Sex Differences in the Mediating Role of Chronic Inflammation on the Association between Social Isolation and Cognitive Functioning among Older Adults in the United States

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Abstract

Background—Previous research has reported the association between social isolation and cognitive impairment. However, biological mechanisms underlying this association are understudied. It is also unclear whether there are sex differences in these biological mechanisms.

Objectives—To examine whether chronic inflammation biomarkers are potential mediators of the association between social isolation and cognitive functioning among older men and women.

Methods—Data were the National Health and Nutrition Examination Survey 1999–2002. A total of 2,535 older adults aged 60 and older were included. Chronic inflammation was measured by C-reactive protein (CRP), plasma fibrinogen, and serum albumin. Cognitive functioning was assessed by the Digit Symbol Substitution Test (DSST). Social isolation was defined using a 4-point composite index of items pertaining to the strength of social network and support. Linear regression models and formal mediation analysis were applied.

Results—Social isolation was associated with lower DSST scores [β (SE) = −2.445 (1.180), $p < 0.01$ for men; β (SE) = −5.478 (1.167), $p < 0.001$ for women]. For older men, social isolation was associated with higher levels of CRP (β [SE] = 0.226 (0.110), $p < 0.05$) and fibrinogen (β [SE] = 0.058 (0.026), $p < 0.05$). In mediation analyses, among older men, CRP mediated 6.1% and fibrinogen mediated 12.0% of the association of social isolation with DSST.

Conclusion—Social isolation was associated with poorer cognitive functioning partially via heightened inflammatory responses in older men. Defining these associations' mechanisms in sex-specific contexts could inform preventive and therapeutic strategies for cognitive impairment in older adults.

Keywords

Loneliness; Gender differences; Dementia; Cognitive testing; Mild Cognitive Impairment (MCI)

1. Introduction

Cognitive functioning is one of the major determinants of well-being in later life. Prevention of cognitive decline could prevent cognitive impairment, a major risk factor that contributes to disability and social care needs among the older population globally. In 2021, over 6.2 million older adults in the United States (US) were living with Alzheimer's disease and related dementia (ADRD), and the cost for all individuals with ADRD is $355 billion (Alzheimer's Association, 2021). As poorer cognitive functioning is one of the main manifestations of cognitive impairment and/or ADRD (Plassman et al., 2011), exploring risk factors and pathways underlying poorer cognitive functioning will inform interventions to prevent and/or manage cognitive impairment and/or ADRD.

Being socially connected is a fundamental drive and core human need (Cacioppo et al., 2014). Social isolation, defined as having few social relationships or infrequent social contact with others, has been associated with higher risks for cognitive impairment and ADRD (Biddle et al., 2019; Joyce et al., 2022; Shen et al., 2022; Yu et al., 2020). Behavioral and psychological processes that linking social isolation with ADRD have been proposed. Social isolation may promote unhealthy behaviors such as smoking and physical inactivity (Shankar et al., 2011), which can increase the risks of dementia (Livingston et al., 2020). Moreover, depression is implicated in the association between perceived social isolation and poor cognitive health (Donovan et al., 2017), which can also be extended to dementia (Livingston et al., 2020). Several theories have been proposed to explain the association of social isolation and diminished cognitive functioning. The "use it or lose it" theory (Hultsch et al., 1999), which argues that engaging in social and physical activities stimulates the brain. The decreased engagement in social activities may result in the lack of use of mental faculties, thus, leading to cognitive decline. Another is the stress-buffering theory (Ditzen & Heinrichs, 2014), which proposes that maintaining social connection is beneficial when coping with stressful situations. Social connection may prevent or modulate responses to stressful events that are damaging to cognitive health.

Although behavioral and psychological processes linking social isolation to cognitive impairment and ADRD have been studied (Donovan et al., 2017; Shankar et al., 2011), biophysiological mechanisms underlying these links are not well elucidated. Social isolation is proposed to have a biological impact because it acts as a social stressor and activates the stress response (Cacioppo et al., 2015). Studies have shown that activation of the stress response (e.g., hypothalamic-pituitary-adrenocortical [HPA] axis) has a direct effect on the heightened inflammatory response (Ayoub, 2010; Eisenberger et al., 2017). In addition,

an evolutionary explanation for the activation of the inflammatory system in response to social isolation has been proposed (Cacioppo et al., 2014, 2015; Eisenberger et al., 2017). This is because individuals would have been more likely to be attacked or injured if they were socially isolated than if they were around people who could defend them. Thus, the activation of the inflammatory response when someone is socially isolated could confer an evolutionary advantage as he/she would be prepared to respond biologically to the increased stress. This explanation has also been supported by prior research which found that social isolation is linked to higher systemic, low-grade, chronic inflammation markers, such as C-reactive protein (CRP) (Cudjoe et al., 2021; Das, 2013; Yang et al., 2013), interleukin-6 (IL-6) (Cudjoe et al., 2021; Glei et al., 2012), and high fibrinogen levels (Shankar et al., 2011; Yang et al., 2013)

Inflammation is a biological response to infection or injury in which the body produces more of a number of chemicals that aid in the defense against infection (Ayoub, 2010). An elevation in inflammatory markers is independently associated with smaller regional brain volumes and larger ventricular volume (Walker et al., 2017), and chronic inflammation has been implicated in the neuropathological cascade culminating in ADRD (Gorelick, 2010). Studies suggested that inflammatory markers, such as high-sensitive CRP, IL-6, high fibrinogen levels, and low albumin levels, are predictive of global markers of brain atrophy (Satizabal et al., 2012), an accelerated cognitive decline (Kipinoinen et al., 2022), and the risk of dementia (Lewis & Knight, 2021). However, whether and how inflammatory responses mediate the association between social isolation and cognitive functioning is largely unknown.

Prior research suggests that older men with a higher level of social disconnection are more vulnerable to dementia and mortality than older women (Yang et al., 2013; Zhou et al., 2018). For example, a nationwide cohort study found that older Chinese men who felt lonely were more likely to suffer from dementia than older Chinese women (Zhou et al., 2018). Another 18-year longitudinal study identified notable sex differences in which social isolation has greater mortality effects for men (Yang et al., 2013). Potential explanations for this finding have emerged from studies showing sex differences in the biological processes influenced by social isolation. Reviews of studies on social isolation in relation to health outcomes suggest sex differences in physiological responses to social isolation. For instance, one study found that the association between social isolation and elevated CRP is stronger for older men compared with older women (Loucks et al., 2006). Another study suggests sex differences in the associations of social isolation with inflammation (Yang et al., 2013). However, it remains unclear whether there are significant sex differences in the moderating role of chronic inflammation on the associations between social isolation and cognitive functioning.

Using a nationally representative population-based study, we extend previous research to test the hypothesis that social isolation is associated with poorer cognitive functioning via elevated inflammation. We address additional gaps in the literature by hypothesizing that these associations will be more prominent among older men.

2. Methods

2.1. Study design and population

The National Health and Nutrition Examination Survey (NHANES) is a consecutive cross-sectional survey performed in two-year cycles among non-institutionalized US civilians. The NHANES used a stratified, multistage, clustered probability sampling approach to represent the overall population in the US; it is administered by the US National Center for Health Statistics (NCHS) that collects sociodemographic, dietary, and health information through in-home interviews and clinical examinations in mobile examination centers. The survey oversampled the racial/ethnic minorities and adults aged 60 and above to improve statistical power in analyses. Detailed information on the survey design and data collection can be found elsewhere (Curtin et al., 2012). All data collection procedures for the survey were approved by the NCHS research ethics review board.

The NHANES 1999–2000 and 2001–2002 cycles were selected for analysis because they are the only cycles for which key variables to test our hypotheses were measured. The NHANES 1999–2002 has an overall sample of 3,706 older adults aged 60 and older. We applied the following exclusions in the study: 1) did not complete the "Social Support Questionnaire" (287 excluded), 2) cognitive measurement data were missing (407 excluded), and 3) had no laboratory inflammation markers data (477 excluded). A total of 2,535 eligible participants were included in the analyses. The flowchart of sample selection is present in Figure 1.

2.2. Measurements

2.2.1. Assessment of social isolation—Social isolation in this study is derived from the Yale Health and Aging Study (Seeman & Berkman, 1988) and the social network index developed by Berkman and Syme (Berkman & Syme, 1979), which summarizes the strength of the social network and support across four domains: marital status, number of close friends or confidants, emotional support, and financial support. The first question asked whether the participant was married or living with a partner (0 = married or living with a partner; 1 = widowed, divorced, separated, or never married). The second question asked, "How many close friends or confidants do you have?" (0 = at least one close friend or confidant; 1 = no close friends or confidants). A third question characterized the availability and adequacy of emotional support. Participants were asked if they had no one to provide emotional support (e.g., talking over problems or helping to make a difficult decision) in the past 12 months. Participants who were "at risk" for inadequate emotional support if they answered "yes" (inadequate emotional support = 1). The fourth question asked about the availability of financial support, "If you need some extra financial help (e.g., paying any bills, housing costs, hospital visits, or providing you with food or clothes), could you count on anyone to help?" Those who answered "no" were coded as "1".

The four indicators of social isolation were summed up to create a social isolation score (SIS). The SIS ranged from 0 to 4, with higher scores indicating greater isolation. The Cronbach's alpha for the SIS is 0.703, demonstrating good internal consistency (Tavakol & Dennick, 2011). This valid measure has been used to evaluate social isolation of US adults in previous studies (Coyle et al., 2017; Mick et al., 2014). Theoretically, it would

follow that those with a higher SIS can be considered socially isolated (Shankar et al., 2011). Following the methods of previous studies using NHANES (Coyle et al., 2017; Mick et al., 2014), participants were coded as "socially isolated" if their score was two or greater (social isolation = 1).

2.2.2. Assessment of cognitive functioning—The Digit Symbol Substitution Test (DSST), a performance module from the Wechsler Adult Intelligence Scale III, was the only cognitive test in NHANES 1999–2002. DSST assesses the processing speed, sustained attention, and working memory (Wechsler & Psychological Corporation, 1997). As a screening tool, the DSST has been used extensive to measure cognitive function in screenings, epidemiological, and clinical studies (Jaeger, 2018) and was administered during the in-home interviews to adults aged 60 and older. The DSST is highly sensitive to various types of brain dysfunction and discriminates well between mild cognitive impairment and ADRD (Tsatali et al., 2021). The test is conducted using a paper form with a top key containing nine numbers paired with symbols. Participants have 120 seconds to copy the corresponding symbols in the 133 boxes that adjoin the numbers. The DSST score is the total number of correct matches. A higher score represents better cognitive functioning, with a maximum score of 133.

2.2.3. Markers of chronic inflammation—We measured chronic inflammation using three inflammatory markers available in the NHANES 1999–2002: CRP, plasma fibrinogen, and serum albumin (National Center for Health Statistics (U.S.), 2015). CRP was examined using latex-enhanced nephelometry, an analysis of light scattering of antigen-antibody complexes with latex particles. Fibrinogen was measured through thrombin clotting time, in which thrombin was used to convert fibrinogen into fibrin enzymatically. Albumin was measured by dye binding using bromocresol green reagents and an Astra 8 analyzer (Beckman Instruments, Brea, CA). These markers' detailed laboratory measurements and assay procedures have been described elsewhere (National Center for Health Statistics (U.S.), 2015). We used natural continuous log-transformed CRP, fibrinogen, and albumin to account for the skewness in the distribution of continuous inflammatory markers.

2.2.4. Covariates—Covariates were selected based on studies that examined the association between social isolation and cognitive functioning (Joyce et al., 2022; Shen et al., 2022; Yu et al., 2020). These covariates included: 1) sociodemographic variables: age, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanics, or others), education (less than high school, high school graduate, more than high school), and annual household income (<$20,000, $20,000-$75,000, or >$75,000); 2) behavioral characteristics: smoking status (nonsmokers [<100 cigarettes during one's lifetime], former smoker [100 or more cigarettes during one's lifetime, but not actively smoking during recent time frame], or current smoker [ongoing smoking habit]), alcohol intake (12 drinks/year or <12 drinks/year), and did moderate/vigorous leisure time physical activities over the past month (yes/no); 3) health-related characteristics: obesity defined as body mass index of at least 30 kg/m^2, hypertension defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, and diabetes mellitus defined as self-reported diabetes diagnosis or glycated hemoglobin level of 5.7%.

2.3. Statistical analyses

Continuous variables were described as mean (standard deviation, SD) for normal distributions and median (interquartile range, IQR) for skewed distributions. Categorical variables were described as numbers (percentage, %). Comparisons among socially isolated/not isolated participants were performed using *t*-tests for continuous variables and the chi-square tests for categorical variables. Step-wise linear regression models were conducted to investigate the association of social isolation with the three log-transformed inflammatory markers and cognitive functioning. Model 1 was unadjusted, and the relevant sociodemographic, behavioral, and health factors, as described above, were incorporated into the regression model in Model 2–4. The standardized regression coefficients (β) and their standard errors (SEs) were presented.

We conducted formal mediation analyses to investigate whether each inflammatory marker mediates the associations between social isolation and cognitive functioning. As shown in Supplementary Figure 1, we set three pathways to establish mediation: 1) exposure to mediator (path a), 2) mediator to outcome (path b), and 3) exposure to outcome (path c). The total effect reflected the sum of a direct effect (path c') and an indirect (mediated, a × b) effect. The percentage of variance in the outcome explained by the mediated effect was calculated using the following formula: $(\beta_{\text{total effect}} - \beta_{\text{direct effect}}) / \beta_{\text{total effect}} \times 100\%$ (Ditlevsen et al., 2005). All the mediation analyses standardized estimates with SEs and *p*-values were based on nonparametric bootstrapping with 1,000 resamplings.

To demonstrate the robustness of the results, we performed a sensitivity analysis using dichotomous inflammatory markers to assess possible threshold effects. We identified cut points to dichotomize continuous inflammation marker measurements into variables that distinguished high risk for chronic inflammation. We dichotomized CRP at 3.0 mg/dL, albumin at 4.0 μg/mL, and fibrinogen at the top quartile. The cut-points for high risk for chronic inflammation were defined by clinical practice and previous studies (Myers et al., 2004; Osimo et al., 2019; Pearson et al., 2004). Step-wise logistic regression was used for the analogous models with outcomes of dichotomous inflammatory markers. Based on the conceptual model depicted in Appendix 2, we evaluated the two sets of models for each inflammation marker: 1) social isolation alone, 2) social isolation and dichotomized inflammatory markers. All models were adjusted to all covariates. Additionally, since our focus is on chronic inflammation, we did another sensitivity analysis by excluding six participants whose CRP values were greater than 10 mg/dL, which indicates acute infection or active inflammatory disorders (Pearson et al., 2004). Our results and conclusions were unchanged after excluding individuals with CRP 10.0 mg/dL.

Estimates for means, SD, proportions, effect sizes and their SEs or 95% confidence intervals (CIs) were adjusted for the complex survey design, survey nonresponse, and post-stratification of NHANES. Considering the low percentage of missing data for all the covariates, complete-case multivariable regression was conducted. The comparison of individuals with complete data and those with missing data showed no significant difference in social isolation and cognitive functioning. A *p*-value < 0.05 was considered statistically significant. All statistical analyses were performed using STATA 15.1 (StataCorp, College Station, TX, USA).

3. Results

3.1. Participants' characteristics

Table 1 presents the characteristics of 1,267 men and 1,268 women by social isolation, with weighted descriptive statistics. The mean age was 71.05 (SD = 7.77) years old. A total of 190 (15.0%) older men and 270 (21.3%) older women were socially isolated. Bivariate analyses showed that socially isolated men had a significantly elevated inflammation measured by CRP and fibrinogen ($p < 0.05$). Social isolated older adults had lower cognitive functioning scores ($p < 0.001$) than those not isolated in both sexes.

3.2. Association of social isolation with cognitive functioning

As shown in Model 1 (Table 2), socially isolated older adults were found to have a poorer cognitive functioning than those not isolated (β [SE] = −8.795 [1.772], $p < 0.01$ for men; β [SE] = −9.190 [1.492], $p < 0.001$ for women). The significant association persists after controlling for sociodemographic, behavioral, and health-related characteristics in Model 2–4. Compared with older adults not isolated, socially isolated older adults had poorer cognitive functioning (β [SE] = −2.445 [1.180], $p < 0.01$ for men; β [SE] = −5.478 [1.167], $p < 0.001$ for women).

3.3. Association of social isolation with inflammatory markers

Social isolation was related to higher levels of inflammation measured by log-transformed CRP and fibrinogen in older men but not older women (Table 3). For older men, adjusting for all covariates, Model 2 shows elevated CRP (β [SE] = 0.226 [0.110], $p < 0.05$) and fibrinogen (β [SE] = 0.058 [0.026], $p < 0.05$) for those who were socially isolated. By contrast, for older women, Model 1 reports only slightly significant elevated fibrinogen for the socially isolated than are not (β [SE] = 0.060 [0.022], $p < 0.01$). After adjusting all covariates, social isolation did not significantly affect the inflammatory markers in older women.

3.4. Mediating roles of CRP and fibrinogen

Because of the lack of significant associations between social isolation and albumin for older men and all three inflammatory markers for older women, we focused on the CRP and fibrinogen in the mediation analysis among older men. After adjustment for covariates, the CRP and fibrinogen level was inversely associated with cognitive functioning (β [SE] = −0.653 [0.215], $p < 0.01$ for CRP; β [SE] = −5.066 [1.713], $p < 0.001$ for fibrinogen). The association between social isolation and cognitive functioning mediated by CRP and fibrinogen was 6.1% and 12.0%, respectively (Figure 2). Supplementary Table S1 summarized all standardized path estimates.

3.5. Sensitivity analyses

Results using dichotomized inflammatory markers were qualitatively similar to those for log-transformed markers. For older men, adjusting for all covariates, social isolation was associated with higher risks of elevated CRP (odds ratios [OR] = 1.83, 95% CI = 1.03–3.26) and being at the highest quartile of fibrinogen (OR = 1.66, 95% CI = 1.05–2.62), and

the ORs were not significant in the albumin model. For older women, adjusting for all covariates, there was no significant difference in any of these inflammatory markers for the socially isolated than those not socially isolated (Supplementary Table S2). Supplementary Table S3 presents the results of testing the mediating effects of CRP and fibrinogen for older men. Overall, the inclusion of CRP and fibrinogen significantly reduced the sizes of coefficients of social isolation.

4. Discussion

Using data from NHANES 1999–2002, our hypothesis was supported: social isolation is associated with poorer cognitive functioning through physiological upregulation of chronic inflammation in older men. Further analyses in the older male sample indicated that 6.1% and 12.0% proportion of the association of social isolation on cognitive functioning were mediated by CRP and fibrinogen, respectively. The better cognitive health conveyed by social connection, widely documented in animal and human studies (Biddle et al., 2019; Joyce et al., 2022; Shen et al., 2022; Yu et al., 2020) can be attributed partly to ameliorating subclinical chronic inflammation in older men.

Our findings on the association between social isolation and cognitive functioning in both sexes are in line with studies that indicate social isolation increases the risks of dementia (Joyce et al., 2022; Shen et al., 2022). According to the stress process framework (Pearlin, 2010), social disconnection is a potent factor that can induce stress (Pearlin, 2010) and is thought to cause cognitive decline and dementia by elevating higher amyloid-β levels (Biddle et al., 2019) and lowing gray matter volumes (Shen et al., 2022). Chronic stress exposure and reduced coping strategies associated with social disconnection can induce a cascade of immune, neuroendocrine, and cardiovascular changes (Cacioppo et al., 2015). From a cognitive reserve perspective, social engagement and social participation is cognitively beneficial and contributes to building cognitive reserve and enhancing cognitive function (Stern, 2002). This was potently demonstrated in the Nun Study that an active religious life with numerous opportunities for social connection might stimulate cognition and hence expand cognitive reserve (Bennett et al., 2014).

In this study, the association of social isolation with cognitive functioning is comparable with other well-recognized risk factors to cognitive decline, which include lower education, less household income, smoking, physical inactivity, hypertension, and diabetes mellitus. This finding is in accordance with the Lancet Commission report that estimated social isolation is associated with a 4% reduction in dementia prevalence if this risk factor is addressed. Notably, this reduction is greater than combatting physical inactivity in later life (2%) or hypertension in midlife (2%) alone (Livingston et al., 2020). Given the high prevalence (24%) of social isolation among older adults in the US (Cudjoe et al., 2020), more interventions should be designed in the future to counter the effects of social isolation on the diminished cognitive functioning.

We find that social isolation is strongly associated with a high fibrinogen level in both sexes. The commonly used CRP also appears to be related to social isolation, but this relationship is less consistent across sex. Albumin does not seem to be associated with social

isolation, because it is less specific and is affected by many physiological processes besides inflammation (Yang et al., 2013). The associations between social isolation and markers of chronic inflammation suggested different physiological pathways important to consider in further analysis of the interplay between social and biological factors in dementia etiology. Studies have also demonstrated the association between social isolation and inflammation. Laboratory research has long documented that stress directly affects multiple regulatory systems through activation of the HPA axis and sympathetic nervous system (SNS), which modulate immune function and inflammatory processes (Seeman et al., 2001). And it has been suggested that social isolation may operate to reduce such effects by dampening physiological arousal or reactivity (Shen et al., 2022), whereas social isolation is itself a stressor that produces negative reactivity and affect (e.g., anxiety, depression), promotes chronic elevations in HPA and SNS activation (Cacioppo et al., 2015), and increases inflammation (Cudjoe et al., 2021; Das, 2013; Glei et al., 2012; Shankar et al., 2011). Furthermore, the stress-buffering functions of social support and interpersonal psychological resources can be linked with inflammatory processes in various ways (Ditzen & Heinrichs, 2014). It has been suggested that socially isolated individuals are deprived of opportunities for emotional support and coping resources, which can decrease their sense of control and psychological well-being (Qi et al., 2022).

The mediating analysis provided direct evidence that chronic inflammation can act as important physiological link between social isolation and cognitive functioning in older men. Consistent with findings from previous research that indicate health-risk behaviors and psychological stress as the main explanatory mechanisms (Donovan et al., 2017; Shankar et al., 2011), we found that the independent effects of social isolation on cognitive functioning largely remain after adjusting for a wide array of sociodemographic, behavioral, and health factors. This suggests that inflammation should be included as one physiological mechanism contributing to the detrimental effects of social isolation on dementia independent of conventional factors in future studies.

We also found the sex differences in the extent to which the inflammatory process mediates the effect of social isolation on cognitive functioning. The associations between social isolation and inflammatory markers are significant in older men but not women. Some psychosocial mechanisms have been proposed to explain this difference. For example, when a loss of social support (e.g., loss of a spouse) is expected, it can improve women's capacity to foresee such a loss, encourage them to replace the lost ties with other close ties, or help them cope with the demands and rewards of social support. This may improve women's resilience, which is essential to their health and survival after such loss (Berkman & Syme, 1979). Presumably, socially isolated men are more likely to suffer from lower life satisfaction and less resilient than socially isolated women (Zebhauser et al., 2014). Women have a greater capacity to buffer social isolation than men because they have more multifaceted networks that include close friendships and neighbors, resulting in greater social support (Zebhauser et al., 2014). Physiological mechanisms may also play important roles in sex differences. Previous studies indicate sexual dimorphism in behavioral stress responses (Lu et al., 2015). Men would display the classic "fight-or-flight" response to stressors. In contrast, women react with "tend-and-befriend" responses, characterized by nurturing behaviors that downregulate stress reactivity and by affiliating with social groups

to reduce risk (Taylor et al., 2000). The physiological response typical of women has likely evolved as an adaptation to their maternal and caregiving roles (i.e., tend-and-befriend pattern) and acts to downregulate innate immune responses such as inflammation. Prior studies also found that social isolation and a lack of social support have been related to higher inflammatory responses (Yang et al., 2013) and allostatic load (Seeman et al., 2001), with deleterious effects being more pronounced in men than women.

5. Strengths and limitations

This study has several noteworthy strengths. First, this is a large nationally representative sample of older adults in the U.S., with equal distribution of sexes. Second, we performed sensitivity analyses and arrived at the same results and conclusions, lending robustness to our conclusions. Third, this study is one of the few studies to date that examined social isolation, inflammatory biomarkers, and cognitive functioning in a single study using mediation model.

Several limitations need to be acknowledged. First, the measures of social isolation available in the NHANES 1999–2002 are restricted to social support and social networks that represent structural aspects of social connection. Qualitative and functional aspects of social connection are important to consider (National Academies of Sciences, Engineering, and Medicine, 2020) as psychosocial mechanisms mediating the link between social isolation and cognitive functioning and sex differences therein. Second, we only tested the inflammation mechanism due to the limited biomarkers available in the NHANES 1999–2002. Additional neuroendocrinological mechanisms, such as decreased HPA and sympathoadrenal activities and stress-related neurohormones such as cortisol and norepinephrine, could be explored in future studies to illustrate how social factors impact cognitive health (Cacioppo et al., 2015). Third, it is important to note that a reciprocal relationship between social isolation and cognitive functioning cannot be ruled out due to the cross-sectional nature of this study. Early symptoms of diminished cognitive functioning may also lead to social withdrawal and isolation. Causal direction should be investigated in further longitudinal or interventional studies. Fourth, although Lancet Commission identified 12 modifiable risk factors for dementia (Livingston et al., 2020), we did not test for all of them as measures on head injury, hearing loss, air pollution, and depression were unavailable among older adults in NHANES 1999–2002. Finally, the biobehavioral model of sex differences further suggests that health advantages for women may be conferred through neurobiological mechanisms, such as decreased cholesterol and HPA response to stress, instead of via inflammation (Grant et al., 2009). Future studies that include additional biological measures are needed to elucidate the neuroendocrine processes that mediate the effects of social isolation on cognitive functioning in sex-specific contexts.

6. Conclusions

Using a nationally representative and population-based sample, we found that social isolation was partially associated with poorer cognitive functioning via elevated inflammatory responses. There are sex differences in that they are greater for men and can be attributed partly to their heightened inflammatory responses. While biological

mechanisms may account for the associations between social isolation and poorer cognitive functioning, longitudinal and interventional research are needed to further examine the changes in cognitive functioning induced by social isolation that may predispose older adults to cognitive impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Source

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Highlights

- Social isolation was associated with poorer cognitive functioning in both older men and women in the United States.

- Social isolation is associated with elevated levels of C-reactive protein and plasma fibrinogen in older men.

- The associations between social isolation and cognition can be attributed in part to heightened inflammatory responses.
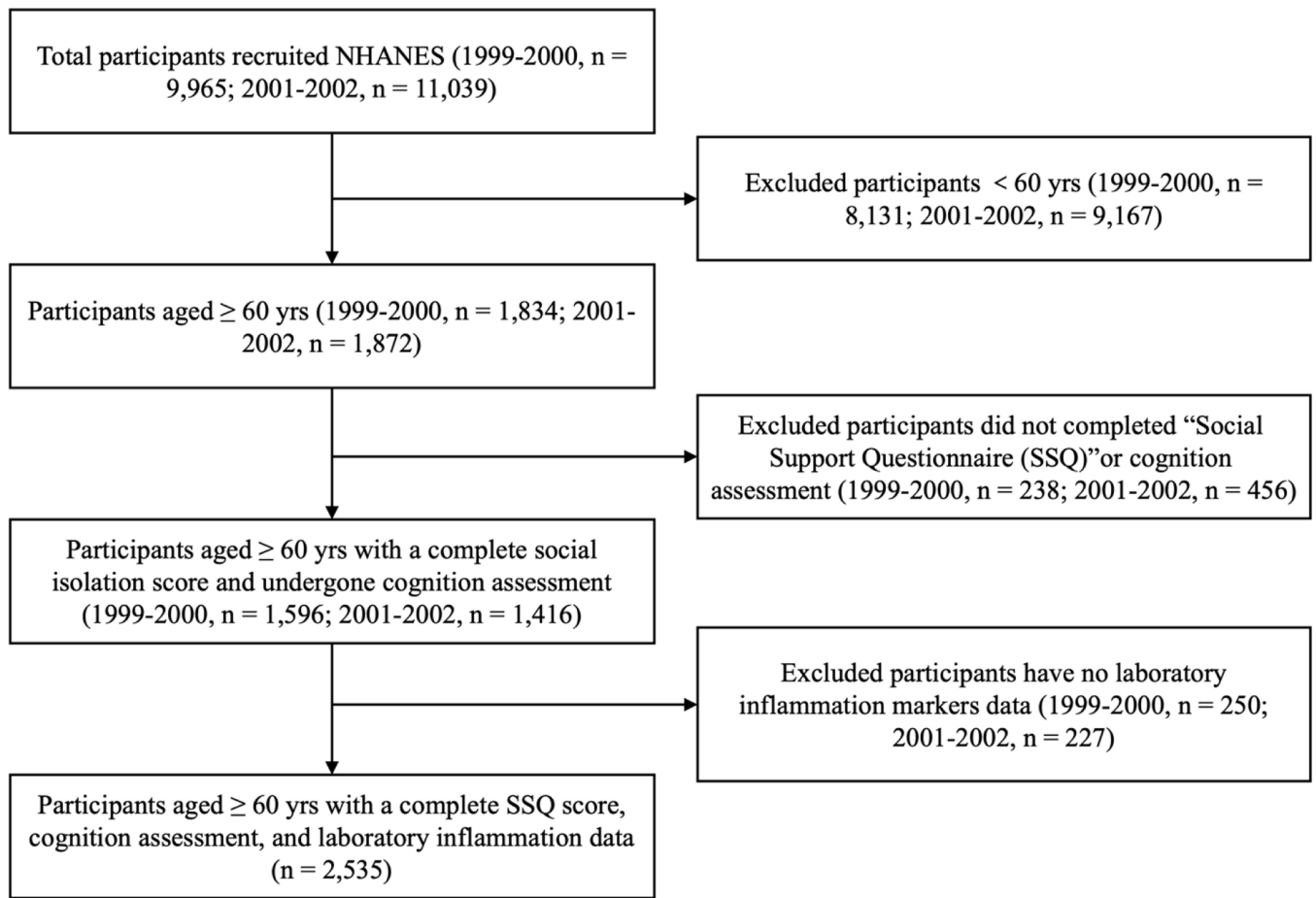
Figure 1. Flow chart of participants in the National Health and Nutrition Examination Survey Study 1999–2002
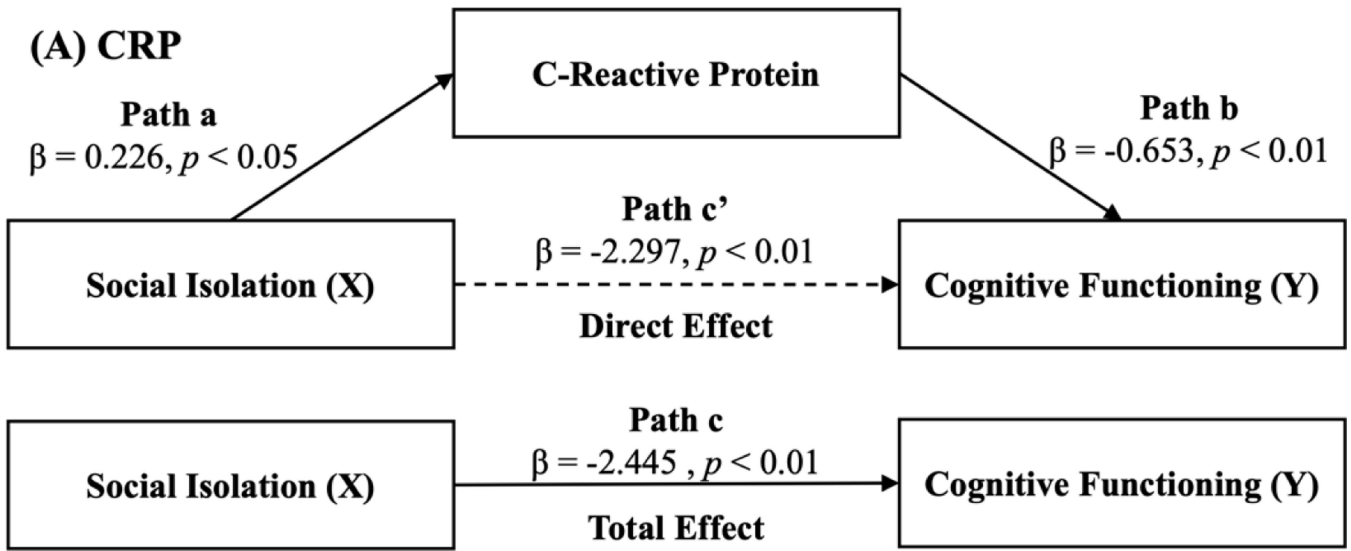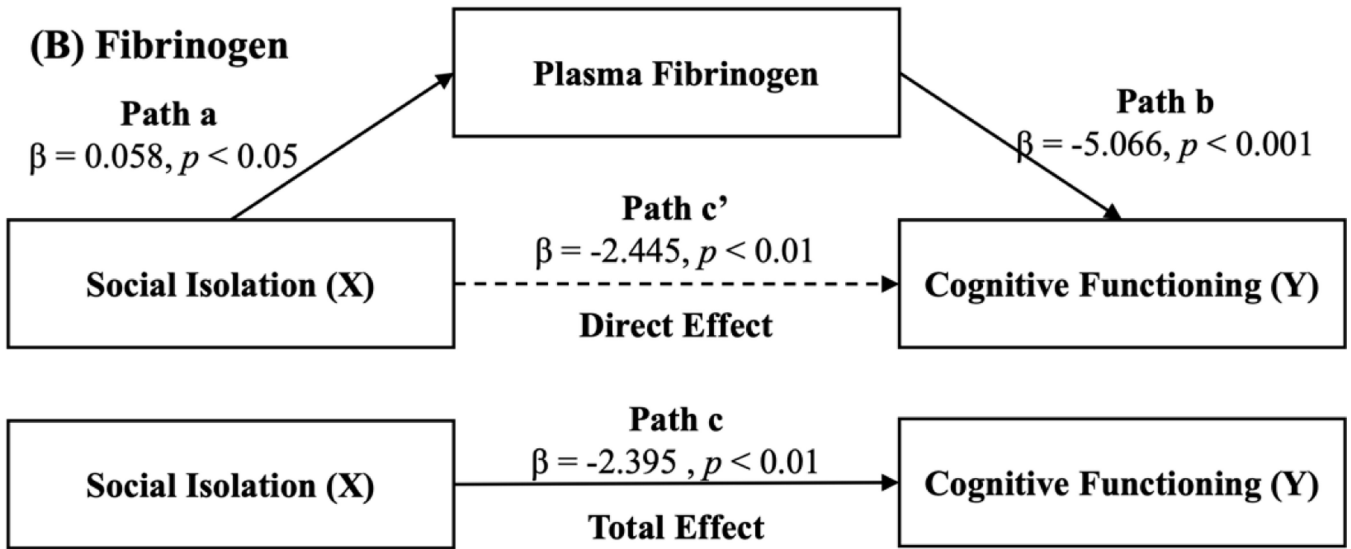
Figure 2. Mediating role of chronic inflammation on the association between social isolation and cognitive functioning in older men

Note: All models are adjusted for sociodemographic variables (age, race/ethnicity, education, and income), behavioral characteristics (smoking, alcohol intake, and physical exercise), and health-related characteristics (obesity, hypertension, and diabetes). The mediated proportion is calculated based on the formula: $(a \times b)/((a \times b) + c)$, where a $\times$ b is the indirect effect of social isolation on cognitive functioning mediated by each inflammatory marker, c is the direct effect of social isolation on cognitive functioning, and

(a × b) + c is the total effect of social isolation on cognitive functioning. (**A**) mediating effect of C-reactive protein. (**B**) mediating effect of plasma fibrinogen.

Table 1.

Selected characteristics among 2,535 older adults aged 60 and stratified by social isolation and sex: NHANES 1999–2002 [a]

Characteristics	Overall (N = 2,535)	Men (n = 1,267)			Women (n = 1,268)		
		Socially isolated (n = 190)	Not isolated (n = 1,077)	*P* - Value	Socially isolated (n = 270)	Not isolated (n = 998)	*P* - Value
Age (years), mean (SD)	71.05 (7.77)	71.20 (7.26)	70.87 (7.65)	0.586	71.89 (8.21)	71.01 (7.87)	0.104
Race/ethnicity (%)							
Non-Hispanic white	59.6	46.8	63.3	<0.001	47.8	61.3	<0.001
Non-Hispanic black	14.8	14.2	14.2		17.0	14.8	
Hispanics	23.4	37.4	20.2		32.6	21.7	
Others	2.2	1.6	2.2		2.6	2.1	
Educational attainment (%)							
Less than high school	40.1	60.0	36.7	<0.001	48.0	37.8	<0.01
High school graduate	24.0	13.7	22.7		23.4	27.6	
More than high school	35.9	26.3	40.6		28.6	34.6	
Annual household income (%)							
<$20,000	43.7	65.1	35.7	<0.001	59.9	44.0	<0.001
$20,000-$75,000	43.8	29.1	49.2		35.2	43.0	
>$75,000	12.5	5.8	15.2		4.9	13.0	
Smoking status (%)							
Nonsmoker	46.3	31.6	31.3	<0.01	57.8	62.2	0.296
Former smoker	41.7	47.4	55.7		30.4	28.6	
Current smoker	12.0	21.1	13.0		11.9	9.2	
Alcohol intake >12 drinks/year (%)	60.9	77.1	77.1	0.996	44.1	47.4	0.336
Moderate/vigorous physical activities (%)	47.0	39.0	55.0	<0.001	32.7	43.8	<0.001
Obesity (%)	31.4	26.5	27.6	0.767	36.0	35.3	0.829
Hypertension (%)	51.7	48.4	46.9	0.702	60.0	55.3	0.168
Diabetes mellitus (%)	19.6	23.6	20.3	<0.05	23.7	17.1	<0.01
Chronic inflammatory markers							
CRP (mg/dL) [b], medium (IQR)	0.29 (0.45)	0.30 (0.45)	0.23 (0.39)	<0.05	0.41 (0.57)	0.32 (0.50)	<0.05
<3.0 (normal/low risk)	91.7	89.5	93.7	<0.05	89.6	90.3	0.739
3.0 (high risk)	8.3	10.5	6.3		10.4	9.7	
Plasma fibrinogen	393.39	401.69	381.58	<0.01	411.72	397.25	<0.05
(mg/dL), mean (SD)	(83.60)	(92.84)	(84.66)		(85.31)	(79.24)	
Serum albumin (µg/mL) [b], medium (IQR)	4.60 (6.9)	4.60 (10.55)	4.70 (7.65)	0.845	4.6 (6.95)	4.50 (5.20)	0.264
4.0 (normal)	86.0	93.5	89.4	0.089	84.3	81.5	0.308

Characteristics	Overall (N = 2,535)	Men (n = 1,267)			Women (n = 1,268)		
		Socially isolated (n = 190)	Not isolated (n = 1,077)	*P* - Value	Socially isolated (n = 270)	Not isolated (n = 998)	*P* - Value
<4.0 (high risk)	14.0	6.5	10.6		15.7	18.5	
Cognitive functioning (DSST), mean (SD)	41.69 (18.59)	34.07 (16.99)	41.28 (17.81)	<0.001	35.79 (17.45)	45.17 (19.13)	<0.001

Note:

[a] Descriptive statistics are weighted to adjust for complex survey design.

[b] Non-normal distribution continuous variable, median (interquartile range).

Abbreviations: SD, standard deviation; IQR, interquartile range; CRP, C-reactive protein; DSST, digit symbol substitution test.

Table 2.

Associations of social isolation with the digit symbol substitution test score (n = 2,535)

	Weighted β coefficients (Standard Error)							
	Men (n = 1,267)				Women (n = 1,268)			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
Variables								
Social isolation (Ref. No)	−8.795 (1.772)***	−3.542 (1.471)**	−2.828 (1.188)**	−2.445 (1.180)**	−9.190 (1.492)***	−5.072 (1.213)***	−5.761 (1.166)***	−5.478 (1.167)***
Age		−0.688 (0.061)***	−0.710 (0.063)***	−0.724 (0.067)***		−0.870 (0.069)***	−0.827 (0.074)***	−0.816 (0.079)***
Race/ethnicity (Ref. Non-Hispanic white)								
Non-Hispanic black		−7.392 (1.679)***	−7.163 (1.620)***	−7.258 (1.669)***		−14.162 (1.649)***	−13.330 (1.607)***	−13.045 (1.648)***
Hispanics		−3.489 (1.937)	−4.127 (1.920)*	−3.362 (1.977)		−0.160 (1.829)	−0.097 (1.821)	−0.222 (1.856)
Others		−11.573 (3.649)**	−12.075 (3.744)**	−12.230 (3.795)**		−6.758 (3.796)	−4.650 (3.545)	−4.584 (3.594)
Educational attainment (Ref. Less than high school)								
High school graduate		8.635 (1.362)***	7.957 (1.387)***	8.108 (1.425)***		9.880 (1.393)***	9.862 (1.382)***	9.604 (1.420)***
More than high school		12.943 (1.263)***	11.952 (1.271)***	12.120 (1.305)***		13.774 (1.397)***	13.030 (1.362)***	12.039 (1.414)***
Annual household income (Ref. <$20,000)								
$20,000-$75,000		6.860 (1.108)***	6.233 (1.141)***	5.978 (1.184)***		4.236 (1.228)***	4.046 (1.238)**	4.249 (1.259)***
>$75,000		11.912 (1.533)***	10.945 (1.515)***	10.518 (1.568)***		5.292 (1.757)**	4.952 (1.755)**	4.929 (1.745)**
Smoking status (Ref. Nonsmoker)								
Former smoker			−2.716 (1.038)**	−2.407 (1.087)*			0.413 (1.261)	0.902 (1.293)
Current smoker			−3.295 (1.590)*	−3.565 (1.671)*			0.795 (1.663)	1.115 (1.703)
Alcohol intake 12 drinks/year (Ref. No)			2.143 (1.081)*	1.750 (1.127)			2.361 (1.185)*	1.817 (1.223)
Moderate/ vigorous physical activities (Ref. No)			2.310 (1.050)*	1.981 (0.880)*			2.530 (1.096)*	2.360 (1.107)*

	Weighted β coefficients (Standard Error)							
	Men (n = 1,267)				Women (n = 1,268)			
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Variables								
Obesity (Ref. No)				−0.987 (1.062)				−0.601 (1.185)
Hypertension (Ref. No)				−1.479 (0.457) *				−0.671 (0.576)
Diabetes mellitus (Ref. No)				−1.818 (0.476) **				−2.869 (0.654) **
Model Fit								
F	24.633	81.630	43.033	56.245	37.924	79.809	43.591	57.390
Significance	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R^2	0.027	0.439	0.439	0.447	0.037	0.427	0.438	0.443

Note:

Model 1: unadjusted.

Model 2: adjusted for sociodemographic variables (age, race/ethnicity, education, and income).

Model 3: additionally adjusted for behavioral characteristics (smoking, alcohol intake, and physical exercise).

Model 4: additionally adjusted for health-related characteristics (obesity, hypertension, and diabetes).

*
$p < 0.05$,

**
$p < 0.01$,

***
$p < 0.001$

Table 3.

Associations of social isolation with inflammatory markers

Variables	Log C-reactive Protein				Log Plasma Fibrinogen				Log Serum Albumin			
	Weighted β coefficients (Standard Error)											
	Men		Women		Men		Women		Men		Women	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Social isolation (Ref. No)	0.284 (0.109) **	0.226 (0.110) *	0.040 (0.099)	0.011 (0.103)	0.069 (0.025) **	0.058 (0.026) *	0.060 (0.022) **	0.040 (0.022)	0.375 (0.157) *	0.280 (0.156)	0.135 (0.102)	0.035 (0.101)
Age		0.017 (0.006) **		−0.015 (0.006) **		0.005 (0.001) ***		0.004 (0.001) ***		0.012 (0.006) *		0.019 (0.007) *
Race/ethnicity (Ref. Non-Hispanic white)												
Non-Hispanic black		0.062 (0.139)		0.040 (0.122)		0.050 (0.037)		0.036 (0.023)		0.119 (0.161)		0.166 (0.152)
Hispanics		0.429 (0.172) *		−0.073 (0.141)		0.127 (0.040) **		0.023 (0.025)		0.261 (0.197)		0.208 (0.180)
Others		−0.503 (0.411)		−0.572 (0.286) *		0.004 (0.061)		−0.010 (0.048)		−0.160 (0.203)		0.308 (0.341)
Educational attainment (Ref. Less than high school)												
High school graduate		0.068 (0.108)		−0.161 (0.110)		0.019 (0.022)		−0.015 (0.021)		−0.071 (0.131)		−0.123 (0.128)
More than high school		0.087 (0.112)		−0.107 (0.107)		0.013 (0.023)		0.007 (0.020)		−0.119 (0.117)		−0.054 (0.123)
Annual household income (Ref. <$20,000)												
$20,000–$75,000		−0.101 (0.098)		−0.026 (0.090)		0.001 (0.020)		−0.026 (0.017)		−0.022 (0.106)		−0.053 (0.090)
>$75,000		−0.218 (0.151)		−0.123 (0.146)		−0.007 (0.028)		−0.066 (0.023) **		0.011 (0.133)		−0.212 (0.125)
Smoking status (Ref. Nonsmoker)												
Former smoker		0.195 (0.095) *		0.132 (0.097)		0.015 (0.018)		0.011 (0.017)		−0.075 (0.092)		0.120 (0.095)
Current smoker		0.794 (0.157) ***		0.030 (0.142)		0.157 (0.028) ***		0.044 (0.025)		0.020 (0.132)		0.000 (0.116)
Alcohol intake 12		−0.077 (0.111)		0.052 (0.088)		−0.031 (0.021)		−0.006 (0.015)		0.122 (0.109)		0.031 (0.100)

	Log C-reactive Protein				Log Plasma Fibrinogen				Log Serum Albumin			
	Weighted β coefficients (Standard Error)											
	Men		Women		Men		Women		Men		Women	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Variables												
drinks/year (Ref. No)												
Moderate/ vigorous physical activities (Ref. No)		−0.167 (0.092)		−0.168 (0.084) *		−0.026 (0.018)		−0.043 (0.015) **		−0.092 (0.100)		−0.090 (0.085)
Obesity (Ref. No)		0.417 (0.090) ***		0.492 (0.091) ***		0.032 (0.017)		0.056 (0.016) ***		0.129 (0.098)		0.177 (0.115)
Hypertension (Ref. No)		0.041 (0.085)		0.164 (0.084)		0.012 (0.016)		−0.016 (0.015)		0.136 (0.078)		0.109 (0.081)
Diabetes mellitus (Ref. No)		0.022 (0.114)		0.075 (0.113)		0.057 (0.022) **		0.044 (0.021) *		0.425 (0.141) **		0.142 (0.147)
Model Fit												
F	5.668	4.162	4.940	6.759	3.845	4.749	6.380	7.246	5.669	6.200	6.320	7.736
Significance	0.017	0.000	0.000	0.000	0.050	0.005	0.000	0.000	0.017	0.004	0.000	0.188
R^2	0.007	0.098	0.106	0.112	0.006	0.099	0.108	0.128	0.012	0.059	0.062	0.092

Note:

Model 1: unadjusted.

Model 2: adjusted for sociodemographic variables (age, race/ethnicity, education, and income), behavioral characteristics (smoking, alcohol intake, and physical exercise), and health-related characteristics (obesity, hypertension, and diabetes).

*
$p < 0.05$

**
$p < 0.01$

***
$p < 0.001$