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# Physical Activity and Cognitive Function among Older Adults with an Elevated Gamma Gap

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## Significance of the Study

- This novel study demonstrates that an elevated gamma gap is associated with worse cognition, and that among subjects with an elevated gamma gap, those who are physically active have greater cognition.

## Keywords

Cognition · Elderly · Epidemiology · Exercise

## Abstract

**Objective:** An elevated gamma gap is indicative of high serum concentrations of globulin proteins, some of which elicit acute inflammatory responses. An impaired cognitive function has been linked to central and peripheral inflammation, while exercise is associated with protective, anti-inflammatory benefits. In this study, we evaluated whether the gamma gap is associated with cognitive function among older adults and whether physical activity is favorably associated with cognitive function among those with an elevated gamma gap. **Materials and Methods:** Data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) were used to identify 2,352 older adults aged between 60 and 85 years. The gamma gap was evaluated by subtracting albumin from total protein, i.e., gamma gap =

total protein (g/dL) – albumin (g/dL). Those at or above 3.1 g/dL (31.0 g/L) were considered to have an elevated gamma gap. The Digit Symbol Substitution Test (DSST) was used to assess cognitive function tasks of pairing and free recall among participants. Participants were asked open-ended questions about participation in leisure-time physical activity over the previous 30 days. **Results:** Those with an elevated gamma gap (DSST, 44.8) had a lower cognitive function score when compared to those without an elevated gamma gap (DSST, 50.1) ( $p < 0.001$ ). After adjustments, and among those with an elevated gamma gap, those meeting the moderate-to-vigorous intensity physical activity (MVPA) guidelines (vs. not meeting them) had a DSST score of 6.42 units higher ( $\beta = 6.42$ , 95% CI 3.85–8.99,  $p < 0.001$ ). **Conclusion:** In this national sample of older adults, the gamma gap was associated with cognitive function, and among those with an elevated gamma gap, meeting the physical activity guidelines was associated with a higher cognitive function. Relevant clinical implications are discussed, as the gamma gap

may be predictive of the risk for early mortality and reduced quality of life. Experimental work is needed to investigate whether physical activity training programs are effective in reducing an elevated gamma gap and preserving optimal cognitive functioning among at-risk individuals.

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## Introduction

The gamma gap is known as the globulin fraction, an indicator for cardiovascular risk factors [1] associated with morbidity and mortality [2]. Globulins are dissolved plasma proteins, clinically measurable in plasma serum concentrations. The gamma gap is calculated by subtracting albumin (g/dL) from total plasma protein concentration (g/dL) [3]. The globulin fraction is divided into four separate fractions,  $\alpha_1$ ,  $\alpha_2$ ,  $\beta$ , and  $\gamma$ , which are classified according to their migratory sequence during electrophoresis. An increase in plasma globulin proteins results in an elevated globulin fraction, usually due to changes in immunoglobulin content [3].  $\beta$  and  $\gamma$  globulins may be higher in chronic disease states, such as diabetes or heart disease. These globulin proteins are significant determinants of acute inflammatory responses [4]. In addition, pathogenic states characterized by infection, plasma cell malignancy, as well as varied autoimmune disorders that often exhibit elevated immunoglobulin and albumin-independent protein content may all be predictive of an increased gamma gap [5]. An elevated gamma gap has been associated with all-cause mortality in nonclinical populations, with inflammation compromising sufficient albumin production, and subsequently promoting an increased serum C-reactive protein level, a likely mechanism for significant health complications and/or early mortality [5]. An impaired cognitive function has been linked to central and peripheral inflammation [6]. The globulin proteins, characteristic of a gamma gap elevation, are positively associated with inflammation, contributing to the likelihood for those with an elevated gamma gap to be at a higher risk for cognitive dysfunction. Previous work has further detailed and described this gamma gap [2, 7, 8].

To our knowledge, no study has specifically evaluated the effect of an elevated gamma gap on cognitive function among the elderly. Based on the current understanding of the gamma gap, and its role in inflammatory disease processes [4, 9], it is conceivable that those with an elevated gamma gap would have a diminished cognitive function,

and that physical activity may offer a protective effect among those with an elevated gamma gap. Exercise is associated with numerous health outcomes [10] and has been shown to elicit protective, anti-inflammatory benefits [11, 12], which could potentially have a moderating effect on inflammatory-based cognitive dysfunction in individuals with an elevated gamma gap. Thus, the purpose of this study was to (1) determine whether the gamma gap is associated with cognitive function, and (2) evaluate whether meeting physical activity guidelines (150 min of moderate-to-vigorous intensity physical activity [MVPA] per week) [13] is favorably associated with cognitive function among older adults with an elevated gamma gap. Such an investigation will have important public health implications in identifying the potential putative role that physical activity may play in influencing cognition among older adults with an elevated gamma gap.

## Methods

### *Study Design*

Data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) were used. Study procedures were approved by the National Center for Health Statistics ethics review board, with informed consent obtained prior to data collection.

The NHANES is an ongoing survey conducted by the Centers for Disease Control and Prevention that uses a representative sample of noninstitutionalized United States civilians selected by a complex, stratified, and clustered probability design. The multi-stage design consists of 4 stages, including the identification of counties, segments (city blocks), random selection of households within the segments, and random selection of individuals within the households. Further information on NHANES methodology and data collection is available on the NHANES website (<http://www.cdc.gov/nchs/nhanes.htm>).

### *Gamma Gap*

Using the Hitachi Model 704 multichannel analyzer, the gamma gap was evaluated by subtracting albumin (bromocresol purple reagent using the Beckman Synchron LX20) from total protein (colorimetric assay using the Beckman Synchron LX20), i.e., gamma gap = total protein (g/dL) – albumin (g/dL). As in previous reports [2, 7, 8], those at or above 3.1 g/dL (31.0 g/L) were considered to have an elevated gamma gap.

### *Cognitive Function*

The Digit Symbol Substitution Test (DSST) was used to assess cognitive function [14–16], which was administered to adults over 60 years of age. The DSST, a component of the Wechsler Adult Intelligence Test and a test of visuospatial and motor speed-of-processing, has a considerable executive function component and is frequently used as a sensitive measure of frontal lobe executive functions [17]. The DSST was used to assess participant cognitive function tasks of pairing (each digit, 1–9, has a symbol it is associated with) and information processing. Participants were asked to

**Table 1.** Weighted characteristics of the study variables among a national sample of adults with and without an elevated gamma gap according to 1999–2002 NHANES data

Variables	Normal gamma gap ( <i>n</i> = 1,230)	Elevated gamma gap ( <i>n</i> = 1,121)	<i>p</i> value
Mean DSST	50.1 (48.5–51.7)	44.8 (42.9–46.0)	<0.001
Mean age, years	69.5 (68.94–70.13)	70.4 (69.58–71.27)	0.03
Mean energy intake, kcal	1,862.7 (1,809.59–1,915.84)	1,701.2 (1,642.94–1,759.5)	<0.001
Mean A1C level, %	5.6 (5.61–5.75)	5.9 (5.85–6.0)	<0.001
Mean hypertension, %	46.0 (0.43–0.50)	53.0 (0.49–0.51)	0.01
White race, %	89.7 (0.87–0.92)	75.0 (0.69–0.81)	<0.001
Female gender, %	52.0 (0.50–0.55)	59.0 (0.56–0.61)	0.002
Current smoker, %	12.0 (0.10–0.13)	14.0 (0.10–0.13)	0.22
Meeting MVPA guidelines, %	42.0 (0.36–0.47)	31.0 (0.26–0.35)	<0.001
Overweight/obese, %	69.0 (0.64–0.73)	72.0 (0.68–0.76)	0.18

Values are point estimates with 95% CI in parentheses. A1C, glycated hemoglobin; DSST, Digit Symbol Substitution Test; MVPA, moderate-to-vigorous physical activity.

draw as many symbols as possible that were paired with numbers within 2 min. Following the standard norm-referenced scoring method, one point is given for each correctly drawn and matched symbol, and one point is subtracted for each incorrectly drawn and matched symbol, with a maximum score of 133.

#### Physical Activity

As described elsewhere [18], participants were asked open-ended questions about participation in leisure-time physical activity over the previous 30 days. Data was coded into 48 activities, including 16 sports-related activities, 14 exercise-related activities, and 18 recreational-related activities. For each activity, Metabolic Equivalent of Task (MET)-min-month was calculated by multiplying the number of days, by the mean duration, by the respective MET level (MET-min-month = days•duration•MET level). Those at or above 2,000 MET-min-month (equivalent to 150 min/week) were defined as physically active.

#### Covariates

For all models, covariates included age, gender, race/ethnicity (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other), self-reported smoking (yes/no), energy intake (kcal, continuous), physician-diagnosed hypertension (yes/no), weight status (overweight/obese [measured body mass index or higher] vs. normal weight), and glycated hemoglobin (% continuous).

Participants were classified as smokers if they self-reported smoking every day or some days; otherwise, they were classified as nonsmokers. Previous research demonstrates evidence of validity for self-reported smoking assessment [19]. Energy intake (kcal) was assessed from the mobile examination center interview, per NHANES guidelines, and the follow-up telephone interview. The average of these values was used. If data were missing from the telephone interview, only energy intake obtained from the mobile examination center was used. Glycated hemoglobin was determined from the Primus instrument, which is a fully automated glycohemoglobin analyzer that utilizes the principle of boronate affinity high-performance liquid chromatography.

#### Analysis

All statistical analyses, computed in Stata (v. 12), accounted for the complex survey design employed in NHANES. An adjusted Wald test was used to examine statistical differences for continuous variables among those with and without an elevated gamma gap (Table 1). A design-based likelihood ratio test was used for categorical variables. A weighted multivariable linear regression model was used to examine the association of meeting physical activity guidelines ( $\geq 2,000$  MET-min-month) and cognitive function (outcome variable). Statistical significance was established as an alpha  $< 0.05$ .

#### Results

The analyzed sample included 2,352 older adults (60–85 years). Among these, 1,121 had an elevated gamma gap (3.1–6.3 g/dL) and 1,230 did not (2.0–3.0 g/dL). Characteristics of the study variables, stratified by the gamma gap status, are displayed in Table 1. Those with an elevated gamma gap, compared to those without, had a worse DSST score (44.8 vs. 50.1). This was even further accentuated among those with a more severe gamma gap. For example, when comparing those with a gamma gap level of  $> 4.0$  g/dL to those with a level of  $< 3.0$  g/dL, respectively, the mean DSST scores were 35.7 versus 50.1. As shown in Table 1, other differences emerged when comparing those with and without an elevated gamma gap. Those with an elevated gamma gap were older, had a lower energy intake, had a higher A1C level, were more likely to be hypertensive, were more likely to be a minority, were more likely to be female, and were less likely to meet the MVPA guidelines. Notably, there were no differences in

**Table 2.** Association between meeting physical activity guidelines and cognitive function among those with and without an elevated gamma gap

	Normal gamma gap ( <i>n</i> = 1,230)			Elevated gamma gap ( <i>n</i> = 1,121)		
	$\beta$	95% CI	<i>p</i> value	$\beta$	95% CI	<i>p</i> value
Meeting MVPA guidelines vs. not	5.40	3.10, 7.71	<0.001	6.42	3.85, 8.98	<0.001
Covariates						
Age, 1-year increase	-1.0	-1.11, -0.9	<0.001	-0.78	-0.91, -0.64	<0.001
Female vs. male	5.27	2.71, 7.84	<0.001	5.05	2.11, 8.00	0.001
Race/ethnicity						
Mexican American vs. white	-14.5	-18.1, -10.9	<0.001	-15.2	-19.0, -11.5	<0.001
African American vs. white	-16.4	-20.8, -12.0	<0.001	-14.4	-17.3, -11.6	<0.001
Other vs. white	-10.2	-16.5, -3.9	0.003	-12.4	-18.2, -6.7	<0.001
Nonsmoker vs. smoker	1.3	-1.7, 4.4	0.37	5.0	1.3, 8.6	0.009
Energy intake, 1-kcal increase	0.001	0.00007, 0.003	0.04	0.001	-0.0005, 0.003	0.14
A1C level, 1% increase	-2.2	-3.2, -1.3	<0.001	-1.3	-2.3, -0.43	0.006
Overweight/obese vs. not	0.29	-2.7, 3.3	0.84	0.16	-3.0, 3.3	0.91
Hypertension vs. not	-2.3	-4.2, -0.5	0.01	-2.8	-5.9, 0.16	0.06

Two multivariable linear regression models were computed: one for those with a normal gamma gap (<3.1 g/dL) and one for those with an elevated gamma gap ( $\geq 3.1$  g/dL). In both models, covariates included age, gender, race/ethnicity, smoking status, energy intake, A1C level, weight status, and hypertension status. MVPA, moderate-to-vigorous physical activity.

smoking status and weight status among those with and without an elevated gamma gap.

Table 2 displays the weighted multivariable linear regression results among those with and without an elevated gamma gap. Those meeting the MVPA guidelines and not having an elevated gamma gap had a DSST score of 5.4 units higher than their counterparts not meeting the MVPA threshold ( $\beta = 5.40$ , 95% CI 3.10–7.71,  $p < 0.001$ ). Those meeting the MVPA guidelines and having an elevated gamma gap had a DSST score 6.42 units higher than their counterparts not meeting the MVPA threshold ( $\beta = 6.42$ , 95% CI 3.85–8.98,  $p < 0.001$ ).

## Discussion

The gamma gap is an important clinical measure, as it is useful in the differential diagnosis of chronic diseases associated with physical inactivity and inflammation [7]. The deleterious inflammatory consequences of an elevated gamma gap may potentially influence both physical and cognitive parameters. Previous studies have examined the effects of an elevated gamma gap on cognitive function. Klimkowitz et al. [20] found that increased serum  $\gamma$ -globulin concentrations are an independent hematological marker of cognitive decline among elderly, prestroke dementia patients. Moreover, expansion of the

gamma gap may be a function of senescence. Studies on mice and nonhuman primates suggest that autoimmunity may be proliferated in old age, contributing to progressive cognitive dysfunction via neural degeneration [21]. In this context, autoimmune responses are stimulated by globulin-mediated antibody formation [22]. These antibodies appear to have an increased affinity to neuronal binding sites within the aging brain [23]. This evidence is a cause for concern, as health status, quality of life, and all-cause mortality may be significantly diminished by the risks associated with an elevated gamma gap.

To our knowledge, no study has previously evaluated the direct association between the gamma gap and cognitive function and whether physical activity is favorably associated with cognitive function among those with an elevated gamma gap. However, many studies have examined potential relationships between physical activity and cognitive function [24–28]. Hamer and Chida [26] identified 16 prospective studies that investigated the proposed inverse association between physical activity and cognitive decline. Various analyses point to regular physical activity as a crucial mediator in controlling blood pressure, cholesterol, and the accumulation of proinflammatory cytokines [29], which may impede neural signaling pathways [26, 27]. Therefore, our present study adds to the research and supplies a clearly defined explanation of physical activity frequency and duration, which has

been lacking in previous experiments. We found that adequate physical activity levels may attenuate negative neurocognitive outcomes among older individuals with an elevated gamma gap. Indeed, our results demonstrate that those with an elevated gamma gap had worse cognitive function when compared to those with a normal gamma gap. Furthermore, those with an elevated gamma gap who met physical activity guidelines had greater cognitive function when compared to their less active counterparts.

The need for tailored physical activity programs for older adults is of critical importance. Modifiable risk factors for morbidity and mortality increase with age and are manifest among older populations [30, 31]. Moreover, the globulin fraction has been shown to increase in old age [32], while optimal cognitive function may be impaired [33]. Our results are suggestive of a possible inverse relationship between age-associated increases in the gamma gap and insufficient physical activity levels. Furthermore, our findings demonstrate a positive association between physical activity and cognitive function among those with an elevated gamma gap. We have also demonstrated that older age, race/ethnicity minority status, hypertension, and A1C level increase were significantly associated with lower cognitive function among individuals with a normal gamma gap, as well as those with an elevated gamma gap. Female gender and increased energy intake were significantly associated with improved cognitive functioning for those with a normal gamma gap, while female gender and nonsmoking status were significantly related to improved cognition among participants with an elevated gamma gap. Collectively, these results are of clinical importance for medical professionals and exercise physiologists aiming to improve physical and mental outcomes for the elderly.

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This study is not without limitations, which include the subjective assessment of physical activity and cross-sectional design. In addition, this study utilized participant responses to a single cognitive task (DSST), which may not necessarily be generalizable to other cognitive domains. Cognitive impairment associated with an elevated gamma gap in older adults may also limit the validity of self-report data although we do not believe that a mild level of cognitive impairment associated with aging would affect the ability of participants to accurately respond to interview questions. Nevertheless, there is a possibility that this level of cognitive dysfunction may attenuate self-report accuracy for some aging individuals evaluated for this study. Notable strengths include the national sample and study novelty. Thus, future prospective work on this topic using an objective measure of physical activity is warranted.

## Conclusions

This study has important clinical implications, as the gamma gap may be predictive of the risk for early mortality and reduced quality of life. Future work is also needed to examine the extent to which the observed differences in cognition in the present sample are clinically meaningful differences. Clinicians and health professionals may look at prescribing safe and tailored physical activity participation as a potential strategy to offset or mitigate the deleterious effects of gamma gap inflation during older age. However, experimental work is needed to investigate whether physical activity training programs are efficacious in meaningfully reducing an elevated gamma gap and preserving optimal cognitive functioning among at-risk individuals.

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