test of the Mendelian Randomization

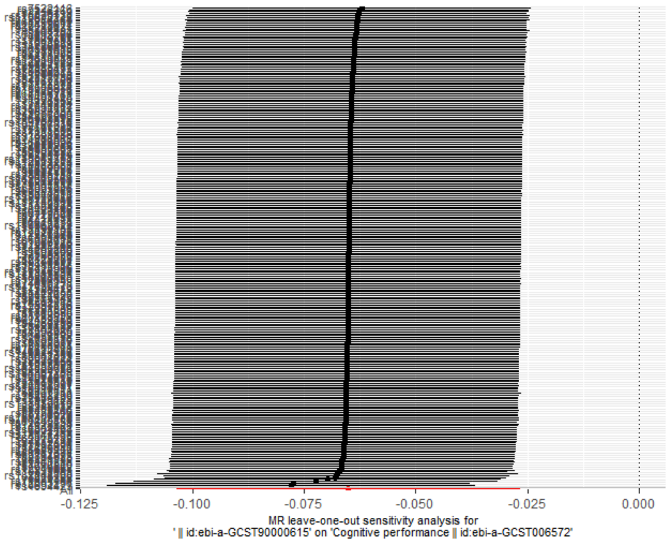
| Exposure | Outcome | Analysis | *β* | SE | T-Stat | *P* | Global Test *P* | Number of Removed SNP | Distortion Test *P* |
|---|---|---|---|---|---|---|---|---|---|
| Serum Vitamin D | Cognitive performance | Raw | −0.0737 | 0.0207 | −3.5600 | 4.4453e−04 | < .001 | 22 | .534 |
| | | Outlier | −0.0660 | 0.0165 | −3.9971 | 8.6271e−05 | | | |

SE: standard error.

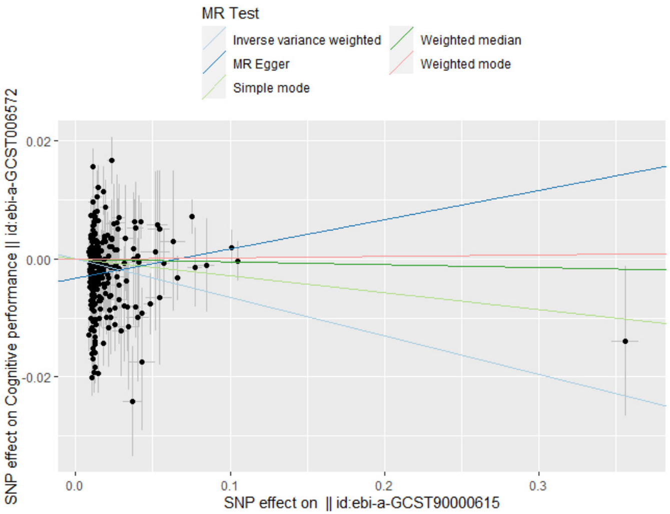
**Supplementary Table 5.** Threshold effect analysis of serum vitamin D on the Animal Fluency test score using the 2-piecewise linear regression model.

| Threshold of Serum Vitamin D | Adjusted *β* | 95% CI | *P* |
|---|---|---|---|
| <79.9 nmol/L | 0.043 | 0.023, 0.063 | < .001 |
| >79.9 nmol/L | −0.007 | −0.025, 0.010 | .420 |
| Log-likelihood ratio test | | | .002 |

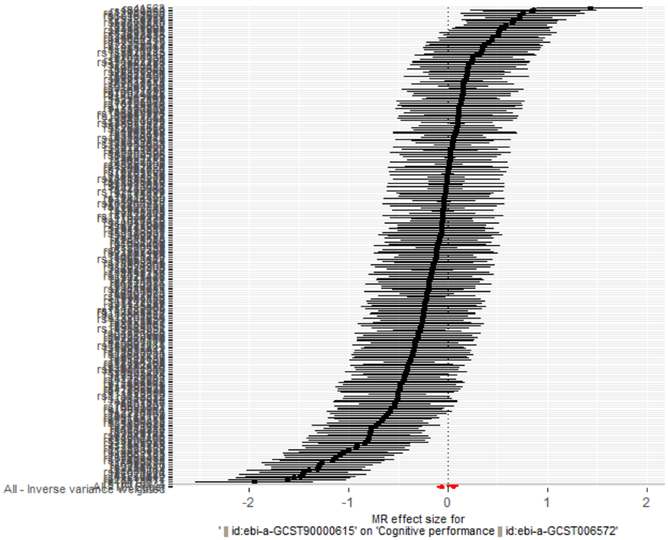
Age, gender, of examination, education, weight, height, BMI, minutes of sedentary activity, vigorous work activity, moderate work activity, walking or bicycle, hypertension and sleep time were adjusted.BMI, body mass index.



**Supplementary Figure 1. Results of the single and multiple SNP analyses for the SNP effect of natural logarithmic transformed vitamin D on cognitive performance.**



Supplementary Figure 2. The scatter plot of Mendelian randomization from vitamin D on cognitive performance.



Supplementary Figure 3. Plot product from leave-one-out method about the effect of vitamin D on cognitive performance.