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Original Article

Genetic Variation in *FOXO3* is Associated with Self-Rated Health in a Population-Based Sample of Older Individuals

Anna Zettergren, PhD,[1,*] Silke Kern, MD, PhD,[1,2] Lina Rydén, MD,[1] Svante Östling, MD, PhD,[1] Kaj Blennow, MD, PhD,[2,3] Henrik Zetterberg, MD, PhD,[2,3,4] Hanna Falk, PhD,[1,†] and Ingmar Skoog, MD, PhD[1,†]

[1]Neuropsychiatric Epidemiology Unit, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, Centre for Ageing and Health (AgeCap) at the University of Gothenburg, Sweden. [2]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden. [3]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Sweden. [4]Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK.

*Address correspondence to: Anna Zettergren, PhD, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology at the Sahlgrenska Academy, University of Gothenburg, Wallinsgatan 6, 43141 Mölndal, Sweden. E-mail: anna.zettergren@neuro.gu.se

[†]These authors contributed equally to this work.

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Abstract

Self-rated health (SRH) strongly predicts mortality. Twin studies estimate that genetic factors account for a substantial part of the variability in SRH. Variations in the gene *FOXO3* (forkhead box O3), and in genes located at the *APOE* (apoplipoprotein E) locus, are associated with longevity. This study explores the relationship between SRH and genetic variation related to longevity, in a population-based cohort of older individuals. SRH was assessed among 1,520 individuals aged 75–87, and five single nucleotide polymorphisms (SNPs), in *APOE*, *TOMM40* (translocase of outer mitochondrial membrane 40 homolog), and *FOXO3* were genotyped. Two SNPs (rs10457180 and rs2802292) in *FOXO3* were associated with SRH (OR = 2.18 [CI: 1.27–3.76], p = .005 and OR = 1.63 [CI: 1.11–2.40], p = .013), while no associations were found with SNPs in *APOE* and *TOMM40*. Several factors, such as depression, cardiovascular disease (CVD), and diabetes, were related to SRH, but the only factor that had any influence on the association with *FOXO3* was CVD. Still, after including CVD as a covariate, the associations between *FOXO3* SNPs and SRH remained significant. Our results suggest that *FOXO3* is related to SRH in older individuals. This relationship seems to be influenced by CVD, but not by mental and cognitive status.

Keywords: Longevity, Single nucleotide polymorphism, Cardiovascular disease, Dementia, Depression.

Self-rated health (SRH) is the individuals' subjective perception of their general health (ie, responses to the question "How do you rate your overall health?"), with response options ranging from "excellent" to "poor". This seemingly simple question has been one of the most frequently employed health indicators in research since the 1950s, and despite its subjective nature, it has been found to be a strong predictor of mortality (1,2). Important domains known to influence SRH, and subsequent mortality, include chronic illness, depression, cognitive function, socioeconomic status, functional impairment, and physical activity (3–6).

Twin studies estimate that genetic factors account for a substantial part of the variability (25–64%) in SRH (7–9). One of the few molecular genetic studies of SRH presented so far is a large genome-wide association study (GWAS) of individuals aged 37–73 years (10). This study reported the strongest associations with a single nucleotide polymorphism (SNP) close to the gene *KLF7* (kruppel-like factor 7), previously associated with obesity and diabetes, and with SNPs located in the major histocompatibility complex (MHC) region, which is of importance for the immune system. Another GWAS, including individuals aged 18–92 years, suggested that genes (ie, *MAML2*, *PROM1*, and *PROC*) related to a variety of health-related conditions, such as inflammation, coronary heart disease, cardiovascular disease (CVD), thrombosis, and protein C deficiency

[for refs see Mosing *et al.* (11)], might be of importance for SRH. A study performed in the oldest old, including SRH as a secondary outcome, showed an association with the gene *MnSOD*, encoding the antioxidant enzyme Manganese superoxide dismutase (12).

Since SRH strongly predicts mortality, it can be hypothesized that genetic factors of importance for longevity may be related to SRH as well. Genes repeatedly associated with longevity have been those located at the core of the *APOE* (apolipoprotein E) locus [*APOE, TOMM40* (translocase of outer mitochondrial membrane 40 homolog), and *APOC1* (apolipoprotein C-1)] (13–16), and the *FOXO3* (forkhead box O3) gene (16–20). The *APOE* gene is involved in lipid metabolism and has been associated with several aging phenotypes, particularly dementia and CVD (21,22). The genes *TOMM40* and *APOC1* have, similar to *APOE*, been associated with dementia (ie, Alzheimer's disease) (23). Genetic variations in *TOMM40* and *APOC1* are linked to variation in *APOE* (23,24), and positive association signals of markers in these genes are often an effect of LD (linkage disequilibrium) with the *APOE* ε4 allele. The gene *FOXO3* is part of the insulin/insulin-like growth factor 1 signaling pathway, and belongs to a family of transcription factors known to be of importance for several biological processes, such as apoptosis, DNA repair, oxidative stress, cell differentiation, and glucose metabolism (25).

Genes at the *APOE* locus and the gene *FOXO3* show well-established associations with longevity. The aim of this project was to explore the relationship between SRH and genetic variation related to these genes, in a population-based cohort of older individuals aged 75–87.

Methods

Study Sample

Participants in the study originate from three epidemiological studies in Gothenburg, Sweden; the Prospective Population Study of Women (PPSW) and the Gerontological and Geriatric Population Studies (H70 and H85), which have been described in detail previously (26–30). The participants were sampled from the Swedish Population Register on the basis of birth date. The present study is based on examinations in 2005 of individuals born in 1918, 1922, and 1930 (PPSW and H70), and examinations in 2009 of individuals born in 1923–24 (H85). Adults living in private households and in residential care were included. Examinations were done at an outpatient department or in the participants' home. In 2005, there were 1,715 eligible individuals and 1,131 agreed to participate (response rate 66%). Among these participants, 1,051 (93%) answered the question about SRH, and 1,022 of these individuals agreed to take part in genetic analyses. In 2009, there were 944 eligible individuals and 571 agreed to participate (response rate 60%). Among the participants this year, 533 (93%) answered the question about SRH, and 498 of those agreed to take part in genetic analyses. The study was approved by the Regional Ethical Review Board in Gothenburg, and written informed consent was obtained from all participants and/ or their relatives in cases of dementia.

Examinations and Diagnoses

Clinical examinations included comprehensive social, functional, physical, neuropsychiatric, and neuropsychological examinations, as well as close informant interviews (28). SRH was assessed using the question "How do you rate your overall health", with response options ranging from very good to very poor. All examinations were carried out by health professionals, such as nurses or physiotherapists. Dementia was diagnosed by geriatric psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders 3rd Edition Revised (DSM-III-R) (31), based on symptoms rated during the neuropsychiatric examinations and information from the close informant interviews, as described previously (32,33). Cognitive function was also measured with the Mini-Mental State Exam (34). Major and minor depression were diagnosed based on the neuropsychiatric examination according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) (35) criteria for minor depression, and Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) (36) for major depression. Cardiovascular disease was defined as angina pectoris according to the Rose questionnaire (37) or myocardial infarction (MI) according to self-report or ECG criteria (Minnesota code 1-1-1 to 1-2-5 or 1-2-7). Diabetes was diagnosed based on self-report or use of antidiabetic drugs. Activities of daily living (ADL) were assessed according to Katz' index of ADL (38), assessing bathing, dressing, toileting, transfer, and feeding. The score was categorized into "disabled" = could do maximum two items, "moderately disabled" = could do three or four items, and "not disabled" = could do all five items.

SNP Selection and Genotyping

Single nucleotide polymorphisms (SNPs), defined as top-findings in relation to longevity, were selected based on previous literature (13–20,39). The selection criteria were similar to the ones used in the study on longevity by Shadyab *et al.* (40), but only SNPs located in or near genes were included. SNPs chosen for genotyping were: rs7412 and rs429358 in *APOE* (which together define the three *APOE* isoforms ε2, ε3, and ε4), rs2075650 in *TOMM40*, and rs10457180, rs2802292, and rs479744 in *FOXO3*. We chose not to genotype rs4420638 in *APOC1*, since the association between this SNP and longevity is to a large extent explained by LD with the *APOE* ε4 allele (24). Selected SNPs in *FOXO3* included rs10457180, which was the top-finding in a recent study on longevity in the CHARGE Consortium (16), and rs2802292, the original longevity-finding reported for this gene. Among the other seven *FOXO3* SNPs analysed in the study by Shadyab and colleagues, we only genotyped rs479744, since all the others were in high LD ($r^2 > 0.80$) with rs10457180 and/or rs2802292.

Blood samples were collected and DNA was extracted according to standard procedures. The SNPs rs10457180, rs2802292, and rs479744 in *FOXO3* (genomic region: 6q21), and rs2075650 in *TOMM40* (genomic region: 19q13.32) were analyzed with KASPar® PCR SNP genotyping system (LGC Genomics, Hoddesdon, Herts, UK). The SNPs rs7412 and rs429358 in *APOE* (genomic region: 19q13.32) were analyzed with KASPar® PCR SNP genotyping system or by mini-sequencing [as previously described in detail (41)]. The genotyping success rate was >95%; failed for 20 individuals (rs1045718), for 12 individuals (rs2802292 and rs479744), and for no individuals (rs2075650, rs7412, and rs429358). All SNPs were found to be in Hardy–Weinberg equilibrium.

Statistical Analysis

The question concerning SRH had response options ranging from very good to very poor. These options were combined into two categories; good (including very good/good/fairly good), and poor (including very poor/poor/not really good). Individuals who chose the option "neither good or poor" (available in 2005; $n = 182$) were excluded from the analyses. Differences in distribution or mean values of sample characteristics between individuals rating their SRH

as good and poor, were investigated with Fischer's exact test (chi-squared test if more than two categories) or *t*-test, respectively. The distributions of the genotypes of investigated SNPs in relation to SRH were investigated using chi-squared test or Fischer's exact test. Subsequently, findings below a significance level of $p \leq .05$ were analyzed in logistic regression models, where sex and age at examination were preselected covariates. Additional covariates considered as potential confounders were depression (major or minor), dementia, MMSE-score, CVD, diabetes, and ADL-score (0–2). Firstly, we investigated in univariate linear or logistic regression models if these factors were associated ($p \leq .1$) with both the outcome (SRH) and the "exposure" (in this case the gene *FOXO3*). Secondly, factors which fulfilled these criteria (meaning that they could have a possible impact on the association between *FOXO3* and SRH) were included in a multivariate logistic regression model.

Possible associations between the SNPs and longevity (defined as reaching age 90) were investigated in sensitivity analyses performed in a sub-sample consisting of 893 individuals, who had either died or reached age 90 up to June 2016, using logistic regression models adjusted for sex.

Results

Characteristics of the study sample are presented in Table 1. All variables included, except for dementia and MMSE score, were found to be significantly related to SRH. Individuals who rated their health as poor more often had depression, CVD, diabetes, and ADL disability, compared to those who rated their health as good.

The distribution of genotypes of the investigated SNPs in *FOXO3* was found to differ significantly (rs10457180 and rs2802292), or close to significantly (rs479744), between those who rated their health as good and poor (see Table 2). For both rs10457180 and rs2802292, good SRH was associated with carrier ship of two copies of the longevity alleles (the G-alleles). No significant difference in genotype distribution could be seen for the two *APOE* SNPs (rs429358 and rs7412) or the SNP rs2075650 in *TOMM40*.

Table 1. Sample Characteristics.

	Good SRH (n = 935)	Poor SRH (n = 403)	p*
Women, *n* (%)	589 (63.0)	303 (75.2)	≤.0001
Age at exam, mean (*SD*)	79.4 (4.9)	80.5 (5.0)	.0001
Age at death*, mean (*SD*)	87.6 (4.2)	86.6 (4.9)	.01
MMSE-score, mean (*SD*)	26.9 (3.5)	26.8 (3.5)	.55
Dementia†, *n* (%)	102 (10.9)	39 (9.8)	.63
Major depression, *n* (%)	23 (2.5)	61 (15.1)	≤.0001
Minor depression, *n* (%)	113 (12.1)	113 (28.0)	≤.0001
CVD‡, *n* (%)	131 (14.4)	86 (22.8)	.0003
Diabetes, *n* (%)	106 (11.3)	71 (17.6)	.003
ADL: disabled, *n* (%)	31 (3.3)	16 (4.0)	.001
Moderately disabled, *n* (%)	94 (10.1)	70 (17.5)	
Not disabled, *n* (%)	806 (86.6)	315 (78.6)	

Note: ADL = activities of daily living; CVD = cardiovascular disease; SRH = self rated health.

*Among those who rated their health as good 388 have died and among those who rated their health as poor 235 have died up to June 2016. †Ten individuals have a missing value on dementia. ‡Forty-nine individuals have a missing value on CVD. *p values based on Fischer's exact test (Chi-squared test in case of ADL-score) or *t*-test.

The significant associations between the SNPs in *FOXO3* and SRH were further investigated in logistic regression models, based on a dominant genetic model, where carrier ship of the A-allele (AA or AG) of rs10457180, or the T-allele (TT or TG) of rs2802292, were significantly associated with poor SRH (see Table 3). As described, several of the covariates considered were related to SRH (Table 1). However, the only one that was associated ($p \leq .1$) with the *FOXO3* SNPs was CVD (rs10457180: p = .03, OR = 2.1 [CI: 1.08–4.11] for carriers of the A-allele; rs2802292: p = .03, OR = 1.7 [CI: 1.06–2.71] for carriers of the T-allele). After including CVD in the logistic regression model the odds ratios were reduced, but the associations between the SNPs rs10457180 and rs2802292 and SRH remained significant (Table 3).

The total population investigated in this study is not suitable for analyses of longevity, since only 623 of 1,338 individuals have died. Among the 715 who are still alive, 270 have reached an age of 90 years or above (which is a commonly used definition for longevity cases), but whether the other 445 will reach age 90 is still unknown. However, after excluding these 445 individuals, sensitivity analyses of longevity as a dichotomous outcome variable (reaching age 90 or not) showed significant associations, in expected directions, with both *APOE* SNPs, but not with the SNPs in *FOXO3* and *TOMM40* (results not shown).

Since this study is clearly based on a pre-defined hypothesis, the results presented in the tables are not corrected for multiple testing. In addition, the SNPs located in the same gene are not independent of each other, making a Bonferroni correction for analyses of six SNPs very strict. If we correct the results for analyses of three genes, the association between rs10457180 in *FOXO3* and SRH remain significant.

Table 2. Genotype Distribution of Investigated SNPs in Relation to Self-Rated Health.

SNP	Genotype	Good SRH	Poor SRH	Chi-Square	p*
FOXO3		*n* (%)	*n* (%)		
rs10457180	AA	467 (50.8)	217 (54.4)	8.51	**0.014**
	AG	371 (40.4)	165 (41.4)		
	GG	81 (8.8)	17 (4.3)		
rs2802292	GG	135 (14.6)	38 (9.5)	6.71	**0.035**
	TG	441 (47.7)	197 (49.1)		
	TT	349 (37.7)	166 (41.4)		
rs479744	GG	605 (65.3)	270 (67.5)	5.30	0.071
	TG	278 (30.0)	122 (30.5)		
	TT	43 (4.6)	8 (2.0)		
TOMM40		*n* (%)	*n* (%)		
rs2075650	AA	695 (75.5)	294 (75.2)	0.48	0.79
	GA	207 (22.5)	87 (22.3)		
	GG	18 (2.0)	10 (2.6)		
APOE		*n* (%)	*n* (%)		
rs429358	CC	13 (1.4)	7 (1.7)	0.23	0.89
	CT	231 (24.8)	100 (24.9)		
	TT	688 (73.8)	295 (73.4)		
rs7412**	CC	798 (85.6)	351 (87.3)	—	0.44
	CT+TT	134 (14.4)	51 (12.7)		

Note: SRH = self-rated health.

*p values based on Chi-squared test or Fischer's exact test. **For rs7412 very few individuals carried the TT-genotype (five of those with good SRH and two of those with poor SRH) and therefore this genotype was collapsed with the CT genotype.

Table 3. Associations Between *FOXO3* SNPs and Self-Rated Health Analyzed by Adjusted Logistic Regressions

SNP	Good SRH	Poor SRH	OR (95% CI)*	*p**	OR (95% CI)†	*p*†
FOXO3						
rs10457180	*n* (%)	*n* (%)				
AA+AG	838 (91.2)	382 (95.8)	2.18 (1.27–3.76)	**.005**	1.87 (1.08–3.26)	**.025**
GG	81 (8.8)	17 (4.3)				
rs2802292	*n* (%)	*n* (%)				
TG+TT	790 (85.4)	363 (90.5)	1.63 (1.11–2.40)	**.013**	1.53 (1.03–2.28)	**.037**
GG	135 (14.6)	38 (9.5)				

Note: SRH = self-rated health.
*Based on logistic regression adjusted for age and sex. †Based on logistic regression adjusted for age, sex, and cardiovascular disease (CVD).

Discussion

In this study, we found an association between genetic variations in the *FOXO3* gene and SRH among individuals aged 75–87 years, while no association was found between this measure and genetic variations at the *APOE* locus (SNPs located in the genes *APOE* and *TOMM40*). Several factors, such as depression (major and minor), CVD, diabetes, and ADL disability, were related to SRH in the investigated population, but the only factor that had any influence on the association between *FOXO3* and SRH was CVD. Importantly, after including CVD as a covariate in a logistic regression analysis, the associations between SNPs in *FOXO3* (rs20457180 and rs2802292) and SRH were still significant.

So far, there have been quite few studies on genetics in relation to SRH, and none of them are performed on the specific age group included in our study. A large GWAS of SRH in individuals aged 37–73, from the UK Biobank sample, found the strongest associations with SNPs of relevance for obesity, type 2 diabetes, and the immune system (42). Mosing and colleagues performed a GWAS of SRH including Australian individuals aged 18–92 years (11). Although no genome-wide significant findings were reported, two promising regions on chromosome 2 were identified, and some of the top-50 SNPs were located close to genes related to a variety of health-conditions, such as inflammation, CVD, thrombosis, and protein C deficiency. SNPs in the *FOXO3* gene were not among the top-findings in previous GWASs, but the broad age ranges in these studies make them hard to compare with our study including only older individuals. The meaning of good versus poor SRH will probably not be the same for young and old individuals, and genes of importance for this measure may vary between age groups.

The hypothesis in our study was that genes of importance for longevity, often defined as living to age 90 or longer, may be associated with SRH among older individuals below 90 years of age. *FOXO3* was originally identified and replicated in candidate studies of longevity (17–19,38,43), and the finding has been confirmed in meta-analysis of GWAS data from populations of European ancestry, performed by the CHARGE consortium (16). The strongest signal in the study by Broer and colleagues (the CHARGE consortium) was found for the intronic SNP rs10457180, which also showed the strongest association in the present study. Broer *et al.* (16) reported that the A-allele of this SNP was significantly underrepresented among persons who reached 90 years and above, compared to controls who died at age 55–80. In view of the relation between SRH and mortality, this is in line with our result showing that carriers of the A-allele were overrepresented among individuals who rated their health as poor at ages 75–85.

No association between SRH and *FOXO3* was found in a genetic study of aging phenotypes in 1,088 Danes aged 92–93, investigating 15 *FOXO3* SNPs (including rs2802292, rs479744, and several SNPs in high LD (r2>0.95) with rs10457180) (44). One reason could be that the mean age in this study was about 13 years higher than in our study. One can speculate that the association between SRH and *FOXO3,* as seen in our study, disappears in groups with extreme old age, probably as a consequence of a higher rate of mortality among individuals carrying *FOXO3* genotypes related to poor SRH. Alternatively, poor and good health are interpreted in a different way in the oldest-old. Still, it has been shown that individuals reaching an extreme old age (at least 95 years) present more phenotypes linked to healthy aging, such as better SRH, lower prevalence of cancer and CVD, and high physical and cognitive function, compared to average lived individuals (age at death 73–81 years) (17).

FOXO3 SNPs display a high degree of LD. In a recent study, performed in a Japanese American population in Hawaii (45), 41 of 110 genotyped SNPs in *FOXO3* were associated with longevity, and LD analysis on 64 SNPs (those with minor allele frequency ≥0.05) showed that the majority was located within a single haplotype block comprised of four haplotypes. When evaluated in a Caucasian population, the same SNPs were spread over three haplotype blocks. Further, 13 of the SNPs were identified as putative functional variants. All of these variants are in LD with the minor allele of rs2802292 (included among the genotyped SNPs in our study), previously shown to be associated with elevation in *FOXO3* expression in skeletal muscle (46).

The FoxO3 protein has a large number of downstream targets, affecting a wide range of cellular and physiological processes. Therefore, the association between *FOXO3* and SRH may be explained, or influenced, by relations to several phenotypes. Some studies in older populations have shown associations between genetic variation in *FOXO3* and insulin sensitivity, coronary heart disease, stroke, and cardiovascular mortality (17,47–49), while others found associations with bone fractures and ADL impairment (44). In our study, we noted a relation with CVD, but not with diabetes, ADL, depression or cognitive health (results not shown). Still, a lack of association, in our study and others, can arise as a consequence of limited power, but the divergent findings may also be due to varying age of the study populations, or differences in environmental factors between populations. Interestingly, a recent study showed that offspring of individuals with exceptional longevity has a lower prevalence of CVD, independent of lifestyle factors, and nutrition, possibly indicating an association between genetic factors related to longevity and CVD (50).

Previous studies of the relation between SRH and *APOE* reported no association in oldest-old Danes (51), while an association was found in Taiwanese individuals aged 54–91 (52). The SNP rs2075650 in *TOMM40* was not included in any of these studies. However, according to previous studies on longevity, the effect of rs2075650 is most likely mediated through the isoforms of *APOE* (24). Our results are in line with the Danish study, and may be explained by the non-existing association between cognitive status/dementia and SRH in the investigated population. Still, CVD was associated with SRH in the investigated population, and, in addition to being a risk factor for dementia (53), the *APOE* ε4 allele is also a risk-factor for CVD (22). Possibly, the lack of association between variants at the *APOE* locus and SRH is explained by sex-specific effects, since previous studies have reported sex-specific roles of *APOE* variants in survival (54). However, we could not find such effects in our sample (results not shown), and even if they exist we may probably not detect them due to limited power.

Based on sensitivity analyses in a subsample of the total population included in our study, *APOE* was found to be associated with longevity, while *FOXO3* was not. Still, *FOXO3* was associated with SRH in the total population. It is possible that this association is driven by factors weakly related to mortality, but the lack of association between *FOXO3* and longevity in our subsample may also be explained by limited power, or lack of a comparison group consisting of individuals dying at an early age. Another explanation is the age of our sample, since the effect of *FOXO3* on longevity has been reported to increase with age and was strongest when centenarians were compared with younger controls (19). Recent results indicate, however, that the evidence for an effect of the gene on survival beyond the oldest one percentile of age is not compelling (55).

The strengths with this study are the representative population-based cohort, the comprehensive examinations performed by trained psychiatric nurses, and diagnoses made by geriatric psychiatrists. However, the study also has limitations. Self-rated health is a complex phenotype, believed to be influenced by a large number of genetic variants with small effect sizes, and our relatively small sample means limited power to detect such associations. Several studies suggest that SRH may act as a proxy for other factors known to predict health, but the mechanisms responsible for healthy aging, underlying the association between SRH and mortality, are largely unknown (2). In this study, we investigated well-known longevity-genes, but other genes, not related to longevity, may be of similar, or greater, importance for SRH in old individuals. In addition, the response options on the question about SRH varied slightly between the examinations and this might have had an influence on the results. Another possible limitation may be the response rate. Although the response rate was satisfactory in the age groups studied, we cannot exclude the possibility that responders differed from non-responders in SRH and different other health parameters.

In conclusion, our results suggest that genetic variation in *FOXO3*, which belongs to a family of transcription factors of importance for various biological mechanisms, is related to SRH in older individuals aged 75–87. This relationship seems to be influenced by somatic health, more specifically CVD, but not by mental and cognitive status.

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Conflict of Interest

The authors report no biomedical financial interests or potential conflicts of interest.

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