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Systemic Inflammation Is Associated with MCI and Its Subtypes: The Sydney Memory and Aging Study

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Key Words
Inflammation · Cytokines · Inflammatory markers · Mild cognitive impairment · Dementia

Abstract
Background/Aims: Raised low-grade systemic inflammation has been associated with dementia, and preliminary studies suggest an association with mild cognitive impairment (MCI). This study examines the relationship between systemic inflammation and MCI subtypes. ***Methods:*** We measured the inflammatory markers C-reactive protein, interleukins (IL)-1β, -6, -8, -10 and -12, plasminogen activator inhibitor-1 (PAI-1), serum amyloid A (SAA), tumor necrosis factor-α (TNF-α) and vascular adhesion molecule-1 (VCAM-1) in the Sydney Memory and Ageing Study (MAS) cohort, a longitudinal study of 1,037 Australians aged 70–90 years. ***Results:*** After adjusting for possible confounding variables, levels of TNF-α and SAA were higher in participants with MCI compared to cognitively normal individuals, and some sex differences were apparent. Nonamnestic multiple domain MCI was associated with higher levels of IL-1β and IL-12, TNF-α and SAA compared to cognitively normal, amnestic MCI (single and multiple domain) and nonamnestic single domain MCI. PAI-1 levels were higher in cognitively normal and nonamnestic multiple domain MCI than in amnestic multiple domain MCI. ***Conclusion:*** Our findings suggest an association between specific inflammatory markers and MCI subtypes, highlight sex differences in the association with MCI, and point to a discrete impact of systemic inflammation on cognition.

Introduction

The proposed revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V; dsm5.org) has included a new diagnostic syndrome of the minor neurocognitive disorder, which recognizes the clinical needs of

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individuals who have mild cognitive deficits but can function independently. This syndrome, currently known as mild cognitive impairment (MCI), has as its hallmark cognitive decline greater than expected for age and education level [1], and has been shown to have a high risk of progression to dementia [2]. MCI is a clinically heterogenous syndrome, and 4 subtypes have been specified to differentiate amnestic and nonamnestic cognitive profiles impaired in 1 or more domains [1], namely nonamnestic single domain MCI (nMCI), nonamnestic multiple domain MCI (nmdMCI), amnestic single domain MCI (aMCI) and amnestic multiple domain MCI (amdMCI) [2]. Recent data [3] suggest that biomarkers such as positron emission tomography imaging and measurement of CSF proteins may assist in the prediction of cognitive decline or progression to dementia in patients with MCI. These biomarkers have been incorporated into the proposed terminology for categorizing risk of developing Alzheimer's disease (AD) in patients with MCI [4], but access and tolerability issues limit the utility of these measures in routine clinical practice. The identification of other biomarkers for MCI and evaluation of their impact on progression to dementia is therefore of key importance.

Inflammation may have direct relevance to dementia [5]. Early postmortem work in AD brains found the presence of C-reactive protein (CRP), an inflammatory biomarker, in neurofibrillary tangles [6] and subsequent studies report raised levels of CRP in individuals with dementia [7, 8]. In other cross-sectional analyses, raised levels of other inflammatory biomarkers, such as cytokines interleukin-1 (IL-1β), IL-6 and tumor necrosis factor-α (TNF-α), have been consistently associated with dementia [9–15]. Recent investigations have reported differences in inflammation in dementia subtypes. For example, TNF-α was shown to be higher in vascular dementia (VaD) than in late onset AD, while IL-6 was higher in AD than in VaD [14], after controlling for cardiovascular factors. Similarly, TNF-α has been found to be lower in mild-to-moderate AD compared to severe AD and VaD [16]. Furthermore, inflammatory markers may be increased before onset of dementia [8, 17] and may predict cognitive decline [18–23].

In addition, studies in the elderly have shown that increased levels of inflammatory markers are associated with impairment of cognitive function [24–28]. Specifically, elevated levels of IL-6 have been associated with poor cognitive performance in older cohorts [26]. Similarly, raised IL-8 has been shown to be associated with impaired cognitive performance in the elderly [25]. It has been proposed that other interleukins, such as IL-12p70 and IL-10, may be implicated in age-related neurodegenerative conditions [29, 30]. Markers such as vascular cell adhesion molecule-1 (VCAM-1) may play a role in the pathophysiology of age-related cognitive decline [31] by virtue of an impact on endothelial function [7, 15].

Given the possible links between systemic inflammation and cognitive function in the elderly, it is important that the precise relationships between systemic inflammation and age-related cognitive syndromes such as MCI are investigated. To date, few studies have examined this association, and no studies have comprehensively explored the relationship between a broad array of inflammatory markers, MCI and its subtypes. Raised levels of TNF-α have been found in MCI patients compared to cognitively normal [9, 10], but 1 study failed to find an association [32]. Higher CRP levels have been found in individuals with cognitive impairment without dementia [33] and in those with nonamnestic MCI [32], in keeping with that found in AD. Another study found that individuals with multiple domain MCI had levels of IL-1β comparable to those with AD and significantly higher than those with aMCI and nMCI [34].

This study aims to expand the understanding of the relationship between systemic inflammation and MCI by determining the cross sectional relationship of MCI and its subtypes with a comprehensive array of systemic inflammatory markers. As some studies on MCI and inflammation have included a limited number of covariates [9, 10, 32], we aim to control for a range of possible confounding variables that have been shown to have an impact on inflammation or cognition, including sex, age, education, cardiovascular risk factors, metabolic factors, depression and *APOE* ε4 genotype. Sex differences on MCI and its association with inflammation will be also explored.

Participants

Participants were drawn from the Sydney Memory and Aging Study (MAS), the detailed methodology of which has been described elsewhere [35]. In brief, the Sydney MAS sample is a large, well-characterized prospective cohort of nondemented community-dwelling adults aged 70–90 years who underwent extensive cognitive examination, brief medical assessment, brain MRI and blood tests, including measurement of inflammatory biomarkers. From the 1,037 participants in the baseline co-

hort of the Sydney MAS, 770 were classified as cognitively normal or with MCI. The 267 participants who were unclassifiable due to missing data were significantly younger (p = 0.012), had a significantly higher rate of past or current smoking (p = 0.000), a lower BMI (p = 0.030), and a lower prevalence of the *APOE* ε4 allele (p = 0.005) than those who were retained in the study. Diagnosis of MCI was based on the most recent international MCI consensus criteria [75] and 4 MCI subtypes were defined [1]. A further 60 subjects did not have measurements of the inflammatory markers, leaving a sample of 710 subjects included in the study. Specifically, there were 433 cognitively normal individuals, 83 individuals diagnosed with aMCI, 98 individuals with nMCI, 72 individuals with amdMCI and 24 individuals with nmdMCI. Ethics approval for this study was granted by the University of New South Wales and the South-Eastern Illawarra Area Health Service – Eastern sector (HREC 05037); consent was obtained for all participants.

Methods

Inflammatory Biomarkers

In order to measure these inflammatory biomarkers, an early morning blood sample was collected following an overnight fast. Samples were clotted, aliquoted and frozen by an accredited lab. An array of inflammatory blood markers was analyzed including CRP, TNF-α, IL-1β, IL-6, IL-8, IL-10, IL-12p70, VCAM-1, plasminogen activator inhibitor (PAI-1) and serum amyloid A (SAA). Plasma was used to measure CRP levels, whereas serum was used for the other inflammatory markers.

High-sensitivity CRP was measured via near infrared particle immunoassay rate methodology using the Beckman Coulter Synchron LXi (Beckman Coulter, Calif., USA). Cytokine concentrations were measured using cytometric bead array (CBA, BD Biosciences, Calif., USA) for IL-1β, IL-6, IL-8, IL-10, IL-12p70 and TNF-α. Six bead populations with distinct fluorescence intensities were coated with capture antibodies specific for the cytokine proteins. The 6 bead populations were mixed together to form the BD CBA, which resolved in the FL3 channel of a flow cytometer (BD FACSCalibur™, BD Biosciences). The capture beads, PE-conjugated detection antibodies, and recombinant standards or test samples were incubated together to form sandwich complexes. Following acquisition of sample data using the flow cytometer, sample results were generated using BD CBA Analysis Software. The intra-assay coefficients of variation were 4–7% for IL-1β, 5–8% for IL-6, 2–5% for IL-8, 5–6% for IL-10, 3–6% for IL-12p70 and 6–10% for TNF-α. The interassay coefficients of variation were 8–13% for IL-1β, 8–10% for IL-6, 4–7% for IL-8, 8–11% for IL-10, 6–9% for IL-12p70 and 8–15% for TNF-α.

Serum VCAM-1, PAI-1 and SAA levels were measured using commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. The serum VCAM-1 and PAI-1 ELISA kits were obtained from Bender Medsystems GmbH (Austria). The detectable range is 3.1–100 ng/ml for serum VCAM-1 and 78–5,000 pg/ml for PAI-1. The SAA ELISA kit, with a detectable range of 9.4–600 ng/ml, was obtained from United States Biological (USA).

Covariates

Analyses of covariance included adjustment for participant age, sex and years of education. Further covariates were selected based on the impact on cognition and inflammation in our sample as well as the current literature describing their effects on inflammation or cognitive function, such as depression, cardiovascular factors, metabolic factors and *APOE* genotype [36–41]. Depression was assessed by the 15-item Geriatric Depression Scale [42], which has been shown to be valid and to have excellent test/re-test reliability [43]. A participant was said to be depressed if he/she scored a 5 or higher on the Geriatric Depression Scale. Cardiovascular factors included acute myocardial infarction, cerebrovascular accident, transient ischemic attack, diagnosed history of angina, and past or current regular cigarette smoking. Metabolic factors included calculated BMI, diagnosis of diabetes mellitus and fasting blood glucose level. Glucose concentration was measured on a Beckman Coulter Synchron LXi (Beckman Coulter) by the oxygen rate method using a Beckman oxygen electrode (Beckman Coulter) and a glucose oxidase solution.

The apolipoprotein gene *(APOE)*, especially the ε4 allele, has been shown to be a risk factor of AD by nearly doubling the lifetime risk, and has been demonstrated to directly promote an inflammation reaction [44]. Genomic DNA was extracted from peripheral blood leukocytes or saliva using standard procedures. *APOE* genotyping was undertaken by genotyping the 2 single nucleotide polymorphisms (SNPs, rs7412 and rs429358) that distinguish between the 3 *APOE* alleles: ε2, ε3 and ε4. Genotyping was performed using Taqman assays (Applied Biosystems Inc., USA) and the validity of the *APOE* genotyping was confirmed in a subsample using an alternate method [45]. Results were available for more than 99% of the DNA samples, and the allele frequencies in Caucasians for each of the 2 SNPs were in Hardy-Weinberg equilibrium ($p > 0.05$). In the analyses, participants were coded as either carriers or noncarriers of the ε4 allele.

Statistical Analyses

The results were statistically analyzed with the use of PASW version 18.0.0 [46]. Due to the positively skewed distribution of the biomarker levels, these were normalized using Blom's formula [47]. An ANCOVA was performed to examine MCI diagnostic classification as the independent variable in relation to inflammatory biomarkers as the dependent variable. Covariates included in the analyses are described above. Planned contrasts between the 4 types of MCI classifications and the cognitively normal were conducted. Group A contrasted all individuals with MCI with those cognitively normal; Group B contrasted all amnestic MCI (whether single or multiple domain), all nonamnestic MCI (whether single or multiple domain) and cognitively normal; Group C contrasted all single domain MCI, all multiple domain MCI and cognitively normal; and Group D contrasted the individual MCI subtypes (amnestic MCI, amdMCI, nonamnestic MCI and nmdMCI) and cognitively normal. The analysis for Group A was also carried out for males and females separately to examine any sex differences.

Table 1. Demographics and covariates for cognitively normals, all MCIs and each of the MCI subtypes (mean ± SD or percentages are presented)

	Cognitively normal	All MCI	aMCI	nMCI	amdMCI	nmdMCI
Sex, female	59.2	52.2	41	43.8	65	62.5
Age	78.3 ± 4.66	78.9 ± 4.7	79.8 ± 4.9	78.8 ± 4.4	78.8 ± 4.85	75.8 ± 2.5
Years of education	11.6 ± 3.4	11.5 ± 3.6	12.3 ± 3.7	10.9 ± 3.4	11.7 ± 3.5	10.8 ± 4.1
Smoked tobacco regularly	52	50.5	57	42	53	50
BMI	27.3 ± 4.8	26.8 ± 4.4	26.8 ± 4.2	26.7 ± 4.2	27 ± 5	25.9 ± 3.3
No diabetes	86.7	86.1	78.7	82.4	77.5	87.5
Fasting glucose, mmol/l	5.9 ± 1.3	5.9 ± 1.0	6.0 ± 1.2	5.7 ± 0.9	5.7 ± 1.1	5.3 ± 0.6
Ever had a heart attack	10.3	13	16.9	13.9	8.8	8.7
Diagnosed angina	12.8	12.8	13.6	13.1	10.1	16.7
Current depression	10.9	10.6	14.8	8.3	7.8	16.7
ApoE4 present	19.1	23.6	25.3	13.9	28.2	45.8
Ever had a transient ischemic attack	5.7	7.7	9	9.5	2.5	12.5
Ever had a stroke	3.7	4.7	5.7	4.7	5.1	0

Table 2. Contrast estimate (p values): normalized inflammatory markers and MCI diagnosis

	VCAM-1	PAI-1	SAA	CRP	TNF-α	IL-1β	IL-6	IL-8	IL-10	IL-12p70
Group A										
Normal < MCI			0.203 (0.010)		0.163 (0.031)					
Males: normal < MCI			0.342 (0.002)	0.197 (0.052)						
Females: normal < MCI					0.249 (0.019)					
Group B										
Normal < (n+nmd)MCI			0.268 (0.010)		0.255 (0.011)					
Group C										
Multivariate not significant										
Group D										
Normal < nmdMCI	0.424 (0.080)		0.789 (0.001)		0.704 (0.002)	0.571 (0.016)				0.694 (0.004)
aMCI < nmdMCI	0.454 (0.085)		0.631 (0.015)		0.631 (0.011)	0.672 (0.009)				0.744 (0.004)
nMCI < nmdMCI	0.469 (0.070)		0.627 (0.014)		0.532 (0.029)	0.562 (0.026)				0.662 (0.009)
amdMCI < nmdMCI	0.511 (0.057)	–0.625 (0.018)	0.663 (0.012)		0.597 (0.018)	0.534 (0.041)				0.656 (0.013)
amdMCI < normal		–0.271 (0.041)								

Covariates include sex, age, years of education, ever smoked tobacco regularly, diabetes, glucose, stroke, transient ischemic attack, heart attack, angina, BMI, depression and *APOE ε4*.

Results

Demographics

Table 1 presents general characteristics and covariates of the study sample according to cognitively normal and MCI classifications. There were no significant differences between cognitively normal and MCI individuals on any of the covariate measures.

Main Analyses

Results for the main analyses can be found in table 2. For Group A, the multivariate Wilks' Lambda F value was 1.97 (p = 0.034). Further contrasts revealed that individuals with MCI had higher levels of SAA (p = 0.010) and TNF-α (p = 0.031) compared to cognitively normal. The database was split by sex and it was found that for males, individuals with MCI had higher levels of SAA (p = 0.002)

Table 3. OR (95% CI) for the significant contrasts in table 2

	PAI-1	SAA	CRP	TNF-α	IL-1β	IL-12p70
Group A						
Normal < MCI		1.16 (0.87–1.55)		1.21 (0.91–1.63)		
Males: normal < MCI		1.55 (1.01–2.40)	1.30 (0.84–2.01)			
Females: normal < MCI				1.40 (0.94–2.14)		
Group B						
Normal < (n+nmd)MCI		1.43 (0.97–2.12)		1.51 (1.01–2.25)		
Group D						
Normal < nmdMCI		1.55 (0.67–3.61)		3.33 (1.19–9.06)	2.70 (1.05–6.91)	2.13 (0.86–5.22)
aMCI < nmdMCI		1.36 (0.53–3.48)		2.96 (1.01–8.65)	4.21 (1.53–11.6)	2.48 (0.94–6.57)
nMCI < nmdMCI		1.10 (0.44–2.74)		2.51 (0.87–7.23)	2.22 (0.82–6.0)	1.87 (0.72–4.88)
amdMCI < nmdMCI	2.0 (0.77–5.21)	1.36 (0.53–3.47)		3.61 (1.23–10.6)	2.10 (0.76–5.87)	1.79 (0.67–4.80)
amdMCI < normal	1.38 (0.86–2.21)					

The reference is the group that was shown to have significantly lower inflammation than the other group.

and CRP (p = 0.052), whereas for females, individuals with MCI had higher levels of TNF-α (p = 0.019), reflecting a sex-specific effect.

For Group B, the multivariate Wilks' Lambda F value was 1.44 (p = 0.095). This result is an evident trend and since Roy's Largest Root F value was F = 2.03 (p = 0.028), it was decided to proceed with the contrasts. These revealed that nonamnestic MCI patients (single and multiple domain grouped together) had increased levels of TNF-α (p = 0.011) and SAA (p = 0.010) compared to cognitively normal.

For Group C, the multivariate Wilks' Lambda F value of 1.37 was not significant (p = 0.127) and contrasts were not performed.

For Group D, the multivariate Wilks' Lambda F value was 1.54 (p = 0.017). Further contrasts revealed that nmdMCI had higher levels of TNF-α and SAA than cognitively normal (TNF-α: p = 0.002; SAA: p = 0.001), aMCI (TNF-α: p = 0.011; SAA: p = 0.015), nMCI (TNF-α: p = 0.029; SAA: p = 0.014) and amdMCI (TNF-α: p = 0.018; SAA: p = 0.012), after controlling for the covariates. Interestingly, nmdMCI participants also had increased levels of IL-12p70 compared to cognitively normal (p = 0.004), aMCI (p = 0.004), nMCI (p = 0.009) and amdMCI (p = 0.013) participants. IL-1β was also higher in nmdMCI than in cognitively normal (p = 0.016), nMCI (p = 0.026) and amdMCI (p = 0.041).

The inflammatory marker PAI-1 was significantly higher in nmdMCI than in amdMCI (p = 0.018), and it was also higher in cognitively normals than in amdMCI (p = 0.041).

OR and 95% CI calculations were performed for each significant contrast to estimate the effect size. These are presented in table 3.

Discussion

This is the first population-based study to investigate the relationship between a comprehensive array of inflammatory biomarkers, MCI and its 4 subtypes. Higher levels of some inflammatory markers, particularly SAA and TNF-α, were found in the MCI group compared to those with normal cognitive function. This relationship appeared to be driven predominantly by an association between higher levels of SAA and TNF-α and nonamnestic MCI. However, there were notable sex differences, with male MCI individuals having higher levels of SAA and CRP, whereas female MCI individuals had higher levels of TNF-α than the cognitively normal. This could explain why Roberts et al. [32] failed to find an association between TNF-α and MCI, especially since their MCI sample had more (p = 0.06) men than the non-MCI sample.

Our findings related to TNF-α are congruent with previous studies by other groups investigating MCI [9, 10]. Elevated TNF-α levels have been found in individuals with AD, but at an even greater magnitude [10], suggesting a dynamic relationship between neurodegeneration and this acute phase protein. It would be best to investigate the dynamics of this relationship in future longitudinal studies of elderly populations that measure

change in both inflammatory marker level and cognition.

This is the first study to show that the association between TNF-α and MCI is specific to females. Our results highlight the need to incorporate examination of sex differences into future studies, but the sex-specific effect of TNF-α on cognitive function could have a number of explanations. At one level, our observation of sex differences in the association between TNF-α and MCI may reflect a true sex difference. However, we cannot exclude an impact of the inaccuracy of BMI, a covariate in our analysis, as a measure of adiposity in the elderly. TNF-α has been repeatedly associated with measures of adiposity [48–52] and adiposity has itself been shown to be associated with cognitive deficits throughout life [53–58]. We attempted to account for adiposity and its effects by including BMI as a covariate. However, BMI is not an accurate measure of adiposity in the elderly and fails to capture discrepancies in body fat distribution between sexes [59]. We will have the opportunity to further investigate this issue in our cohort as we have commenced collection of more comprehensive body composition measures, including dual-energy X-ray absorptiometry.

The results suggest that the relationship between TNF-α in nondemented community-dwelling elderly is more complex than previously recognized, in that TNF-α is more strongly associated with nonamnestic MCI subtypes. Indeed, compared to those with 'low' levels of TNF-α, individuals designated as having 'high' levels of TNF-α (as defined by median split of TNF-α levels) were more than 3 times as likely to have nmdMCI compared to cognitively normal (OR: 3.33). Those with nmdMCI are considered to be at risk of progression to non-AD dementias [60]. Indeed, as described earlier, TNF-α has been found to be higher in VaD than in late onset AD [14], even after controlling for cardiovascular factors.

To the best of our knowledge, this is the first study to show that individuals with MCI have higher levels of SAA compared to cognitively normal, and this effect seems stronger in males. Our results appeared to be dominated by the association between SAA level and nonamnestic MCI. When compared to those with 'low' levels of SAA, those individuals designated as having 'high' SAA levels (as defined by median split), were almost 1.5 times as likely to have nonamnestic (multiple and single domain) MCI compared to normal cognitive function (OR: 1.43). Our work examining the association between SAA and cognitive domains suggests that raised SAA is specifically associated with poorer performance on psychomotor function and processing speed [Trollor et al., unpubl. data]. Together with the current results, we hypothesize that SAA interacts with vascular risk factors to adversely affect subcortical structures. The differences between men and women are not clearly understood, but will be investigated longitudinally. A previous study, using a smaller and younger Afro-Caribbean sample and a limited cognitive test battery, failed to find a relationship between SAA and cognitive decline after 3 years of follow-up [61], but they did not stratify by sex.

Our study found a trend ($p = 0.052$) that individuals with MCI have higher levels of CRP compared to cognitively normal, especially in males. Higher CRP levels have been found in individuals with cognitive impairment without dementia [33] and in those with nonamnestic MCI [32]. Both CRP and SAA are usually found to be high at the same time in other diseases [62] since both are released by the liver as part of an acute phase response to proinflammatory stimuli [63]. CRP has been repeatedly associated with increased risk of cardiovascular disease [64, 65]. Longitudinal data relating to the outcome of our male participants with MCI will be of particular interest, especially if shown to be more likely to develop VaD. The higher incidence of VaD observed in men is consistent with this hypothesis [66].

Our study found significantly higher levels of IL-12p70 in individuals with nmdMCI compared to cognitively normal, aMCI, nMCI and amdMCI. When compared to those with 'low' levels of IL-12p70, those individuals designated as having 'high' IL-12p70 levels (as defined by median split), were about twice as likely to be classified as nmdMCI compared to cognitively normal (OR: 2.13), aMCI (OR: 2.48), nMCI (OR: 1.87) or amdMCI (OR: 1.79). Elevated levels of IL-12p70 have been found in individuals with mild and moderate AD [30], but it has not been previously associated with poor cognitive performance [25] in elderly populations in general. This raises a possibility that raised IL-12p70 has a specific association with cognitive impairment, and should be examined in longitudinal studies for its capacity to predict cognitive decline.

Higher levels of PAI-1, a biomarker suggested to be neuroprotective [67], were found in cognitively normal and nmdMCI compared to amdMCI, raising the possibility that PAI-1 may offer specific protection from memory impairment. This is supported by several studies that have shown PAI-1 protects hippocampal neurons from

oxygen-glucose deprivation injury [68]. Indeed, PAI-1 was positively and significantly ($p = 0.007$) correlated to the memory scores that we used to determine the classification of our participants.

Our study found an association between IL-1β and nmdMCI, and in this regard resembles a previous finding which showed that multiple domain MCI had levels of IL-1β comparable to those with AD and significantly higher than those with aMCI and nMCI [34]. Unfortunately, Forlenza et al. [34] did not separate multiple domain MCI into amnestic and nonamnestic subtypes in order to identify the specificity of these findings, making further comparison difficult.

It is interesting to note that the majority of the associations relate higher inflammation to nmdMCI, while PAI-1 was downregulated among amdMCI when compared to controls and nmdMCI. These findings suggest a differential pattern of over- and underexpression of inflammatory markers that point towards particular impairments, rather than a single diagnostic measure. It could be hypothesized that a threshold effect exists where an increase in low-grade inflammation increases the risk for amnestic MCI and AD while broad overexpression over a number of inflammatory markers changes the risk to nonamnestic MCI and non-AD dementia. This hypothesis requires further investigation by use of a longitudinal design.

The current study did not identify an association between IL-8 and MCI, yet an association between high levels of IL-8 and poor cognitive performance, particularly in tests of executive function, has previously been reported [25] in a sample of community-dwelling elderly. Our own analysis of data from this sample [Trollor et al., unpubl. data] revealed a selective impact of IL-8 on executive function, in itself insufficient to influence MCI classification.

This study did not find associations between MCI and IL-6, yet IL-6 has been shown in some studies to accompany dementia and predict cognitive decline. The relationship between IL-6 and inflammation is complex and context-specific. Indeed, overexpression of IL-6 has been shown to be both detrimental to disorders of the central nervous system and also to have anti-inflammatory, immunosuppressive and other benefits in special conditions [69]. Thus, IL-6 may be elevated in the context of established and widespread pathology, but may not be elevated in conditions such as MCI, which is known to have a range of possible origins and a variety of outcomes.

It has been suggested that measuring a single biomarker will not be sufficient to identify preclinical AD [70, 71]. Indeed, a recent study showed the power of combining multiple biomarkers, demonstrating that such a combination of 18 biomarkers could predict the progression to AD among 22 MCI individuals with 90% accuracy [72]. Further investigations that measure a range of biomarkers at different stages of decline are needed in order to better understand the role of inflammation on cognition [73]. The role of measurement of systemic inflammation in this context awaits exploration in longitudinal studies.

This study has a number of strengths. Specifically, it has a large population-based design, measuring 10 inflammatory biomarkers and adjusting for multiple potential confounding covariates. Our diagnosis of MCI was informed by detailed history and comprehensive neuropsychological assessment. This sample will be followed to investigate the longitudinal association between inflammation and cognitive decline and progression to dementia.

The study also has various limitations that must be acknowledged. First, no cause-effect relationship could be established in this study due to its correlational design, but as stated earlier, this sample is being followed longitudinally, providing prospective data for hypotheses regarding causal links. Second, the cognitively normal were aged individuals who did not fit our criteria for MCI; however, it is possible that some of this group already had preclinical disease-related changes, including early cognitive decline not captured by the current MCI criteria. Therefore, associations that approached but did not reach significance should be evaluated positively. Third, we recognize the limitations of the 'MCI' syndrome [74] as currently defined [75], given its shifting boundary related to the specific criteria used to establish cognitive impairment [76] and its limited capacity to convey reliable information regarding clinical trajectory.

In conclusion, this study supports the concept that those with MCI, particularly nmdMCI, are more likely to have higher levels of low-grade systemic inflammation. Given the recognized association between systemic inflammation and dementia, future study of the impact of systemic inflammation on the further progression of MCI is indicated.

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