Brain, Behavior, & Immunity - Health 22 (2022) 100465

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Women with lower systemic inflammation demonstrate steeper cognitive decline with age: Results from a large prospective, longitudinal sample

Melody Moloci Noss [a], Summer N. Millwood [b], Kate R. Kuhlman [a,c,d,*]

[a] Department of Psychological Science, University of California Irvine, Irvine, CA, USA
[b] Department of Psychology, University of Denver, Denver, CO, USA
[c] Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA
[d] Institute for Interdisciplinary Salivary Bioscience Research, School of Social Ecology, University of California Irvine, Irvine, CA, USA

ARTICLE INFO

Keywords:
C-reactive protein
CRP
Women's health
Neurodegeneration
Cognitive decline
Aging

ABSTRACT

Background: Men and women experience large disparities in prevalence, detection, and clinical course of neurodegenerative diseases. Inflammation has been implicated in the pathogenesis of neurodegenerative diseases, yet there is a paucity of literature documenting sex differences in this phenomenon in prospective, longitudinal studies.
Methods: Participants were 4217 non-smoking individuals (62.2% female; aged 46–91 at enrollment) enrolled in the Health and Retirement Study who provided dried blood spots and completed a standardized assessment of cognitive function 3 times across 8 years. Inflammation was indexed using C-reactive protein (CRP).
Results: Higher CRP was associated with lower concurrent cognitive function, $b = -0.13$ ($SE = 0.06$), $p < .05$, but less decline in cognitive function over time, $b = 0.02$ ($SE = 0.01$), $p < .05$. Sex moderated the association between CRP and decline in total cognitive function, $b = 0.02$ ($SE = 0.01$), $p < .05$, such that the steepest declines in cognitive function were observed among women with the lowest CRP concentrations.
Conclusions: Women with lower systemic inflammation as measured by CRP may be at risk of going undetected for neurodegenerative disease, especially given their overall higher cognitive scores. This may perpetuate sex-related disparities in prevention and clinical course. Attention to the underlying biological mechanisms explaining the link between lower CRP and risk for cognitive decline for women and its potential clinical implications are needed.

1. Introduction

Many domains of cognitive function decline across adulthood (Harada et al., 2013). Patterns of steep cognitive decline have been associated with 10–15% increased risk for progression to dementia (Plassman et al., 2008). There are over 46 million individuals living with dementia worldwide and this number has been projected to increase to 131.5 million by 2050 (Prince et al., 2015). Additionally, costs associated with caring for the increasing number of individuals with cognitive impairment is on the rise as we expect the geriatric population to nearly double from 2015 to 2050 (World Health Organization, 2018). Indeed, dementia is expected to become a trillion-dollar disease (Podcasy and Epperson, 2016). More research is warranted to identify mechanisms that contribute to abnormal cognitive function as well as risk factors that presage steep cognitive decline.

The natural, chronic increase in pro-inflammatory markers as one ages, known as "inflammaging" (Franceschi et al., 2000), has been associated with age-related diseases and has been implicated in steeper cognitive decline and neurodegenerative diseases (Xia et al., 2016). These measures of systemic inflammation have been correlated with inflammation in the brain and spinal cord (Lasselin et al., 2018), and can be activated by peripheral inflammation (Lin et al., 2018). For this reason, elevated inflammation may contribute to age-related cognitive decline and increased risk of developing dementia and Alzheimer's Disease (AD) (Hanamsagar and Bilbo, 2016). Elevated systemic inflammation in midlife (ages 50–65), as indexed by C-Reactive Protein (CRP), has been prospectively associated with steeper cognitive decline over the next 20 years (Walker et al., 2019; Zheng and Xie, 2018). That being said, other longitudinal studies have observed no association between CRP and rate of cognitive decline among adults in their 70s (Metti

* Corresponding author. 4201 Social & Behavioral Sciences Gateway, Irvine, CA, 92697, USA.
E-mail address: krkuhl@uci.edu (K.R. Kuhlman).

https://doi.org/10.1016/j.bbih.2022.100465
Received 4 November 2021; Received in revised form 15 April 2022; Accepted 21 April 2022
Available online 2 May 2022

et al., 2014). Clarifying when and for whom systemic inflammation predicts declines in cognitive function is critical to advances in our basic understanding and their translation to clinical contexts.

For many evolutionary and biological reasons (Metcalf et al., 2020), sex may moderate the link between inflammation and age-related changes in cognitive function, but results are mixed. Cardiovascular risk factors such as hypertension and obesity predict differential patterns of cognitive decline for males and females (aged 55–92) followed for up to 20 years (Armstrong et al., 2019). Cognitive impairments and neurodegenerative diseases proceed more rapidly in females once diagnosed (Podcasy and Epperson, 2016), which may be the result of altered communication between the brain and immune system following the post-menopausal decrease in estrogen (Benedusi et al., 2012; Vegeto et al., 2008). To that end, both prospective longitudinal and cross-sectional studies have reported stronger associations between elevated inflammation and decline of global cognitive function among women compared to men (aged 51–90 years) (Boccardi et al., 2019; Milan-Mattos et al., 2019; Sohn et al., 2018). Contrastingly, in a study of inflammation and global cognitive function among Black individuals in their 60s with hypertension, elevated CRP and interleukin (IL)-6 were associated with global cognitive decline over the following 7 years in men but not women (West et al., 2020). Given the paucity of research in this area and equivocal findings, there has been a call to action for more prospective work exploring the specific moderating role of sex on the association between inflammation and cognitive decline in later adulthood (Carter et al., 2012; Nebel et al., 2018).

The current study aimed to address this gap in the literature using a large, nationally representative sample in which we assessed the association between CRP and cognitive function over 8 years. Based on previous literature, we expected that older adults with elevated systemic inflammation would demonstrate lower cognitive function and greater decline in cognitive function over time. Additionally, we predicted that sex would moderate the association between inflammation and cognitive function, such that women would experience steeper decline in cognitive function over time.

2. Methods

2.1. Participants

Participants in the present analytic sample included 4217 participants enrolled in the Health and Retirement Study (HRS) who provided blood samples 3 times in the biennial assessments that occurred between 2006 and 2016, who had at least one CRP observation <12 mg/L, and did not smoke (O'Connor et al., 2009). Of these participants, 62.2% were female, 84.8% identified as White/Caucasian, 7.7% identified as Hispanic, 11.9% identified as Black or African American, and 3.4% identified as Other; 69.3% were married at the start of the study, while 14.4% were widowed and 8.6% were divorced.

The data for this study were from the HRS 2006/2010/2014 (cohort A) and 2008/2012/2016 (cohort B) interview waves, resulting in 3 timepoints: 2006/2008 (T1), 2010/2012 (T2), and 2014/2016 (T3). This analytic sample of 4217 participants (2236 from cohort A, 1981 from cohort B) represented about 22.3% and 20.7% of the 10,026 and 9587 HRS participants *eligible* to participate in the blood collection and assessments of cognitive function in 2006 or 2008, respectively. Each wave had an 88.6% response rate. They represent 25.2% and 23.3% of those who responded in 2006 and 2008. See HRS documentation for more details (Staff, 2017; Sonnega et al., 2014).

2.2. Procedures

The HRS is an ongoing, nationally representative and longitudinal panel study that has interviewed Americans over the age of 50 every 2 years since 1992 (Sonnega et al., 2014). The HRS has a steady-state design, with new participants recruited every 6 years. The HRS has collected data via enhanced face-to-face (EFTF) interviews since 1992. Beginning in 2006, approximately 50% of HRS participants were randomly selected for an EFTF, which included physical health measures as well as assessments of cognitive function that occurred in the participant's home. Blood collection also took place during this EFTF at the participant's home. After the interview, participants completed a psychosocial questionnaire, which they mailed to the University of Michigan upon completion. The other half of the HRS population participated in the EFTF two years later, creating two cohorts.

2.3. Measures

Cognitive Function. Cognitive function, assessed at each timepoint, was measured using an adapted version of the Telephone Interview for Cognitive Status (TICS; Brandt et al., 1988) in addition to other items that assess cognitive function at each EFTF. The battery of cognitive assessments evaluated immediate and delayed word recall, a serial 7s subtraction test of working memory, counting backwards from 20 to assess attention and processing speed, and tests of abstract reasoning, fluid reasoning, and vocabulary to assess intelligence (Ofstedal et al., 2005; Sonnega et al., 2014). For respondents ages 65 and older or those who had not been interviewed in a prior wave (i.e., new cohorts), additional tasks included an object naming test to assess language and recall of the date and current president and vice-president to assess orientation. Because the assessment battery was identical at each wave, several measures were taken to reduce the influence of learning or practice effects on scores. For example, 4 different but equivalent word lists were developed for the word recall assessment, and counterbalanced across participants (see Ofstedal et al., 2005 pages 17–19 for details). A global cognitive function score was calculated by summing the number of correct responses to all of the cognitive items that were common across all waves. Values could range from 0 to 35. Higher scores reflected better cognitive function, and scores below 8 indicated cognitive impairment (Crimmins et al., 2011).

Inflammation. Inflammation was indexed using high-sensitivity CRP collected via dried blood spots (DBS) at each timepoint. Blood samples were taken by trained research assistants after cleaning the participant's finger with an alcohol swab, pricking the finger with a sterile lancet, and then collecting blood droplets on treated filter paper. The sample was dried for 10–15 min and then placed in foil envelopes with a desiccant packet. Samples were shipped to either BioSafe (prior to 2008) or the University of Michigan (after 2008) for cold storage (−70 °C) until processing. CRP was assayed via nephelometry or enzyme-linked immunosorbent assay (ELISA) at either the University of Vermont or the University of Washington. Procedures varied slightly for each wave of data collection and detailed documentation was provided by the HRS team separately for each cohort (Crimmins et al., 2013a,b, 2015, 2017, 2020). Because CRP concentrations based on DBS vary across assays and laboratories, the HRS core constructed an adjusted CRP variable based on plasma-based CRP concentrations in a similarly aged and nationally representative sample, the National Health and Nutrition Examination Survey (NHANES). NHANES equivalent values are recommended for all analyses (Crimmins et al., 2013a,b, 2014). Inter-assay variability was 11.0% and intra-assay variability was 8.1%. The lower limit of detection for these assays was 0.035 mg/L. Up to 13% of samples at each wave were missing due to concentrations below the limit of detection. Valid CRP concentrations were available for 5817 participants in 2006, 5777 in 2008, 7528 in 2010, 6976 in 2012, 6749 in 2014, and 6869 in 2016. Individual CRP observations >12 mg/L were further excluded from analysis in order to attenuate associations between CRP and non-cognitive sickness behaviors (e.g., fatigue) and affective symptoms (Moriarity et al., 2021), which are important confounds in assessments of cognitive function. While exclusion of CRP concentrations >10 mg/L are most common (Mac Giollabhui et al., 2021; O'Connor et al., 2009), it has become clear that this cut-off may truncate sample populations at the expense of generalizability (Giollabhui et al., 2020), therefore a

cut-off of 12 was used to maximize data but exclude participants with CRP >3 standard deviations from the mean at any wave.[1] This resulted in the exclusion of 30 participants whose CRP concentrations were >12 mg/L at all 3 waves, but the inclusion of other participants with at least one CRP concentration in the normal range. These high concentrations represented 6% of the CRP measures.

Sex. Participants reported their biological sex assigned at birth, male or female, at study enrollment.

Covariates. Covariates included anthropometric and sociodemographic variables known to influence inflammation and cognitive decline. Covariates included age, race (White/Caucasian, Black/African American, Other), ethnicity (non-Hispanic, Hispanic) and body mass index (BMI) collected at each assessment. BMI was calculated using height and weight collected by HRS interviewers.

2.4. Data analysis

All continuous variables were assessed for normality and heteroscedasticity. CRP was transformed using the natural log transformation to reduce skewness. All analyses were conducted using linear mixed models with measurements nested within waves within participants. All models employed an unstructured covariance matrix and included random intercepts and slopes. Overall, we estimated cognitive function in six models. The first estimated cognitive function predicted by time (model 1). The second estimated cognitive function predicted by time and CRP (model 2). Concentrations of CRP at each assessment were time-varying, and grand-mean centered in order to estimate the association between individual differences in systemic inflammation and cognitive function. The third estimated cognitive function predicted by time, CRP, and the interaction between time and CRP (model 3). The fourth estimated cognitive function predicted by time, CRP, the interaction between time and CRP, sex, the interaction between time and sex, and the 3-way interaction between time, sex, and CRP (model 4). The fifth model then tested whether the results of model 4 were robust to covariation with key covariates (BMI, age, marital status, ethnicity, race, and current depressive symptoms) (model 5). We then stratified our analyses by values of the moderator (sex) to compute simple slopes for males and females separately. The final step in our analyses was to conduct sensitivity analyses to determine whether the results changed meaningfully when individuals without clinically meaningful elevations in CRP (CRP >12 mg/L) were or were not excluded.

3. Results

Descriptive statistics for participant characteristics, CRP, and cognitive function across the study are provided in Table 1. On average, females in the sample had higher CRP, $b = 0.26$ ($SE = 0.03$), $p < .001$, and higher cognitive function, $b = 0.92$ ($SE = 0.11$), $p < .001$, throughout the study.

Table 2 provides coefficient estimates predicting cognitive function predicted by time, CRP, sex, and their interactions. Total cognitive scores reliably declined approximately one quarter of a point each year, $b = -0.25$ ($SE = 0.01$), *95%CI*[−0.27, −0.24], $p < .001$, and this observation was robust when accounting for key covariates, $p < .001$. Higher CRP was associated with lower cognitive function, $b = -0.13$ ($SE = 0.06$), *95%CI*[−0.24, −0.01], $p = .03$, but less cognitive decline over time, $b = 0.02$ ($SE = 0.01$), *95%CI*[0.003, 0.04], $p = .019$ (See Model 3 in Table 2).

Sex moderated the association between inflammation and cognitive function. Female participants exhibited better cognitive function initially, $b = 0.82$ ($SE = 0.15$), *95%CI*[0.53, 1.11], $p < .001$, and larger declines in cognitive function over time, $b = -0.04$ ($SE = 0.02$), *95%CI*[−0.08, −0.01], $p = .02$. Declines in cognitive function were mitigated for women with higher CRP, $b = 0.03$ ($SE = 0.01$), *95%CI*[0.01, 0.05], $p = .008$ (See Model 4 in Table 2). This interaction between time, CRP, and sex remained after accounting for key covariates, $b = 0.02$ ($SE = 0.01$), *95%CI*[0.002, 0.05], $p = .029$.

Fig. 1 illustrates cognitive function over time predicted by CRP and sex. We stratified analyses by sex to better understand the association between inflammation and cognitive decline for male and female participants separately. Among male participants, higher concentrations of CRP were associated with lower cognitive function, $b = -0.21$ ($SE = 0.09$), *95%CI*[−0.38, −0.03], $p = .021$, but not change in cognitive function over time, $b = 0.009$ ($SE = 0.01$), *95%CI*[−0.01, 0.03], $p = .43$. Among female participants, CRP was not associated with cognitive function on average, $b = -0.11$ ($SE = 0.08$), *95%CI*[−0.26, 0.04], $p = .17$, but higher CRP was associated with less decline in cognitive function over time, $b = .028$ ($SE = 0.01$), *95%CI*[0.006, 0.05], $p = .01$.

4. Discussion

Despite expecting some degree of cognitive decline with aging, individuals with the steepest declines in cognitive function inspire the greatest concern for underlying pathology. In this large sample of aging adults followed over 8 years, women showed both greater systemic inflammation and better cognitive function than men and, consistent with the previous literature (Komulainen et al., 2007), elevated inflammation was associated with lower concurrent cognitive function. The steepest cognitive declines, however, were observed among women with lower concentrations of circulating CRP. This was partially inconsistent with our hypotheses that higher systemic inflammation would be associated with greater cognitive decline, suggesting that the opposite may be the case for women. One previous longitudinal study observed that women with more *variability* in CRP over time showed the largest declines in cognitive function (Metti et al., 2014). In contrast, other longitudinal studies with similarly large samples of older adults have observed no differences in the patterns of inflammation and cognitive decline for men and women (Walker et al., 2019; Zheng and Xie, 2018), while another observed associations between inflammation and cognitive decline only among men (West et al., 2020). Implications of these sex differences in the potential role of CRP as a risk marker for abnormal cognitive decline are discussed.

Women are at disproportionately high risk for severe neurodegenerative disease (Carter et al., 2012; Nebel et al., 2018). For women in this sample, lower CRP was associated with steeper declines in cognitive function, such that each log unit of CRP conferred about a 10% difference in the rate of cognitive decline over the 8-year observation period. Currently, preclinical and clinical investigations are focused on the role of elevated inflammation in neurodegeneration, which may be creating a gap in our understanding and detection of at-risk patients. Lower concentrations of CRP have been linked to faster cognitive decline in previous samples (Locascio et al., 2008), and can distinguish between individuals with mild or moderate cognitive impairment and healthy controls (Gong et al., 2016). With increasing age, there is an accumulation of damaged or mutated cells, and the corresponding increase in inflammation reflects the immune system's continued effort to eliminate them from the body (Franceshi et al., 2000). Immune cells play a critical role maintaining the structure and function of the central nervous system throughout the lifespan (Leszek et al., 2016; Mayne et al., 2020; Salvador et al., 2021), which may explain why higher concentrations of CRP were not associated with steeper cognitive decline over time in our sample. Thus, one possible explanation for our observation linking *lower* systemic inflammation with *steeper* cognitive decline in females is that these women have a dysregulated immune system which is not actively

[1] Given ongoing debate regarding use of elevated CRP concentrations in data analysis, primary hypotheses were tested using multiple approaches. First, we winsorized all values >12 mg/L to 12 mg/L. Second, we retested our hypotheses without removing or modifying these high values, but stratifying our models by established or commonly used CRP cut-offs (>3 mg/L and >10 mg/L). Neither resulted in a different pattern of results.

Table 1
Participant characteristics across the study (n = 4217; cohort A = 2,236, cohort B = 1981).

		2006	2008	2010	2012	2014	2016
Age (years)	M (SD)	66.67 (7.02)	68.63 (7.03)	70.94 (7.09)	72.73 (7.02)	74.59 (7.03)	76.53 (6.88)
BMI	M (SD)	28.54 (5.55)	28.64 (5.64)	28.63 (5.78)	28.48 (5.74)	28.34 (5.86)	28.21 (5.90)
Underweight	% (n)	0.6 (24)	0.6 (27)	0.9 (38)	1.2 (50)	1.5 (65)	1.8 (77)
Normal	% (n)	25.3 (1069)	25.3 (1068)	25.3 (1069)	25.8 (1087)	27.2 (1149)	26.8 (1104)
Overweight	% (n)	38.8 (1635)	38.8 (1635)	38.3 (1614)	37.8 (1594)	37.5 (1581)	35.5 (1496)
Obese	% (n)	33.6 (1415)	34.1 (1439)	34.5 (1453)	34.2 (1443)	32.6 (1376)	30.3 (1278)
Marital status							
Married/Partnered	% (n)	72.5 (3058)	70.7 (2982)	67.5 (2845)	65.2 (2748)	61.4 (2589)	55.2 (2329)
Divorced/separated	% (n)	9.6 (405)	9.3 (394)	9.4 (397)	9.4 (398)	9.5 (401)	9.1 (385)
Widowed	% (n)	14.4 (607)	16.9 (711)	19.6 (825)	22.3 (939)	25.8 (1086)	27.1 (1142)
CRP (mg/L)	M (SD)	2.74 (2.64)	2.69 (2.44)	2.49 (2.42)	2.47 (2.37)	2.16 (2.43)	2.54 (2.50)
3–9.99 mg/L	% (n)	27.5 (614)	28.0 (554)	24.7 (552)	23.9 (473)	20.7 (462)	23.4 (464)
≥10 mg/L	% (n)	9.8 (219)	8.2 (162)	6.5 (146)	6.8 (134)	7.6 (170)	10.1 (201)
Total cognitive function	M (SD)	23.48 (4.20)	23.30 (4.22)	22.53 (4.47)	22.33 (4.56)	22.08 (4.83)	21.64 (5.07)
	Range	7–35	4–35	4–35	2–35	2–35	1–35
Likely cognitive impairment (score < 8)	% (n)	0.0 (1)	0.3 (6)	0.3 (7)	0.9 (17)	1.2 (29)	2.0 (39)

Table 2
Estimated cognitive function over time as predicted by CRP, sex, and their interactions.

Model	1	2	3	4	5
AIC	52,223.83	52,225.45	52,221.98	52,188.10	51,008.67
	b (SE)	**b (SE)**	**b (SE)**	**b (SE)**	**b (SE)**
Intercept	23.92 (.07)***	23.94 (.08)***	23.98 (.08)***	23.50 (.12)***	25.39 (.22)***
Time	−0.25 (.01) ***	−0.26 (.01)***	−0.26 (.01)***	−0.24 (.01)***	−0.07 (.02)***
CRP (ln)		−0.02 (.04)	−0.13 (.06)*	−0.15 (.06)*	−0.16 (.06)**
Time x CRP			0.02 (.01)*	0.003 (.01)	0.01 (.01)
Sex				0.82 (.15)***	1.02 (.14)***
Time x Sex				−0.04 (.02)*	−0.04 (.02)*
Time x Sex x CRP				0.03 (.01)**	0.02 (.01)*
BMI					.05 (.06)
Age					−0.18 (.01)***
Marital status					0.47 (.10)***
Ethnicity					−2.41 (.22)***
Race					−2.16 (.13)***
Depressive symptoms					−0.18 (.02)***

***p < .001, **p < .01, *p < .05.

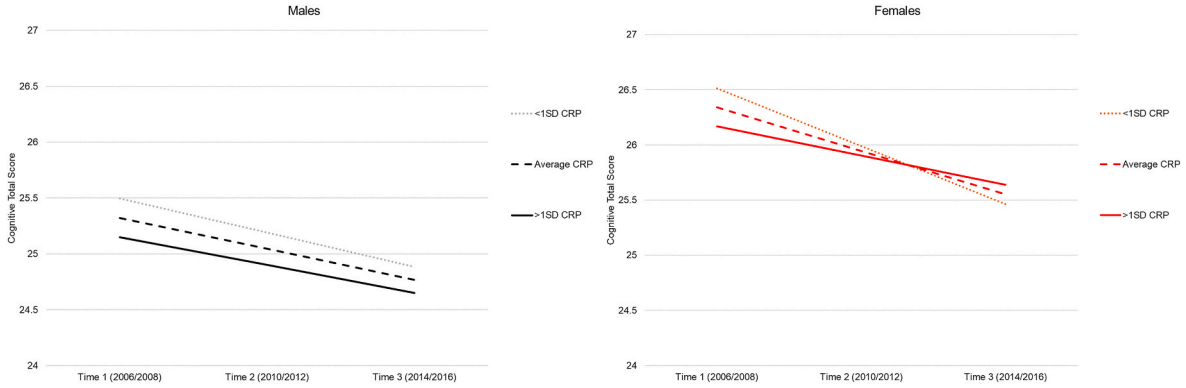

Fig. 1. Cognitive function over time in the Health and Retirement Study as a function of systemic inflammation (C-Reactive Protein) for males and females.

or consistently participating in neural maintenance (Metcalf et al., 2020; Podcasy and Epperson, 2016).

Another explanation for the link between lower CRP and cognitive decline in women pertains to the form of CRP measured. CRP most commonly circulates, and is typically measured, in its native pentamer form, but can be broken down into its monomer form (Wu et al., 2015). Gonadal hormones have been implicated in the increased susceptibility to the accumulation of Aβ plaques among females (Carroll et al., 2010). Markers of neurodegenerative diseases such as Aβ plaques, a hallmark of AD, can actively separate pentamer CRP into its monomer form (Strang et al., 2012). Females with lower CRP in this sample may reflect a subpopulation for whom CRP is breaking down and contributing to local inflammatory processes that contribute to cognitive decline (Luan and Yao, 2018; Wu et al., 2015). Simultaneous measurement of native and monomer CRP in studies of inflammatory processes in cognitive decline may help to address this possibility (Zhang et al., 2018).

The results of this investigation should be interpreted in the context of the study's limitations. Only HRS participants with complete data

were included in the present analyses, creating a sampling bias in favor of healthier and higher functioning participants motivated to contribute to this longitudinal study. Yet, the results of our models are similar for CRP concentrations up to 10 mg/L and a considerable proportion of the sample was in a clinically elevated range for this biomarker (nearly one third of observed CRP concentrations were >3 mg/L). To this point, cognitive function in our sample only changed approximately one quarter of a point between each time-point, indicating that our average participant did not experience much cognitive decline over the assessment period. This may reflect the limitations of using a global cognition score compared to detailed evaluations of specific cognitive domains particularly in a non-clinical sample. Each domain of cognitive function assessed as part of this composite was assessed with only a single subtest, and studies with a more comprehensive approach to neuropsychological assessment may be able to extend these observations by identifying specific domains of cognition that are more strongly associated with inflammation, and determine whether these patterns differ for men and women. CRP is a peripheral, systemic inflammatory marker. Other measures of systemic and neuroinflammation, such as IL-1β, IL-6, TNF, & IFN-γ, may provide further insight into the link between inflammation and factors affecting change in cognitive function (Boccardi et al., 2019; Ng et al., 2018; Rafnsson et al., 2007; Walker et al., 2019; Zheng and Xie, 2018). Finally, sex was indexed using a self-report and binary variable. Given the literature supporting the important role of gonadal hormones in neurodegeneration and regulation of brain-immune communication (Benedusi et al., 2012; Carroll et al., 2010; Vegeto et al., 2008), a direct measure of gonadal hormones would be important to incorporate into future work. Despite these limitations, data from this large, national sample followed longitudinally for 8 years indicated that women with the lowest concentrations of CRP showed the steepest decline in cognitive function, despite higher cognitive scores overall. Importantly, women with lower systemic inflammation, particularly those with higher cognitive scores, may be at risk of going undetected for neurodegenerative diseases which may further contribute to the sex-related disparities in prevention and clinical course.

Conflicts of interest

The authors have no conflicts of interest to report.

Acknowledgements

Collection of the data used in the present study was funded by the National Institute on Aging (U01AG09740) and the Social Security Administration and conducted by the Institute for Social Research at the University of Michigan. Composition of this manuscript was made possible in part by the National Institute of Mental Health (K08MH112773; PI: Kuhlman). We would like to thank the team members of the Teen Resilience Lab (www.teenresilience.org) for their feedback on previous drafts of this manuscript.

References

Armstrong, N.M., An, Y., Beason-Held, L., Doshi, J., Erus, G., Ferrucci, L., Davatzikos, C., Resnick, S.M., 2019. Sex differences in brain aging and predictors of neurodegeneration in cognitively healthy older adults. Neurobiol. Aging 81, 146–156. https://doi.org/10.1016/j.neurobiolaging.2019.05.020.

Benedusi, V., Meda, C., Della Torre, S., Monteleone, G., Vegeto, E., Maggi, A., 2012. A lack of ovarian function increases neuroinflammation in aged mice. Endocrinology 153, 2777–2788. https://doi.org/10.1210/en.2011-1925.

Boccardi, V., Paolacci, L., Remondini, D., Giampieri, E., Poli, G., Curti, N., Cecchetti, R., Villa, A., Ruggiero, C., Brancorsini, S., Mecocci, P., 2019. Cognitive decline and Alzheimer's disease in old age: a sex-specific cytokinome signature. J. Alzheim. Dis. 72, 911–918. https://doi.org/10.3233/JAD-190480.

Brandt, J., Spencer, M., Folstein, M., 1988. The telephone interview for cognitive status. Cognit. Behav. Neurol. 1.

Carroll, J.C., Rosario, E.R., Kreimer, S., Villamagna, A., Gentzschein, E., Stanczyk, F.Z., Pike, C.J., 2010. Sex differences in β-amyloid accumulation in 3xTg-AD mice: role of neonatal sex steroid hormone exposure. Brain Res. 1366, 233–245. https://doi.org/10.1016/j.brainres.2010.10.009.

Carter, C.L., Resnick, E.M., Mallampalli, M., Kalbarczyk, A., 2012. Sex and gender differences in Alzheimer's disease: recommendations for future research. J. Wom. Health 21, 1018–1023, 2002.

Crimmins, E.M., Kim, J.K., Langa, K.M., Weir, D.R., 2011. Assessment of cognition using surveys and neuropsychological assessment: the health and retirement study and the aging, demographics, and memory study. J. Gerontol. B Psychol. Sci. Soc. Sci. 66B, i162–i171. https://doi.org/10.1093/geronb/gbr048.

Crimmins, E.M., Faul, J.D., Kim, J.K., Guyer, H., Langa, K.M., Ofstedal, M.B., Sonnega, A., Wallace, R., Weir, D.R., 2013a. HRS Documentation Report: Documentation of Biomarkers in the 2006 and 2008 Health and Retirement Study.

Crimmins, E.M., Kim, J.K., McCreath, H., Seeman, T., 2013b. Results from the Health and Retirement Study Biomarker Validation Project. Ann Arbor MI Inst. Soc. Res. Univ. Mich.

Crimmins, E.M., Kim, J.K., McCreath, H., Faul, J., Weir, D., Seeman, T., 2014. Validation of blood-based assays using dried blood spots for use in large population studies. Biodemogr. Soc. Biol. 60, 38–48. https://doi.org/10.1080/19485565.2014.901885.

Crimmins, E.M., Faul, J., Kim, J., Weir, D., 2015. Documentation of Biomarkers in the 2010 and 2012 Health and Retirement Study [WWW Document].

Crimmins, E.M., Faul, J., Kim, J.K., Weir, D., 2017. Documentation of Blood-Based Biomarkers in the 2014 Health and Retirement Study.

Crimmins, E.M., Faul, J., Kim, J.K., Weir, D., 2020. Documentation of DBS Blood-Based Biomarkers in the 2016 Health and Retirement Study.

Franceschi, C., Bonafe, M., Valensin, S., Olivieri, F., De Luca, M., Ottsviani, E., Benedictis, G., 2000. Inflamm-aging: an evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 908, 244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x.

Giollabhui, N.M., Ellman, L.M., Coe, C.L., Byrne, M.L., Abramson, L.Y., Alloy, L.B., 2020. To exclude or not to exclude: considerations and recommendations for C-Reactive Protein values higher than 10 mg/L. Brain Behav. Immun. 87, 898–900. https://doi.org/10.1016/j.bbi.2020.01.023.

Gong, C., Wei, D., Wang, Y., Ma, J., Yuan, C., Zhang, W., Yu, G., Zhao, Y., 2016. A meta-analysis of C-reactive protein in patients with Alzheimer's disease. Am. J. Alzheimer's Dis. Other Dementias 31, 194–200. https://doi.org/10.1177/1533317515602087.

Hanamsagar, R., Bilbo, S.D., 2016. Sex differences in neurodevelopmental and neurodegenerative disorders: focus on microglial function and neuroinflammation during development. J. Steroid Biochem. Mol. Biol. 160, 127–133. https://doi.org/10.1016/j.jsbmb.2015.09.039. SI: Steroids & Nervous System.

Harada, C.N., Natelson Love, M.C., Triebel, K.L., 2013. Normal cognitive aging. Clin. Geriatr. Med. 29, 737–752. https://doi.org/10.1016/j.cger.2013.07.002.

Komulainen, P., Lakka, T.A., Kivipelto, M., Hassinen, M., Penttilä, I.M., Helkala, E.-L., Gylling, H., Nissinen, A., Rauramaa, R., 2007. Serum high sensitivity C-reactive protein and cognitive function in elderly women. Age Ageing 36, 443–448. https://doi.org/10.1093/ageing/afm051.

Lasselin, J., Lekander, M., Axelsson, J., Karshikoff, B., 2018. Sex differences in how inflammation affects behavior: what we can learn from experimental inflammatory models in humans. Front. Neuroendocrinol. 50, 91–106. https://doi.org/10.1016/j.yfrne.2018.06.005.

Leszek, J., Barreto G, E., Gasiorowski, K., Koutsouraki, E., Ávila-Rodrigues, M., Aliev, G., 2016. Inflammatory mechanisms and oxidative stress as key factors responsible for progression of neurodegeneration: role of brain innate immune system. CNS Neurol. Disord. - Drug Targets 15, 329–336.

Lin, T., Liu, G.A., Perez, E., Rainer, R.D., Febo, M., Cruz-Almeida, Y., Ebner, N.C., 2018. Systemic inflammation mediates age-related cognitive deficits. Front. Aging Neurosci. https://doi.org/10.3389/fnagi.2018.00236.

Locascio, J.J., Fukumoto, H., Yap, L., Bottiglieri, T., Growdon, J.H., Hyman, B.T., Irizarry, M.C., 2008. Plasma amyloid β-protein and C-reactive protein in relation to the rate of progression of Alzheimer disease. Arch. Neurol. 65, 776–785. https://doi.org/10.1001/archneur.65.6.776.

Luan, Y., Yao, Y., 2018. The clinical significance and potential role of C-reactive protein in chronic inflammatory and neurodegenerative diseases. Front. Immunol. https://doi.org/10.3389/fimmu.2018.01302.

Mac Giollabhui, N., Ng, T.H., Ellman, L.M., Alloy, L.B., 2021. The longitudinal associations of inflammatory biomarkers and depression revisited: systematic review, meta-analysis, and meta-regression. Mol. Psychiatr. 26, 3302–3314. https://doi.org/10.1038/s41380-020-00867-4.

Mayne, K., White, J.A., McMurran, C.E., Rivera, F.J., de la Fuente, A.G., 2020. Aging and neurodegenerative disease: is the adaptive immune system a friend or foe? Front. Aging Neurosci. 12, 305. https://doi.org/10.3389/fnagi.2020.572090.

Metcalf, C.J.E., Roth, O., Graham, A.L., 2020. Why leveraging sex differences in immune trade-offs may illuminate the evolution of senescence. Funct. Ecol. 34, 129–140. https://doi.org/10.1111/1365-2435.13458.

Metti, A.L., Yaffe, K., Boudreau, R.M., Simonsick, E.M., Carnahan, R.M., Satterfield, S., Harris, T.B., Ayonayon, H.N., Rosano, C., Cauley, J.A., 2014. Trajectories of inflammatory markers and cognitive decline over 10 years. Neurobiol. Aging 35, 2785–2790. https://doi.org/10.1016/j.neurobiolaging.2014.05.030.

Milan-Mattos, J.C., Anibal, F.F., Perseguini, N.M., Minatel, V., Rehder-Santos, P., Castro, C.A., Vasilceac, F.A., Mattiello, S.M., Faccioli, L.H., Catai, A.M., 2019. Effects of natural aging and gender on pro-inflammatory markers. Braz. J. Med. Biol. Res. 52 https://doi.org/10.1590/1414-431X20198392.

Moriarity, D.P., Horn, S.R., Kautz, M.M., Haslbeck, J.M.B., Alloy, L.B., 2021. How handling extreme C-reactive protein (CRP) values and regularization influences CRP and depression criteria associations in network analyses. Brain Behav. Immun. 91, 393–403. https://doi.org/10.1016/j.bbi.2020.10.020.

Nebel, R.A., Aggarwal, N.T., Barnes, L.L., Gallagher, A., Goldstein, J.M., Kantarci, K., Mallampalli, M.P., Mormino, E.C., Scott, L., Yu, W.H., Maki, P.M., Mielke, M.M.,

2018. Understanding the impact of sex and gender in Alzheimer's disease: a call to action. Alzheimer's Dementia 14, 1171–1183. https://doi.org/10.1016/j.jalz.2018.04.008.

Ng, A., Tam, W.W., Zhang, M.W., Ho, C.S., Husain, S.F., McIntyre, R.S., Ho, R.C., 2018. IL-1β, IL-6, TNF- α and CRP in elderly patients with depression or Alzheimer's disease: systematic review and meta-analysis. Sci. Rep. 8, 12050 https://doi.org/10.1038/s41598-018-30487-6.

Ofstedal, M., Fisher, G., Herzog, A.R., 2005. Documentation of Cognitive Functioning Measures in the Health and Retirement Study. Institute for Social Research, University of Michigan, Ann Arbor, Michigan.

O'Connor, M.-F., Bower, J.E., Cho, H.J., Creswell, J.D., Dimitrov, S., Hamby, M.E., Hoyt, M.A., Martin, J.L., Robles, T.F., Sloan, E.K., Thomas, K.S., Irwin, M.R., 2009. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. Brain Behav. Immun. 23, 887–897. https://doi.org/10.1016/j.bbi.2009.04.005.

Plassman, B.L., Langa, K.M., Fisher, G.G., Heeringa, S.G., Weir, D.R., Oftedal, M.B., Burke, J.R., Hurd, M.D., Potter, G.G., Rodgers, W.L., Steffens, D.C., McArdle, J.J., Willis, R.J., Wallace, R.B., 2008. Prevalence of cognitive impairment without dementia in the United States. Ann. Intern. Med. 148, 427–434. https://doi.org/10.7326/0003-4819-148-6-200803180-00005.

Podcasy, J.L., Epperson, C.N., 2016. Considering sex and gender in Alzheimer disease and other dementias. Dialogues Clin. Neurosci. 18, 437–446.

Prince, M.J., Wimo, A., Guerchet, M.M., Ali, G.C., Wu, Y.-T., Prina, M., 2015. World Alzheimer Report 2015-The Global Impact of Dementia: an Analysis of Prevalence, Incidence, Cost and Trends.

Rafnsson, S.B., Deary, I.J., Smith, F.B., Whiteman, M.C., Rumley, A., Lowe, G.D.O., Fowkes, F.G.R., 2007. Cognitive decline and markers of inflammation and hemostasis: the Edinburgh artery study. J. Am. Geriatr. Soc. 55, 700–707. https://doi.org/10.1111/j.1532-5415.2007.01158.x.

Salvador, A.F., de Lima, K.A., Kipnis, J., 2021. Neuromodulation by the immune system: a focus on cytokines. Nat. Rev. Immunol. 21, 526–541. https://doi.org/10.1038/s41577-021-00508-z.

Sohn, D., Shpanskaya, K., Lucas, J.E., Petrella, J.R., Saykin, A.J., Tanzi, R.E., Samatova, N.F., Doraiswamy, P.M., 2018. Sex differences in cognitive decline in subjects with high likelihood of mild cognitive impairment due to Alzheimer's disease. Sci. Rep. 8, 7490. https://doi.org/10.1038/s41598-018-25377-w.

Sonnega, A., Faul, J.D., Ofstedal, M.B., Langa, K.M., Phillips, J.W., Weir, D.R., 2014. Cohort profile: the health and retirement study (HRS). Int. J. Epidemiol. 43, 576–585. https://doi.org/10.1093/ije/dyu067.

Staff, H.R.S., 2017. Sample Sizes and Response Rates [WWW Document].

Strang, F., Scheichl, A., Chen, Y.-C., Wang, X., Htun, N.-M., Bassler, N., Eisenhardt, S.U., Habersberger, J., Peter, K., 2012. Amyloid plaques dissociate pentameric to monomeric C-reactive protein: a novel pathomechanism driving cortical inflammation in Alzheimer's disease? Brain Pathol. 22, 337–346.

Vegeto, E., Benedusi, V., Maggi, A., 2008. Estrogen anti-inflammatory activity in brain: a therapeutic opportunity for menopause and neurodegenerative diseases. Front. Neuroendocrinol. 29, 507–519. https://doi.org/10.1016/j.yfrne.2008.04.001.

Walker, K.A., Gottesman, R.F., Wu, A., Knopman, D.S., Gross, A.L., Mosley, T.H., Selvin, E., Windham, B.G., 2019. Systemic inflammation during midlife and cognitive change over 20 years: the ARIC study. Neurology 92, e1256–e1267. https://doi.org/10.1212/WNL.0000000000007094.

West, N.A., Kullo, I.J., Morris, M.C., Mosley, T.H., 2020. Sex-specific associations of inflammation markers with cognitive decline. Exp. Gerontol. 138, 110986. https://doi.org/10.1016/j.exger.2020.110986.

World Health Organization, 2018. Ageing and health [WWW Document]. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health (Accessed 15 July 2021).

Wu, Y., Potempa, L.A., Kebir, D.E., Filep, J.G., 2015. C-reactive protein and inflammation: conformational changes affect function. Biol. Chem. 396, 1181–1197. https://doi.org/10.1515/hsz-2015-0149.

Xia, S., Zhang, X., Zheng, S., Khanabdali, R., Kalionis, B., Wu, J., Wan, W., Tai, X., 2016. An update on inflamm-aging: mechanisms, prevention, and treatment. J. Immunol. Res. 2016, e8426874 https://doi.org/10.1155/2016/8426874.

Zhang, L., Li, H.-Y., Li, W., Shen, Z.-Y., Wang, Y.-D., Ji, S.-R., Wu, Y., 2018. An ELISA assay for quantifying monomeric C-reactive protein in plasma. Front. Immunol. 9.

Zheng, F., Xie, W., 2018. High-sensitivity C-reactive protein and cognitive decline: the English longitudinal study of ageing. Psychol. Med. 48, 1381–1389. https://doi.org/10.1017/S0033291717003130.