The Association Between Sarcopenia and Cognitive Performance: Data from the National Health and Nutrition Examination Surveys 1999 to 2002

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Research article

Keywords: Sarcopenia, Cognitive Performance, Low Lean Mass, Cognitive Impairment

DOI: https://doi.org/10.21203/rs.3.rs-46878/v1
Abstract

Background: Sarcopenia and cognitive impairment are both age-related diseases. And they have many risk factors in common. However, the association between them has been controversial in recent years.

Objective: To investigate the association between sarcopenia and cognitive performance in the U.S. adults through the use of the NHANES data from 1999 to 2002.

Methods: A total of 2550 participants were identified in the National Health and Nutrition Examination Surveys Data Base (1999–2002). The independent variable was sarcopenia and the dependent variables was cognitive performance. Men were classified as sarcopenia if appendicular lean mass (ALM) adjusted for BMI (ALM_{BMI}) <0.789, and women<0.512. The cognitive performance was assessed by Digit Symbol Substitution Test (DSST). Higher scores on the DSST indicated better cognitive performance. The covariates included gender, age, race, poverty income ratio, comorbidity index, educational level, physical activity and smoking status.

Results: For the primary outcome, our multivariate linear regression analysis indicated that sarcopenia negatively correlated with cognitive performance in the model I (crude OR = 5.18; 95% CI: [3.49–6.87]). The negative association remained significant in the adjusted model II and model III (OR=3.40; 95% CI: [1.91–4.90]; OR=1.50; 95% CI: [0.12–2.89]). The subgroup analysis results indicated that participants without sarcopenia were associated with better cognitive performance was similar in different gender, age, race, poverty income ratio, comorbidity index, educational level, physical activity and smoking status.

Conclusions: Participants without sarcopenia were associated with better cognitive performance in a representative sample of older adults in the U.S. We might be able to try to improve cognitive performance by dealing with sarcopenia and provide opportunity for intervention at a younger age and better physical performance.

Background

Sarcopenia, a generalized and progressive skeletal muscle disorder, which includes the accelerated loss of muscle mass and function[1]. The Foundation for the National Institutes of Health (FNIH) proposed to define sarcopenia using low lean mass (LLM), an indicator of muscle mass based on imaging, for LLM could reflect not only muscle mass, but also related strength and function[2]. Sarcopenia is an adverse muscle changes, which can accrue across the lifetime[3]. There are evidence showing that sarcopenia is associated with increased risk of several negative health outcomes, including functional decline, falls, physical frailty, disability and all-cause mortality[1, 4, 5]. Hence, some scholars suggested sarcopenia to be a mortality predictor in the elderly, indicating that the elderly with severe sarcopenia or changes in physical performance had a relatively increased risk of mortality in the short run[6].

Cognitive impairment usually includes two or more following impaired abilities: communication and language, focus and attention, memory, reasoning and judgment, and visual perception[7]. It is a
neurodegenerative process of aging, can transition from mild cognitive impairment (MCI) to dementia[7, 8]. MCI is the symptomatic predementia stage of cognitive decline. The daily activities of MCI patients are usually not greatly affected[9]. Sarcopenia and cognitive impairment are both age-related diseases. However, the association between them has been controversial in recent years. Because they have many risk factors in common, like lack of anabolic hormones, malnutrition, persistent inflammatory reactions, sedentary lifestyle[8, 10]. Current evidence indicated that physical activity could improve the symptoms of MCI patients[9], which might suggest that there might be a link between sarcopenia and cognitive impairment. In terms of research results, some researches showed that sarcopenia was significantly associated with cognitive impairment[8, 11, 12], while some studies showed completely opposite results[13, 14]. Therefore, in the present paper, we aimed to explore the association between sarcopenia and cognitive performance using data that could represent the U.S. population.

Materials And Methods

Data Source and participants

The National Health and Nutrition Examination Surveys (NHANES) is an ongoing repeated cross-sectional study at the Centers for Disease Control and Prevention (CDC), conducted by the National Center for Health Statistics (NCHS). The aim of the NHANES is to investigate the general nutritional status and health of non-institutional population in the United States with a representative sample. Database in five sections (Demographics, Dietary, Examination, Laboratory, and Questionnaire) was collected by well-trained examiner every two years. NHANES program has been approved by NCHS the Ethics Review Board, and all participants have written informed consent. All NHANES data and information are publicly available at https://www.cdc.gov/nchs/nhanes/index.htm.

We performed an analysis based on data from two 2-year NHANES survey cycles: 1999–2000 and 2001–2002. We finally selected 2550 out of 3707 participants aged 60–85 years of NHANES in 1999–2002. We excluded the individuals with missing body composition measures (n = 723), missing questionnaires on cognitive function (n = 434).

Body Composition Measurement

All body compositions were measured by a dual energy X-ray absorptiometry (DXA) QDR-4500 Hologic scanner (Bedford, MA). The measurement limitation of the scanner on height was 192.5 cm in maximum and 136.4 kg on weight. Individuals beyond these ranges were considered missing related data. The NHANES reported the data of total skeletal muscle mass, appendicular lean mass (ALM), lean mass percent, fat mass, total body fat percent and bone mineral content. All measurements were operated by trained technicians normatively, and all metal objects (except false teeth and hearing aids) had to be removed during the measurement procedure. Individuals with other non-removable metal objects were forbidden from measurement.
ALM was the sum of muscle mass of all four upper/lower extremity limbs. In this research, according to the two FNIH definitions\[2\], we classified men whose ALM adjusted for BMI(ALM_{BMI}) < 0.789 as sarcopenia, and women < 0.512, and men whose ALM < 19.75 kg as alternate sarcopenia, and women < 15.02 kg.

Cognitive Performance Assessment

The cognitive performance was assessed by Digit Symbol Substitution Test (DSST), version of the WAIS III (Wechsler adult Intelligence Scale, Third Edition) in NHANES 1999–2002. The test was aimed at participants aged 60 and over, Proxy interviews were ineligible. The DSST is highly sensitive to neuropsychological dysfunction\[15\], it can measure many areas of cognitive function, in particular attention, cognitive and psychomotor speed, executive functions and visual scanning\[16\]. The DSST requires participant to draw the symbol under the corresponding number according to the provided key. The number of correct symbols in 120 seconds is the final score of the test. The maximum score is 133. Higher scores on the DSST indicated better cognitive performance.

Covariates

For covariates, continuous variables included age (year), poverty income ratio (PIR) and comorbidity index. Diabetes mellitus, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema) and hypertension, cancer consisted of comorbid conditions. The number of subjects reported conditions were then combined to generate an ordinal comorbidity index\[17\].

The Categorical variables included sex (male, female), race (Mexican American, other hispanic, non-hispanic white, non-hispanic black, other race), educational level (less than high school, high school or general educational development, above high school, unknown), physical activity (Less than moderate, moderate, Vigorous, unknown) and smoking status (never, former, current, unknown).

Statistical Analysis

All data was downloaded, merged and analyzed following the CDC guidelines (https://wwwn.cdc.gov/nchs/nhanes/tutorials/default.aspx). Marked variance was accounted and the proposed weighting methodology was used in our analyses. We also took sample weight into consideration and assigned it to each participant\[18\]. Continuous variables were presented as mean ± standard deviation (normal distribution) or median (quartile) (skewed distribution), and categorical variables were presented in frequency or as a percentage. The One-Way Anova (normal distribution), Kruscal Whallis H (skewed distribution) test and chi-square tests (categorical variables) were used to determine any statistical differences between the means and proportions between participants having sarcopenia or not. We conducted the following statistical analyses to explore the association between
sarcopenia and cognitive performance. Firstly, adjusted only univariate and multivariate line regression analysis were employed. Three models were constructed and used in our analyses: model 1, no covariate was adjusted; model 2, we adjusted gender, age and race; model 3, we adjusted all covariates presented in Table 1, including gender, age, race, poverty income ratio, comorbidity index, educational level, physical activity and smoking status. Then we used a weighted generalized additive model (GAM) and conducted smooth curve fitting (penalized spline method) to explore the potential nonlinearity between sarcopenia and cognitive performance. In addition, we conducted subgroup analysis through weighted stratified line regression models. We perform an interaction test and hierarchical analysis using all covariates above and continuous covariables of them were converted into categorical variables according to their clinical cut points during the subgroup analysis. Besides, we also conducted sensitivity analysis to ensure the robustness of data analysis. All analyses described above were conducted to assess the association between alternative sarcopenia and cognitive performance.
Table 1
Baseline Characteristics of Participants

| Sarcopenia                  | Overall (n = 2550) | Yes (n = 641) | No (n = 1909) | P value |
|-----------------------------|--------------------|---------------|---------------|---------|
| Mean (mean ± SD)            |                    |               |               |         |
| Age (years)                 | 69.98 ± 7.25       | 71.43 ± 7.44  | 69.60 ± 7.15  | < 0.0001|
| DSST Scores                 | 47.62 ± 17.83      | 43.52 ± 17.40 | 48.70 ± 17.79 | < 0.0001|
| Proportion (%)              |                    |               |               |         |
| Gender                      | < 0.0001           |               |               |         |
| Male                        | 44.28              | 52.04         | 42.22         |         |
| Female                      | 55.72              | 47.96         | 57.78         |         |
| Race                        | < 0.0001           |               |               |         |
| Mexican American            | 2.03               | 3.93          | 1.53          |         |
| Other Hispanic              | 4.49               | 6.71          | 3.91          |         |
| Non-Hispanic White          | 84.32              | 84.3          | 84.32         |         |
| Non-Hispanic Black          | 6.55               | 1.58          | 7.86          |         |
| Other Race                  | 2.61               | 3.48          | 2.38          |         |
| Education level             | 0.003              |               |               |         |
| Less than high school       | 25.74              | 31.53         | 24.21         |         |
| High school or General educational development (GED) | 28.64 | 28.6 | 28.66 |         |
| Above high school           | 43.9               | 38.64         | 45.28         |         |
| Unknown                     | 1.72               | 1.23          | 1.85          |         |
| Poverty income ratio (PIR)  | 0.1554             |               |               |         |
| Below poverty (< 1)         | 10.12              | 12.18         | 9.58          |         |
| Above poverty (> 1)         | 77.86              | 75.12         | 78.58         |         |
| Unknown                     | 12.02              | 12.7          | 11.84         |         |
| Sarcopenia                      | Overall | Yes  | No  | P value |
|-------------------------------|---------|------|-----|---------|
| Physical activity             |         |      |     | < 0.0001|
| Less than moderate            | 41.65   | 52.86| 38.69|         |
| Moderate                      | 32.61   | 27.98| 33.84|         |
| Vigorous                      | 18.74   | 10.18| 21.01|         |
| Unknown                       | 6.99    | 8.98 | 6.47 |         |
| Smoking status                |         |      |     | 0.7971  |
| Never                         | 46.48   | 46.46| 46.49|         |
| Former                        | 42.98   | 43.8 | 42.77|         |
| Current                       | 10.38   | 9.7  | 10.55|         |
| Unknown                       | 0.16    | 0.04 | 0.19 |         |
| Comorbidity index             |         |      |     | 0.013   |
| 0                             | 35.01   | 32.69| 35.63|         |
| 1                             | 42.08   | 40.48| 42.51|         |
| ≥ 2                           | 15.99   | 16.35| 15.89|         |
| Unknown                       | 3.63    | 5.18 | 3.22 |         |
| 4                             | 1.33    | 2.05 | 1.14 |         |
| 6                             | 1.96    | 3.26 | 1.61 |         |

All statistical analyses were conducted using the statistical package R (http://www.R-project.org, The R Foundation) and Empower (R) (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA). Two-sided p values < 0.05 was considered statistically significant.

**Results**

**Baseline Characteristics of Participants**

The sociodemographic characteristics and related covariates of the weighted distribution of included participants according to whether participants with sarcopenia or not were shown in Table 1. The mean age of the participants was 69.98 ± 7.25, and the mean DSST scores was 47.62 ± 17.83. 55.72% of the participants were females. 641 of 2550 participants were clarified into sarcopenia. Significant differences were observed for all included characteristics except poverty income ratio (PIR) and smoking status.
between participants with or without sarcopenia. Comparing with participants without sarcopenia, participants with sarcopenia were more inclined to be older, male, less than moderate physical activity as well as having a lower DSST Scores. In addition, the baseline characteristics of participants in accordance with whether participants with alternate sarcopenia or not were shown in Supplement Table 1.

**Association between Sarcopenia and Cognitive Performance**

The effect sizes of the association between sarcopenia and DSST scores were shown in Table 2. For the primary outcome, our multivariate linear regression analysis indicated that sarcopenia negatively correlated with cognitive performance in the model I (crude OR = 5.18; 95% CI: [3.49–6.87]). The negative association remained significant in the adjusted model II and model III (OR = 3.40; 95% CI: [1.91–4.90]; OR = 1.50; 95% CI: [0.12–2.89]).
Table 2
Association between Sarcopenia and Cognitive Performance

| Exposure | β (95% CI), P value* |
|----------|----------------------|
|          | Model 1<sup>a</sup> | Model 2<sup>b</sup> | Model 3<sup>c</sup> |
|          | n = 2550             | n = 2550             | n = 2550             |

Sarcopenia (ALM<sub>BMI</sub>)<sup>d</sup>

|        | Model 1<sup>a</sup> | Model 2<sup>b</sup> | Model 3<sup>c</sup> |
|--------|----------------------|----------------------|----------------------|
| Yes    | reference            | reference            | reference            |
| No     | 5.18 (3.49, 6.87) < 0.0001 | 3.40 (1.91, 4.90) < 0.0001 | 1.50 (0.12, 2.89) 0.0333 |

Alternate Sarcopenia (ALM-only) <sup>e</sup>

|        | Model 1<sup>a</sup> | Model 2<sup>b</sup> | Model 3<sup>c</sup> |
|--------|----------------------|----------------------|----------------------|
| Yes    | reference            | reference            | reference            |
| No     | 3.92 (2.38, 5.45) < 0.0001 | 2.26 (0.82, 3.70) 0.0021 | 1.48 (0.15, 2.82) 0.0293 |

Note:

<sup>a</sup> Model 1, no covariate was adjusted;

<sup>b</sup> Model 2, adjusted for gender, age and race;

<sup>c</sup> Model 3, adjusted for gender, age, race, poverty income ratio, comorbidity index, educational level, physical activity and smoking status.

<sup>d</sup> Sarcopenia: using the FNIH ALM adjusted for BMI(ALM<sub>BMI</sub>) definition.

<sup>e</sup> Alternative Sarcopenia: using the FNIH ALM-only definition.

*p < 0.05

We used a weighted generalized additive model (GAM) and smooth curve fitting (penalized spline method) to find the nonlinear relationship between sarcopenia and DSST scores. The result was negative which suggested that there was no nonlinear relationship between exposure and outcome variable in this research (Fig. 1).

In addition, to ensure the robustness of data analysis, we conducted sensitivity analysis by assessing the association between alternative sarcopenia and cognitive performance. The effect sizes were also shown in Table 2. In model 3, with all the covariates were adjusted, participants without alternate sarcopenia were still associated with better cognitive performance (2.06 DSST scores higher).

Subgroup Analysis
We conducted interaction test with all covariates presented in Table 1. The results were shown in Table 3 (sarcopenia as exposure) and Supplement Table 2 (alternate sarcopenia as exposure). We did not detect the significant interaction for the correlation on sarcopenia and DSST scores, which indicated that participants without sarcopenia were associated with better cognitive performance was similar in different gender, age, race, poverty income ratio, comorbidity index, educational level, physical activity and smoking status.
|                      | Hierarchical analysis | Interaction test |
|----------------------|-----------------------|------------------|
|                      | n     | β (95%CI), P value* | P interaction |
| Gender               |       |                   | 0.9962         |
| Female               | 1299  | 1.17 (-0.91, 3.25) | 0.2711         |
| Male                 | 1251  | 1.21 (-0.61, 3.03) | 0.1923         |
| Race                 |       |                   | 0.7696         |
| Mexican American     | 511   | 0.22 (-2.59, 3.03) | 0.8783         |
| Other Hispanic       | 97    | 4.21 (-1.20, 9.62) | 0.1312         |
| Non-Hispanic White   | 1512  | 2.03 (0.34, 3.72)  | 0.0186         |
| Non-Hispanic Black   | 376   | -2.55 (-10.08, 4.99)| 0.5084         |
| Other Race           | 54    | 0.59 (-12.83, 14.01)| 0.9319         |
| Age                  |       |                   | 0.5358         |
| < 70                 | 1224  | 0.91 (-1.34, 3.17) | 0.4258         |
| ≥ 70                 | 1326  | 1.70 (-0.11, 3.50) | 0.0656         |
| Education level      |       |                   | 0.6719         |
| Less than high school| 943   | 0.51 (-1.67, 2.69) | 0.6454         |
| High school or GED General educational development | 589 | 3.08 (0.20, 5.96) | 0.0366 |
| Above high school    | 954   | 0.73 (-1.58, 3.04) | 0.5341         |
| Unknown              | 64    | 4.08 (-6.16, 14.32)| 0.4390         |

Note:

*p < 0.05
|                                | Hierarchical analysis | Interaction test |
|--------------------------------|-----------------------|------------------|
| Poverty income ratio (PIR)     |                       | 0.1205           |
| Below poverty (<1)             | 344                   | 1.99 (-1.57, 5.55) 0.2734 |
| Above poverty (>1)             | 1903                  | 0.43 (-1.15, 2.01) 0.5937 |
| Unknown                        | 303                   | 4.05 (-0.39, 8.49) 0.0750 |
| Comorbidity index              |                       | 0.0815           |
| 0                               | 970                   | 3.78 (1.39, 6.18) 0.0020 |
| 1                               | 882                   | 0.45 (-1.69, 2.59) 0.6809 |
| ≥ 2                             | 586                   | -1.76 (-5.12, 1.60) 0.3052 |
| Unknown                        | 112                   | -0.17 (-6.69, 6.35) 0.9590 |
| Physical activity              |                       | 0.3789           |
| Less than moderate             | 1405                  | 1.62 (-0.37, 3.61) 0.1117 |
| Moderate                       | 836                   | 0.52 (-1.96, 2.99) 0.6823 |
| Vigorous                       | 467                   | 3.14 (-0.82, 7.10) 0.1204 |
| Unknown                        | 267                   | -2.33 (-7.10, 2.44) 0.3400 |
| Smoking status                 |                       | 0.1663           |
| Never                          | 1187                  | 2.59 (0.52, 4.66) 0.0145 |
| Former                         | 1099                  | -0.91 (-2.91, 1.10) 0.3748 |
| Current                        | 259                   | 2.71 (-1.90, 7.32) 0.2505 |
| Unknown                        | 5                     | -                |

Note:

*p < 0.05
Discussion

This study investigated the association between sarcopenia and cognitive performance by analyzing nationally representative samples from the NHANES. The results indicated that after adjusting all the other factors, participants without sarcopenia were associated with better cognitive performance. In addition, the association would not be influenced by different covariates either.

Sarcopenia and cognitive performance were thought to have many risk factors in common. Firstly, age-dependence is one of their biggest common characteristics. They were both associated with the aging process, and they were more common in the elderly\[9, 19\]. A research proposed that physical decline was thought to be associated with future cognitive decline\[20\], which might suggest that there was a possible association between sarcopenia and cognitive performance for sarcopenia could influence the elders’ physical activity. There was also biological evidence to support this hypothesis. A decline in physical activity could lead to lower serum levels of and Growth hormone (GH), insulin-like growth factor-1 (IGF-1) brain-derived neurotrophic factor (BDNF). GH and IGF-1 could help sustain a proper brain function\[21\], and BDNF played an important role in the development and maintenance of nervous systems\[22, 23\].

Many researchers have tried to explore the connection between sarcopenia and cognitive performance, but there is still no definite conclusion. Some researches proposed that sarcopenia was associated with an increased risk of cognitive impairment\[8, 11, 12\], while the results of some studies indicated that there was no significant association between them\[13, 14\]. Our findings provided strong evidence for the effect of sarcopenia on cognitive performance, which might help to further explore the association between sarcopenia and cognitive performance.

In subgroup analysis, the interaction test with all presented covariates did not show statistical significance for the correlation on sarcopenia and DSST scores, which meant that participants without sarcopenia were associated with better cognitive performance was similar in different gender, race, age, education level, poverty income ratio, comorbidity index, physical activity and smoking status. Although age was a common risk factor for both sarcopenia and cognitive performance, we did not observe the significant interaction on age, which might be due to insufficient sample size.

As we mentioned before, in this research, we defined sarcopenia by ALM adjusted for BMI (ALM\(_{\text{BMI}}\)) and defined alternative sarcopenia by ALM-only. We explored the association between sarcopenia and cognitive performance and took sensitive analysis to explore the association between alternative sarcopenia and cognitive performance. The negative association was observed in both two kinds of FNIH sarcopenia definition. However, in model 3, after adjusted all presented covariates, the effect of alternative sarcopenia on cognitive performance was more significant than the effect of sarcopenia. The FNIH recommended that ALM adjusted for BMI (ALM\(_{\text{BMI}}\)) should be used over ALM-only, due to the effect of body composition on muscle function\[2\]. Therefore, the results of sarcopenia were thought to have more clinical significance and reference value.
There are some strengthens in the present study. Firstly, our research was conducted based on the NHANES. All data in the NHANES were collected with standardized processes and protocols. Therefore, our sample could represent the U.S. population well. In addition, our analysis was adjusted for many covariates including sociodemographic information, health states and lifestyles, to ensure our results are representative and could be applied to a wider range of people. Furthermore, we used GAM model to address nonlinearity and took sensitive analysis to compare two kinds of FNIH sarcopenia definition. However, there were still some limitations in our study. As the research is cross-sectional study, the presented associations are based on a point in time, so that it could not provide sufficient evidence for the causal inference and temporal relation. Besides, the dataset also has a limited set of survey variables. The NHANES does not collect muscle strength data, which is an important element to assess sarcopenia. The cognitive performance was only assessed by Digit Symbol Substitution Test (DSST), version of the WAIS III in the NHANES from 1999 to 2002. Although DSST has high sensitivity, it could not thoroughly evaluate the cognitive function of individuals. And only individuals whose age was above 60 took DSST, which led to a reduction in the number of samples and we could not analyze the association between sarcopenia and cognitive performance from a broader age.

In conclusion, our research suggested that participants without sarcopenia were associated with better cognitive performance in a representative sample of older adults in the U.S. Although the relationship between sarcopenia and cognitive performance needs to be further explored, we might be able to try to improve cognitive performance by dealing with sarcopenia and provide opportunity for intervention at a younger age.

Abbreviations List

ALM, appendicular lean mass; BDNF, brain-derived neurotrophic factor; CDC, the Centers for Disease Control and Prevention; CRP, C-reactive protein; DSST, Digit Symbol Substitution Test; FNIH, The Foundation for the National Institutes of Health; GH, Growth hormone; IGF-1, insulin-like growth factor-1; LLM, low lean mass; MCI, mild cognitive impairment; NCHS, the National Center for Health Statistics; NHANES, the National Health and Nutrition Examination Surveys; PIR, poverty income ratio; WAIS III, Wechsler Adult Intelligence Scale, Third Edition

Declarations

Statement of Authorship

The authors’ contributions were as follows—JG, LD and SQ designed research; LD, SQ and HB analyzed data; JG and SQ wrote the paper; YC and YL assisted in data analysis; JL, ZQ and QY assisted in manuscript preparation; BD and BS had primary responsibility for final content, and all authors: read and approved the final manuscript.
Funding Sources

This work was supported by the National Natural Science Foundation of China (grant numbers 81902578), Post-doctoral Science Research Foundation of Sichuan University (grant number 2020SCU12041), Post-Doctor Research Project, West China Hospital, Sichuan University (grant number 2018HXBH085), the State Key Research Program of China (grant number 2016YFC1103003), the Key Project of Research and Development of Science and Technology Department of Sichuan Province (grant number 2018FZ0102) and the World-Class University Construction Foundation of Sichuan University (grant number 2040204401012).

Acknowledgements

We thank the volunteers for their participation, gratefully acknowledge the staff of the NHANES (the National Health and Nutrition Examination Surveys) for their involvement in this study and Dr. Changzhong Chen, Chi Chen, Xing-Lin Chen (EmpowerStats X&Y Solutions, Inc, Boston, MA) for providing statistical methodology consultation.

Conflicts of interest

None.

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Figures
Figure 1

Relationship between Sarcopenia and Cognitive Performance. Risk of Cognitive Performance (red) with 95% CIs (blue) determined using the generalized additive model.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement.docx