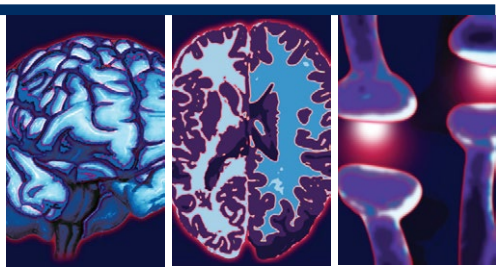

Interactions between Apolipoprotein E Genes and Religiosity in Relation to Mild Cognitive Impairment

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Abstract

Objective

Religion is a social determinant that is positively associated with cognitive function. Several mechanisms have been proposed to explain the link between religion and cognitive function; however, no studies have yet examined the interactions between religion and risk genes. The current study sought to examine the effects of religiosity on cognitive functioning in a large Chinese sample.

Method

A total of 2,410 community residents aged 55 years and older were recruited from the Ningxia province of China. Apolipoprotein E (APOE) gene polymorphisms were detected using the high-resolution melting curve method. The Mini-Mental State Exam and Duke University Religion Index were administered to assess cognitive function and religiosity. The logistic regression model was used to examine the relationships.

Results

Participants with the Ɛ4 allele and without high religiosity had the highest risk of mild cognitive impairment (MCI) (OR=1.95; 95% CI: 1.24-3.07); the synergy index was 0.40 for religiosity and the Ɛ4 allele and was 1.55 for religiosity and the Ɛ2 allele. The logistic regression model revealed a significant negative interaction effect between the Ɛ4 carrier status and high religiosity (OR=0.45; 95% CI: 0.25-0.84).

Conclusion

This study provides the initial evidence of a beneficial modifying effect for religiosity on relationship between the APOE Ɛ4 carrier and MCI, however, further prospective studies are needed to confirm the finding.

Keywords

Apolipoprotein E Genes, Religiosity, Mild cognitive impairment, Interactions, Cognitive function

Introduction

Apolipoprotein E (APOE) is a plasma protein involved in the metabolism of lipoproteins and cholesterol. It plays an important role in the neurobiological system [1]. Human APOE has three isoforms (Ɛ3, Ɛ4, and Ɛ2) due to cysteine-

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arginine interchanges at codons 112 (rs429358) and 158 (rs7412) [2]. The APOE ε4 allele has been widely studied as a risk factor for mild cognitive impairment (MCI) and Alzheimer's disease (AD), and ε2 serves as a protective allele [3-5]. The association between the ε4 carrier status and cognitive impairment has also been demonstrated in Chinese populations [6,7].

Social factors are known to influence cognitive function. Religion as a social determinant of mental health has been demonstrated [8]. Studies have shown that religious attendance is associated with slower rates of cognitive decline among older Mexican Americans, where those who attend religious services more frequently experience a slower rate of cognitive decline [9]. A significant negative association between religious participation and cognitive impairment was also found among the oldest people in China [10]. Different aspects of religion may help to explain the association with cognitive function, including increased social integration [10,11], better behavioral self-control [12], and fewer life event stresses [13,14].

Are there other mechanisms that might help to explain the link between religiosity and cognitive function? Two recent studies have reported that religiosity is associated with greater leukocyte telomere length (TL) [15,16]. TL is also a significant predictor of cognitive function [17,18]. Religiosity may also protect individuals from cognitive dysfunction by modifying the effect of high-risk genes. When Huang, *et al.* found a lower prevalence of Alzheimer's Disease among Tibetans, further analysis revealed that the lower risk may have been due, in part, to the effect of religiosity on genetic factors [19]. Chartier, *et al.* also found that the associations between alcohol dehydrogenase (ADH) enzyme gene variants and alcohol consumption-related phenotypes were modified by the level of religious involvement [20]. These studies suggest that the inverse relationship between religiosity and cognitive dysfunction may be partly explained by an interaction between the risk genes (APOE ε4 allele for example) and cognitive function. To the best of our knowledge, however, no study has yet examined this interaction.

In the current study, we examined the effects of religiosity on cognitive functioning via a Gene × Environment (G×E) paradigm in a large Chinese sample. We hypothesized that associations between APOE gene variants and cognitive impairment would be modified by the level of religiosity (e.g., high-risk gene variants would have a weaker effect on cognitive functioning in those with higher levels of religiosity).

Materials and Methods

■ Subjects

Participants in the present study were acquired from two main resources between May 2013 and July 2015. First, five communities were selected from two cities using a convenience cluster sampling method. Three of those communities were from Yinchuan (the largest city in the Ningxia province), and two were from Wu Zhong (the second largest city in the Ningxia province). A total of 1,022 community residents participated; among whom, 924 completed the questionnaire and provided blood samples for gene variant determination. The full details of the sampling method have been reported elsewhere [7]. Second, 1,612 community residents were recruited from a health care center where physical examinations were conducted in preparation for going on the Hajj (an annual Islamic pilgrimage to Mecca and mandatory for adult Muslims at least once in their lifetime [21]). Among those subjects, 1,486 completed the questionnaire and provided blood samples for gene detection. Thus, 2,410 subjects were included in the final analysis. The inclusion criteria for the study were as follows: (1) permanent residency in Ningxia, (2) aged 55 years or older, (3) the activities of daily living scale scored 21 or below, and (4) agreement to participate. Those who were unable to complete the survey due to vision and hearing disabilities, a history of alcohol consumption, or a history of serious physical illness were excluded.

The demographic characteristics of the participants are displayed in **Table 1**. Subjects were, on average, 64.5 (SD=5.7) years of age, with a range of 55 to 89 years. Slightly more than half (55.8%) were female, and 45.1% had no formal education.

This study was approved by the Institutional Review Board of the Ningxia Medical University (Nos. 2012009 and 2015151). All of the participants provided written informed consent prior to completing the survey.

■ Neuropsychological testing and physical examination

All of the participants underwent a careful physical examination at a health care center to obtain the blood sample for gene analysis and

Table 1: Demographic characteristics.

	Total n=2,410	Community n=924	Hajj# n=1,486	*t/Chi*	*P* value
Age, mean (SD), years	64.5 (5.7)	66.5 (6.8)	63.3 (4.6)	13.74	<0.001
Gender, female, n (%)	1,345 (55.8)	571 (61.8)	774 (52.1)	21.78	<0.001
Education, n (%)					
None	1,086 (45.1)	239 (25.9)	847 (57.0)	288.77	<0.001
Primary school	621 (25.8)	253 (27.4)	368 (24.8)		
Junior high school	438 (18.2)	254 (27.5)	184 (12.4)		
≥Senior high school	265 (11.0)	178 (19.3)	87 (5.9)		
Living status, alone, n (%)	376 (15.6)	187 (20.2)	189 (12.7)	24.46	<0.001
MCI, yes, n (%)	416 (17.3)	181 (19.6)	235 (15.8)	5.68	0.017
MMSE, mean (SD)	23.6 (4.5)	24.3 (4.8)	23.2 (4.3)	5.67	<0.001
GDS, mean (SD)	4.1 (3.9)	5.9 (4.6)	3.0 (2.9)	20.20	<0.001
ADL, mean(SD)	14.9(2.8)	15.4(3.4)	14.2(1.3)	7.95	<0.001
DUREL, mean (SD)	23.1 (5.6)	18.3 (6.5)	26.1 (1.5)	43.78	<0.001
High religiosity, yes, n (%)	1,399 (58.0)	180 (19.5)	1,219 (82.0)	915.42	<0.001
Hypertension, yes, n (%)	1,178 (48.9)	617 (66.8)	561 (37.8)	186.73	<0.001
FPG, abnormal, n (%)	430 (17.8)	237 (25.6)	193 (13.0)	62.31	<0.001
Ɛ4 carrier, yes, n (%)	358 (14.9)	65 (7.0)	293 (19.7)	72.45	<0.001
Ɛ2 carrier, yes, n (%)	350 (14.5)	141 (15.3)	209 (14.1)	0.66	0.418
Ɛ3 carrier, yes, n (%)	1702(70.6)	719(77.7)	983(66.1)	37.03	<0.001
Risk index, mean (SD)	0.00 (0.6)	0.10 (0.55)	-0.06 (0.62)	6.36	<0.001

to review their physical disease and substance abuse history. A face-to-face interview was performed by trained medical students using a structured questionnaire to collect demographic information. One item question "Do you have significant memory decline recently?" asked to identify self-report memory complaint. And the Chinese version Mini-Mental State Exam (MMSE) [22], Activities of Daily Living Scale (ADL) [23], and the Geriatric Depression Scale (GDS) [24] were administered at that time. The Chinese version of the MMSE has high sensitivity (90.8%) and specificity (93%) for detecting significant cognitive impairment in Chinese populations [25]. MCI was diagnosed according to Peterson's criteria [26] with modification as Cui, *et al.* suggested: MMSE was used to assess normal cognitive function instead of verbal memory test. The lower education level in elderly Chinese barred to apply specific verbal memory test (the national population census of year 2010 found that among 60 years old and over, the education level of primary school or below up to 71.4%). The subjects' education level was taken into account when assessing the MMSE scores as follows: MMSE ≤17 for those with no formal education; MMSE ≤ 20 for those with primary school education (≥6 years); and MMSE≤24 for those with junior high school education or above (≥ 9 years) [27].

Religiosity

Religiosity was measured using the Chinese version of the 5-item Duke University Religion Index (DUREL), a brief measure of religious involvement widely used in the literature [28]. The psychometric properties of the Chinese version of the DUREL have been established [29]. The total DUREL score ranged from 5-27, with higher score indicating higher religiosity. In the present study, the high religiosity defined as those participants who prayer more than once a day, and attend the religious service almost every day, and claimed the religion is important or very important in their life (corresponding to DUREL total score >24).

■ APOE gene polymorphism test

DNA was isolated from venous blood leukocytes. Single-nucleotide polymorphisms (SNPs) of the rs429358 and rs7412 genes were detected using the high-resolution melting (HRM) curve method [30]. The analyses were performed at the Biochip Ningxia Center following the manufacturer's instructions. To control for accuracy, twelve DNA samples were retested

using the dideoxy-mediated chain termination method at an independent laboratory (Genex, China). All the genotypes were detected using a sequencing method consistent with the HRM protocol. The Hardy-Weinberg balance test was conducted by Chi-squared analysis (χ^2=1.65, P=0.199).

■ Statistical Analysis

Carriers of the Ɛ2 allele including genotypes Ɛ2Ɛ2 and Ɛ2Ɛ3, and carriers of the Ɛ4 allele including genotypes Ɛ3Ɛ3 and Ɛ4Ɛ4; Due to the rare prevalence of Ɛ2Ɛ4 in general population, the carriers of the Ɛ3 allele including genotypes Ɛ3Ɛ3 and Ɛ2Ɛ4 as the control, in current study 27 participants with Ɛ2Ɛ4 genotype. A gene risk index model, widely used in other studies of this type, was used to evaluate the variation in the APOE polymorphisms [31]. The model assigned +1, 0, or −1 for the Ɛ2, Ɛ3, or Ɛ4 alleles, respectively. The genotypes Ɛ2Ɛ2, Ɛ2Ɛ3, Ɛ2Ɛ4, Ɛ3Ɛ3, Ɛ3Ɛ4, and Ɛ4Ɛ4 had scores of +2, +1, 0, 0, −1, and −2, respectively. The distributions of the APOE genotypes (i.e., the frequency of the allele's Ɛ2, Ɛ3 and Ɛ4, as well as Ɛ2 allele carriers and Ɛ4 allele carriers) and demographic characteristics between the two community samples were analyzed by Chi-squared test. Age and the APOE risk index were analyzed by Student's t test. Two analysis strategies were used to examine the interaction between religiosity and APOE gene variants. First, a crossover analysis was used to detect the gene-environmental interaction [32]. In this analysis, we created a 2*4 cross-tabulation with the APOE-ε4 allele carrier and high religiosity variables. Using neither APOE-ε4 nor high religiosity as the reference group (OR_{00}), the odds ratio (OR) was calculated for (1) APOE-ε4 without high religiosity (OR_{01}), (2) without APOE-ε4 but with high religiosity (OR_{10}), and (3) both APOE-ε4 and high religiosity (OR_{11}). A synergy index (SI) was calculated to assess the degree of interaction, $SI=R_{11}/(R_{01}\times R_{10})$, where SI>1 indicates a synergistic interaction, and SI<1 indicates a negative interaction [33].

Second, a logistic regression model was used to examine the regression coefficients (β), odds ratios (ORs) and 95% confidence intervals (95% CIs) for the Ɛ2 allele carriers, Ɛ4 allele carriers, risk index, high religiosity and G*E interactions after controlling for age, gender, and physical health variables, where $\beta_{GxE}>0$ and $OR_{GxE}>1$ indicate a synergistic interaction between the gene and environment, and $\beta_{GxE}<0$ and $OR_{GxE}<1$ indicate a negative interaction between the gene and environment [34]. The Ɛ2 allele carriers, Ɛ4 allele carriers, and risk index variables were entered into the model separately. Statistical significance was set at $P < 0.05$. All of the analyses were performed using the Statistical Package for Social Sciences version 22.0 (IBM Corp, Armonk, NY, USA).

Results

■ Prevalence of MCI and religiosity of the subjects

Nearly one of five participants (17.3%) met the criteria of MCI (Table 1). The average MMSE score was 23.6 (SD=5.6). The average score on the DUREL was 23.1 (SD=5.6), with 58.0% of subjects classified as highly religious. Fifteen percent of the participants carried the at-risk Ɛ4 allele, and 15% carried the Ɛ2 allele.

■ Interaction between the APOE genotype and religiosity

Table 2 presents the results examining the relationship between the APOE genotype and religiosity. Participants with the Ɛ4 allele and without high religiosity had the highest risk of MCI (OR=1.95; 95% CI=1.24-3.07). Those with the Ɛ4 allele and high religiosity had a lower risk of MCI (OR=0.70; 95% CI=0.47-1.04) than those without the Ɛ4 allele and without high religiosity. As a result, the synergy index was 0.40 with $OR_{11}<OR_{01}\times OR_{10}$, indicating a negative interaction between the Ɛ4 allele and high religiosity. By contrast, those with the Ɛ2 allele had a lower risk of MCI, although there was a synergistic interaction when high religiosity was present together with the Ɛ2 allele (SI=1.55, $OR_{11}>OR_{01}\times OR_{10}$).

■ Logistic regression model

The logistic regression model is presented in Table 3. When controlling for demographic variables and physical health (blood pressure, fast plasma glucose), the Ɛ4 carrier was associated with a higher risk of MCI (OR=1.78; 95% CI: 1.12-2.83; P<0.05). No significant association was found between high religiosity and MCI. No significant relationship was found between the Ɛ2 carrier status and MCI, although the trend was in the expected direction. There was, however, a significant negative interaction effect between the Ɛ4 carrier status and high religiosity (β_{GxE}=-0.79, OR_{GxE}=0.45, 95% CI: 0.25-0.84, $P<0.05$), again indicating a lower risk for MCI among those with the Ɛ4 carrier status in the presence

Table 2: Interaction between APOE genotype and religiosity on MCI.

	with Ɛ4		without Ɛ4	
	HR+	**HR-**	**HR+**	**HR-**
MCI (yes)	34	31	187	164
MCI (no)	221	72	957	744
OR	OR_{11}=0.70	OR_{01}=1.95	OR_{10}=0.89	OR_{00}=1.00
95%CI	(0.47,1.04)	(1.24,3.07)	(0.70,1.12)	----
SI	0.40	$OR_{11}<OR_{01}\times OR_{10}$		
	with Ɛ2		without Ɛ2	
	HR+	HR-	HR+	HR-
MCI(yes)	32	21	189	174
MCI(no)	170	127	1008	689
OR	OR_{11}= 0.75	OR_{01}=0.65	OR_{10}=0.74	OR_{00}=1.00
95%CI	(0.49, 1.13)	(0.40, 1.07)	(0.59, 0.93)	----
SI	1.55	$OR_{11}>OR_{01}\times OR_{10}$		

OR: Odds ratio； MCI: Mild cognitive impairment; 95% CI; 95% Confidence Intervals; HR+: with high religiosity; HR-: without high religiosity; SI: synergy index

Table 3: Logistic regression model for interaction between APOE genotype and religiosity on MCI.

	B(SE)	***P* value**	***OR (95%CI)***
High religiosity [a]	0.04 (0.12)	0.730	1.04 (0.82, 1.33)
Ɛ4 carrier	0.58 (0.24)	0.015	1.78 (1.12, 2.83)
Ɛ4 carrier × High religiosity	-0.79 (0.31)	0.012	0.45 (0.25, 0.84)
High religiosity [b]	-0.11 (0.12)	0.377	0.90 (0.71, 1.14)
Ɛ2carrier	-0.43 (0.26)	0.091	0.65 (0.40, 1.08)
Ɛ2carrier × High religiosity	0.37 (0.33)	0.265	1.45 (0.75, 2.78)
High religiosity [c]	-0.06 (0.11)	0.570	0.94 (0.75, 1.17)
Risk index	-0.26 (0.14)	0.070	0.77 (0.59, 1.02)
Risk index×High religiosity	0.35 (0.19)	0.059	1.42 (0.99, 2.05)

SE: standard error; OR: Odds ratio; 95% CI; 95% Confidence Intervals
All models were controlled for age, gender, living status, hypertension, and fast plasma glucose
a: for the ε4 carrier model; b: for the ε2 carrier model; c: for the risk index model

of high religiosity. There was also a synergistic interaction between the Ɛ2 carrier status and high religiosity (β_{GxE}=0.37; OR_{GxE}=1.45; 95% CI: 0.75-2.78), but it did not reach statistical significance. For the APOE risk index model, there was a synergistic interaction between the APOE risk index and high religiosity (β_{GxE}=0.35; OR_{GxE}=1.42; 95% CI: 0.99-2.05), with a borderline significant p value (0.059).

The logistic regression model revealed inconsistent associations between the Ɛ4 carrier and MCI when the analyses were stratified by sample group (communities vs. Hajj). In those communities, Ɛ4 was positively associated with the risk of MCI (OR=2.44), and the APOE risk index was negatively associated with the risk of MCI (OR=0.66), although those associations were not present for those going on the Hajj **(Table 4)**. No significant interaction between religiosity and APOE high or low risk alleles on MCI were found in either group.

Discussion

Religion plays an especially important role in later life because religious involvement helps older people face impending death, find and maintain a sense of meaningfulness and significance in life, accept the inevitable losses of old age and discover and utilize the compensatory values that are associated with old age [35]. To our knowledge, this is the first study to examine the modifying effect of religiosity on the association between the APOE genotype and the risk of MCI. In the presence of without high religiosity, there is an increased risk of MCI among those with the Ɛ4 allele. This is not present among those with high religiosity. There is also a lower risk of MCI in those with high religiosity in the absence of the protective Ɛ2 allele. Overall, it appears that the positive relationship between religiosity and cognitive functioning might be, at least partly, due to the distribution of APOE high- and low-risk genotypes. Lower religiosity may exacerbate the risk of MCI in those with the high-risk Ɛ4 allele, whereas high religiosity

Table 4: Logistic regression for interaction of APOE genotype and religiosity on MCI stratified by sample group.

	Communities		Hajj	
	OR (95%CI)	***P* value**	***OR (95%CI)***	***P* value**
High religiosity[a]	0.72 (0.45,1.16)	0.184	1.10 (0.73,1.66)	0.621
Ɛ4 carrier	2.44 (1.33,4.47)	0.004	1.11 (0.49,2.51)	0.799
Ɛ4 carrier × High religiosity	1.48 (0.30,7.28)	0.626	0.64 (0.25,1.60)	0.341
High religiosity [b]	0.73 (0.45,1.17)	0.199	0.97 (0.66,1.43)	0.897
Ɛ2 carrier	0.63 (0.35,1.11)	0.111	0.68 (0.22,2.07)	0.501
Ɛ2 carrier × High religiosity	0.84 (0.20,3.53)	0.819	1.49 (0.45,4.93)	0.513
High religiosity [c]	0.74 (0.47,1.16)	0.196	1.01 (0.70,1.46)	0.930
Risk index	0.66 (0.47,0.93)	0.018	1.12 (0.65,1.94)	0.669
Risk index × High religiosity	0.64 (0.22,1.86)	0.418	1.05 (0.57,1.92)	0.860

OR: Odds ratio; 95%CI;95% Confidence Intervals. All the models were under controlling the age, gender, living status, hypertension, fast plasma glucose; a: for the Ɛ4 carrier model; b: for the Ɛ2 carrier model; c: for the Risk index model

may lower the risk of MCI in those without the protective Ɛ2 allele. Those findings are partly supported by the study of alcohol metabolism genes and religious involvement [20], which found that an increasing frequency of religious attendance leads to a weaker association between alcohol dehydrogenase enzymes risk genes and alcohol consumption.

As mentioned previously, there were several aspects of religiosity that may have positive effects on cognitive function. The effects of religiosity on MCI risk are likely due to its role as a powerful coping behavior in response to life stresses. The effects of without high religiosity on MCI risk in persons with the Ɛ4 allele may be due to the absence of this coping resource, leading to greater emotional distress or depression, thereby increasing the risk of MCI. Similarly, the presence of high religiosity in the absence of the protective Ɛ2 allele may help to compensate for this lack of genetic protection by helping to reduce distress that might more easily bring on MCI. Nose, *et al.* found that MCI was associated with depression symptoms, and the prevalence of MCI among APOE Ɛ4 carriers was higher than that of MCI among non-carriers [36]. In addition, Skoog, *et al.* reported that the presence of the Ɛ4 allele predicted future depression in a Swedish cohort [37].

Normal changes in memory with aging may be difficult to differentiate from MCI. Given that religious involvement is associated with longer telomere length (a measure of biological aging) [16], it may be that religious involvement slows the aging process (by reducing psychological stress-induced inflammation that shortens telomeres). If the risk of MCI increases with aging in those with the APOE Ɛ4 allele and if the aging process is slowed in those who are involved in religious activity, this may help explain why those with the ApoE Ɛ4 allele in the presence of without high religiosity are associated with a greater risk of MCI.

Finally, many of the participants in this study were Muslim (with ancestors from Middle Eastern Arabic regions) with a desire to go on the Hajj. There is evidence from research in Arab Muslims in Israel that devout religious practices during mid-life (which tend to be stable in later life as well) are associated with a lower risk of MCI in later life [38]. This finding is consistent with the results from our study because those going on the Hajj were also the most religious participants here.

When stratified by community and Hajj samples, the interaction between religiosity and APOE risk gene disappeared. This may have been a result of the reduced sample size. For example, 19.5% of the community sample met the criteria for high religiosity; among whom, 11 participants were Ɛ4 carriers, reducing the statistical power to detect an interaction effect. Another possible explanation is a ceiling effect. For example, in the Hajj group, 82.0% of the participants have a DUREL total score greater than 24, while the average DUREL total score was 26.1 (SD:1.5) with a range from 21 to 27. Finally, the significant interaction between the Ɛ4 carrier state and religiosity in the overall sample may have been due to the low association between the Ɛ4 carrier state and MCI in the Hajj group together with their high religiosity compared with the inverse relationship between the Ɛ4 carrier state and MCI in the community sample with without high religiosity.

There is a religious awakening happening in China. Religiosity has good prospects. First, religious beliefs influence the ability to cope with illness and may affect the patient's emotional

state and motivation towards recovery, affecting their ability to provide self-care [39]. Second, religious beliefs affect important health-related behaviors and likely influence medical outcomes, as is increasingly being documented [40]. Third, religious beliefs influence medical decisions made by both patients [41,42]and physicians. The number of people who indicate a religious practice has increased rapidly during the past several decades (from 7.0% in 2001 to 23.9% in 2007) [43]. Given the high prevalence of MCI in the Chinese population, the present findings have value for understanding the mechanisms by which MCI develops. In addition, this finding is the interaction of gene and environment, it may be useful for others to a further research; Also, this study is associated with religion and there is a religious awakening happening in China, it is essential to study more about religion.

Limitations

This study has several limitations. First, given its cross-sectional design, causal relationships between religiosity and MCI cannot be determined. Second, most of the participants in the Hajj group were highly religious (82.0%), analyses could not be conducted in each sample separately, thus leaving the possibility that these results were tied to the ethnic/religious background of the participants. Third, participants were selected from a very limited region of China where more than 30% of the population is Muslim; thus, caution should be demonstrated when generalizing these findings to other areas of mainland China.

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Conflicts of interest

The authors have no conflicts of interest to report.

Author contributions

WZ and HK participated in the design of the study. WZ, WL conducted the data collection and the statistical analysis, WL wrote the first draft of the manuscript. Saad oversaw the data analysis, and reviewed the draft manuscript. All of the authors have read and approved the final manuscript.

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