Peripheral Inflammatory Biomarkers and Cognitive Decline in Older Adults With and Without Alzheimer’s Disease
A Systematic Review

ABSTRACT
Peripheral inflammatory biomarkers may play an important role in the cognitive decline of aging and incidence of Alzheimer’s disease (AD); however, data from epidemiological studies present conflicting findings. The purpose of the current review was to systematically determine the current state of the science on the association between peripheral inflammatory biomarkers and cognitive decline. Articles published from January 1, 2006 to October 28, 2016 were searched using the Medline and Embase databases. Nine studies met inclusion criteria (two examined participants with AD dementia and seven examined participants without dementia). Although a wide range of peripheral inflammatory biomarkers was examined, C-reactive protein and interleukin 6 were the most studied. Findings show conflicting results for the association between peripheral inflammatory biomarkers and cognitive decline. Peripheral inflammation may harm and help the brain, and therefore, the challenge of modulating immunity will be to find ways of fine tuning inflammation to delay, prevent, or treat AD. [Journal of Gerontological Nursing, 43(12), 53-60.]

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ALzheimer’s disease (AD) is the most common type of dementia and affected 5.4 million individuals (or one in three older adults) in the United States in 2016. It is projected to afflict 13.8 million Americans by 2050. The financial and social impacts of AD are astronomical, costing $236 billion. In 2015, 15.9 million family caregivers provided an estimated 18.1 billion hours of unpaid care valued at $221.3 billion (Alzheimer’s Association, 2016).

Unfortunately, no treatment exists to prevent, slow, or cure AD, with 99.6% of drug trials having failed in the past two decades (Cummings, Morstorf, & Zhong, 2014). This failure rate highlights the importance and urgency of finding alternative therapeutic targets for AD.

Most failed drug trials focused on the amyloid cascade hypothesis, which argues that amyloid deposition in the brain is the earliest and main pathological process in AD (Cummings et al., 2014). However, drugs targeting amyloid deposition have failed, suggesting the importance of pursuing other AD pathology to target treatments. Modulation of the immune system...
system plays an important role in regulating brain aging and neurodegeneration (Heneka et al., 2015). The crosstalk between the immune system and brain cannot be ignored and may be facilitated by soluble immune factors, such as peripheral inflammatory biomarkers. Therefore, a good understanding of how peripheral inflammation contributes to AD development or progression will be therapeutically critical.

Peripheral inflammatory biomarkers have been studied extensively in case-control or cross-sectional studies in individuals with mild cognitive impairment and/or AD. Although results sometimes conflict, most studies have demonstrated that increased peripheral inflammation is positively associated with AD (Koyama et al., 2012). These conditions, particularly acquired in midlife, have been shown to significantly contribute to the risk or development of AD and other dementias (Bangen et al., 2016; Brunner et al., 2016; Chuang et al., 2016; Lafortune et al., 2016). These findings suggest that peripheral inflammatory biomarkers might play an important role in cognitive decline in aging and the incidence of AD.

Despite this recognition and comprehensive reviews that propose mechanistic pathways by which peripheral inflammatory biomarkers may affect the central neural system (Heneka et al., 2015; Lucin & Wyss-Coray, 2009; Wyss-Coray & Rogers, 2012), data from epidemiological studies show conflicting findings. The degree to which peripheral inflammatory biomarkers can be used clinically to predict future cognitive decline or risk of AD and other dementias remains unclear. Conflicting findings have become common in recent years, during which time data on cognitive changes and a diverse group of peripheral inflammatory biomarkers became more available in epidemiological cohort studies.

For example, a systematic review in 2005 of the C-reactive protein (CRP) indicated that raised CRP concentrations were associated with faster cognitive decline (Kuo et al., 2005). Since then, studies have suggested an opposite association between CRP and cognitive decline (Lima et al., 2014; Locascio et al., 2008). Hence, the objective of the current review is to systematically determine the current state of the science on the association between peripheral inflammatory biomarkers and cognitive decline since 2006. The current review particularly focuses on two populations: (a) participants with AD dementia and (b) those without dementia.

**METHOD**

**Literature Search**

The current systematic review followed the procedure for conducting systematic reviews established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). The literature search was conducted using the Medline and Embase databases for articles published from January 1, 2006 to October 28, 2016. Keywords used included “dementia” (or explosion of “dement*” or “Alzheimer*”), “blood” (or explosion of blood or plasma or serum), and “inflammation” (or explosion of inflammatory or neuroinflammatory or neuroinflammation). Search results were limited to the English language and publication year (“2006 to current”). Searches also excluded results using the keywords “animals” or “mice” (or explosion of mice or mouse) or “rat” (or explosion of rat or rats), as well as case reports, editorials, or reviews. A total of 1,596 articles (486 from Medline and 1,110 from Embase) were found. After removing duplicates, 1,168 articles were retained for further evaluation of eligibility.
Eligibility Criteria and Study Selection

The Figure illustrates the screening and selection process. Article titles or abstracts were reviewed to determine if they met the inclusion criteria: epidemiological cohort studies of older adults (e.g., with normal cognition, mild cognitive impairment, dementia, or AD), had peripheral inflammatory biomarkers measured in blood, and had cognitive function evaluated at baseline and repeated at least once more at follow up. If the title or abstract did not provide enough information to determine its eligibility, the full article was reviewed. Case-control or cross-sectional studies in which cognition function was only assessed at one time point were excluded. The first author (D.L.) first screened the 1,168 articles retained using the titles only and identified 156 articles for further screening using abstracts, and finally selected 17 articles for full-text evaluation. After further evaluation, eight articles were excluded because of inconsistency with eligibility criteria (one lacked evaluation of inflammatory biomarkers, four had cognitive assessment evaluated at only one time point, one’s cohort population did not comprise older adults, one defined cognitive decline as incidence of MCI, and one evaluated basic daily living and activities of daily living, but not cognitive function).

Data Collection Process

For the nine included articles, information was extracted on study characteristics (e.g., age, percent female), inflammatory biomarkers measured, measures used to assess cognitive function, and duration, frequency, and rate of follow up (Table A, available in the online version of this article). In addition, the Newcastle-Ottawa Quality Assessment Scale (NOSGEN; Stang, 2010) tool for cohort studies was used to assess the methodological quality of each study. The NOSGEN assigns a study a maximum of 9 points, one for each item within the NOSGEN Selection ($n = 4$) and Outcome categories ($n = 3$), and a maximum of 2 points for the Comparability category. The Selection category evaluates four items: (a) representativeness of the exposed cohort (i.e., higher level of inflammatory biomarkers), (b) selection of the non-exposed cohort (i.e., lower level of inflammatory biomarkers), (c) ascertainment of exposure (i.e., measurement of inflammatory biomarkers), and (d) demonstration of the outcome of interest was not present at start of study (i.e., baseline cognitive function assessment). The Outcome category evaluates three items: (a) assessment of outcome, (b) if follow up was long enough for outcomes to occur, and (c) adequacy of follow up. The Comparability category evaluates two items: (a) controls for age, sex, APOE genotypes, and education; and (b) controls for other additional factors (e.g., hypertension, diabetes, stroke, cardiovascular diseases).

Risk of Bias

Risk of bias was evaluated in each study and across studies using
the Cochrane Collaboration’s tool. Because this tool was designed to study risk of bias in randomized controlled trials, evaluation domains of sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, and selective outcome reporting do not apply to the current systematic review. Therefore, the current authors only focused on missing data and how each study appropriately addressed this issue. Criteria for a judgment of “yes” (i.e., low risk of bias) included no missing outcome data (≥80% follow-up rate) or missing data imputed using appropriate methods. Criteria for a judgment of “no” (i.e., high risk of bias) included a follow-up rate <80% and missing data imputed using inappropriate methods. Criteria for a judgment of “unclear” (i.e., high unknown risk of bias) included insufficient reporting of attritions/exclusions to permit judgment of “yes” or “no.”

RESULTS

Study Characteristics

Table A summarizes the characteristics of the nine studies. Samples ranged from 43 to 1,298 participants. Two studies examined participants with AD (Blasko et al., 2007; Holmes et al., 2009), in which AD was ascertained according to the National Institute of Neurological and Communicative Disorders and AD and Related Disorders Association guidelines (McKhann et al., 1984). The remaining seven studies examined participants without dementia, although dementia status was ascertained differently across studies. For example, Beeri et al. (2006) defined “without dementia” by a Clinical Dementia Rating score of 0 and Mini-Mental State Examination (MMSE) score greater than the 10th percentile of the age and education norms. Chi et al. (2016) and Sharma et al. (2016) excluded dementia according to Clinical Dementia Rating scores >0.5.

Measures of cognitive function varied across the nine studies (e.g., Consortium to Establish a Registry for Alzheimer’s Disease, Alzheimer’s Disease Assessment Scale cognitive subscale [ADAS-Cog], MMSE), as well as their follow-up durations, frequencies, and rates (Table A).

Table A summarizes the studies’ NOSGEN scores. Two studies of individuals with AD dementia received a score of 8, with 1 point taken off for no adjustment of additional covariates (Blasko et al., 2007; Holmes et al., 2009). Of seven studies of individuals without dementia, two received a score of 6, with 3 points taken off each for no adjustment of additional covariates, follow up not long enough for outcomes to occur, and follow up rate <80% and no description of those lost (Economos et al., 2013; Marioni et al., 2009). One study received a score of 7, with 2 points taken off each for follow up not long enough for outcomes to occur and follow up rate <80% and no description of those lost (Jordanova, Stewart, Davies, Sherwood, & Prince, 2007). Two studies received a score of 8, with 1 point taken off for no adjustment of additional covariates (Beeri et al., 2011; Lima et al., 2014). Two studies received a score of 9 (Chi et al., 2016; Sharma et al., 2016) and examined the same cohort of community-dwelling older adults from the Ginkgo Evaluation of Memory Study but different sets of inflammatory biomarkers on cognitive function decline globally and in five domains (i.e., memory, construction, language, psychomotor speed, and executive function).

Measures of Peripheral Inflammatory Biomarkers

A wide range of inflammatory biomarkers was evaluated, including: neopterin, CRP, fibrinogen, tissue necrosis factor (TNF)-alpha, interleukin(IL)-6, IL-10, IL-2, pentraxin 3 (PTX3), serum amyloid A and P (SAP), plasminogen activator inhibitor (PAI)-1, adiponectin, resistin, receptor for advanced glycation end products, endothelin 1, and serum derivatives of methylglyoxal. Six studies examined CRP and four examined IL-6. The remaining biomarkers were investigated by one study.

Association Between Peripheral Inflammation and Cognitive Decline in Participants With Alzheimer’s Disease Dementia

In the two studies of participants with AD dementia, CRP was not associated with cognitive decline (Blasko et al., 2007; Holmes et al., 2009). For other peripheral biomarkers examined, evidence is strong that higher levels of TNF-alpha were associated with faster cognitive decline up to 6 months (Holmes et al., 2009), but it was only evaluated once.

Association Between Peripheral Inflammation and Cognitive Decline in Participants Without Dementia

CRP and IL-6 were examined in four studies that included participants without dementia. Higher CRP at baseline was associated with slower cognitive decline in participants without dementia and APOE 4 allele (Lima et al., 2014). Furthermore, CRP may have opposite associations with cognitive function decline when evaluated by different cognitive tests. For example, Marioni et al. (2009) demonstrated higher plasma CRP levels were associated with an improvement in performance on the Auditory Verbal Learning Task (which evaluates verbal memory), but were associated with poorer performance on the Raven’s Standard Progressive Matrices (which evaluate nonverbal reasoning). However, two studies found no associations between CRP and global cognitive decline (Economos et al., 2013; Jordanova et al., 2007).

Four studies found that IL-6 also gave inconsistent results. Economos
et al. (2013) demonstrated that participants with IL-6 levels above the median (1.5 pg/mL) showed greater decline in global cognition compared to those with levels below the median, after adjusting for sociodemographic and vascular factors in an ethnically diverse community-based sample. Raised levels of IL-6 (>3.1 pg/mL) were only associated with cognitive decline after adjustment of body mass index (Jordanova et al., 2007). Two other studies found no association between IL-6 and global cognitive decline or any specific domain (e.g., memory, construction, language, psychomotor speed, executive function) in adults 75 or older without dementia after multiple adjustments (Chi et al., 2016; Sharma et al., 2016).

Other biomarkers associated with global cognition included PTX, although the evidence is not strong and only present in participants with MCI (Sharma et al., 2016). Higher PTX3 was associated with increased psychomotor speed and decreased executive function (Chi et al., 2016).

Risk of Bias

Missing data were handled differently across studies. Only three studies discussed methods used for missing data: Tobit regression to manage differences in length of follow up and missing values (Beeri et al., 2011), sensitivity analysis to manage missing APOE 4 data (Sharma et al., 2016), and an inverse probability weighting method to manage missing cognitive data (Chi et al., 2016). The combination of no missing data discussion and no missing data (>80% follow-up rate) identified one study as having an “unclear” risk of bias (Marioni et al., 2009), two studies as being at risk of bias (Economos et al., 2013; Jordanova et al., 2007), and the remaining six studies as having no risk of bias.

There was potential selection bias and variability in measurement of inflammatory biomarkers, which may have contributed to the heterogeneous results. Use of a convenience sample may not be epidemiologically representative (Beeri et al., 2011), and the possibility of regression dilution existed because of the variability in peripheral inflammatory biomarker measurement (Economos et al., 2013; Jordanova et al., 2007). However, no studies provided data on variability on biomarker measurement and, therefore, dilutional bias among studies could not be evaluated.

DISCUSSION

The main findings from the current systematic review illustrated that from 2006-2016, CRP and IL-6 were the most studied biomarkers (six and four studies, respectively) associated with cognitive decline. However, the association between CRP or IL-6 and cognitive decline remains uncertain. Two studies of CRP in participants with AD found no association. Two studies in participants without dementia showed no association, but one study showed higher levels of CRP associated with slower global cognitive decline and one showed opposite associations between CRP and cognitive decline in the domains of verbal memory and nonverbal reasoning. Two studies of participants without dementia demonstrated higher levels of IL-6 associated with faster global cognitive decline; two studies found no associations.

The current findings are consistent with the emerging evidence that some components of peripheral inflammation may promote pathological processes leading to cognitive decline, whereas others may protect cognitive decline (Wyss-Coray & Rogers, 2012). In other words, inflammation may harm and help the brain (Chakrabarty et al., 2010; Cribbs et al., 2012; Lucin & Wyss-Coray, 2009). Most studies published before 2006 found that higher CRP levels were associated with cognitive impairment (Koyama et al., 2012). However, one study published after 2006 challenged this finding and showed higher plasma CRP was associated with slower global cognitive decline in participants without AD (Lima et al., 2014). One reason for these conflicting findings is that older adult participants with evaluated CRP and normal cognition may represent a group of resilient participants with immune activation (Silverman et al., 2009). Resilience is heritable, as demonstrated by family members of the individual with normal cognition and elevated CRP who were also at a lower risk of dementia (Silverman et al., 2012).

Higher PTX3 levels were associated with increased psychomotor speed and decreased executive function (Chi et al., 2016), consistent with the emerging view that inflammation may have biphasic effects in cognitive domains. Therefore, therapeutic modulation of the immune system to the right balance...
may be critical. The current findings further showed that a range of inflammatory biomarkers (e.g., TNF-alpha, IL-10, IL-2, SAP, PAI-1, adiponectin) have been studied since 2006, demonstrating increasing attention to the neuro-inflammatory mechanism of AD. Most of these biomarkers were only investigated by one study, and the strength of their associations with cognitive change was modest. Although the modest strength may be attributable to methodological reasons, such as adequate follow-up duration, it raises the question of whether inflammatory biomarkers could be used clinically for identifying participants with risk of future cognitive decline (Beeri et al., 2006; Chi et al., 2016). Furthermore, these peripheral inflammatory biomarkers were likely associated with chronic diseases that predispose older adults to cognitive decline and AD.

The current systematic review examined the association of peripheral inflammatory biomarkers with cognitive declines separately in participants with AD dementia and in participants without dementia, with the assumption that the interaction of immunity and inflammatory pathways would be different in these two populations. In the nine studies, CRP was the only inflammatory biomarker examined in both populations; none demonstrated associations in participants with AD, but there were conflicting associations in participants without AD. There were not enough data to determine whether peripheral biomarkers affect cognitive decline differently in participants without dementia or with AD.

STRENGTHS AND LIMITATIONS

One strength of the current systematic review was evaluating the temporality of whether peripheral inflammation contributes to cognitive decline. However, the review is limited by the heterogeneity of the studies (e.g., measurement of cognitive function infrequently over a long-term follow up). Factors such as transient elevations in inflammatory markers due to acute infections may have contributed to cognitive decline, but were not captured in many of these studies. Because a variety of different instruments was used for measurement of cognitive changes, results across the nine studies were not easily comparable. The current review is further limited by the lack of knowledge on age-specific cognitive decline rates and a core minimum data set of neuropsychological tests. It is also unknown what the optimal follow-up duration should be to reliably assess cognitive decline, which makes it challenging to evaluate the studies in terms of adequacy of follow up.

IMPLICATIONS FOR NURSING

The current findings have several implications for nursing research and practice. In 2016, the National Institute of Nursing Research (NINR) published its strategic plan for advancing science and improving lives. The plan emphasizes symptom science, particularly improving understanding of the underlying biological mechanisms of a range of symptoms, as one of the areas of scientific focus to promote personalized health strategies. Consistent with the vision, the NINR has issued a corresponding call for the proposal of “Applying Metabolomics to Drive Biomarker Discovery in Symptom Science.” The current review was conducted within this context to analyze the current state of the science of biomarker research in preventing cognitive decline.

Based on the current findings, future studies are needed to examine the relationship between biomarkers of peripheral inflammation and cognitive decline. Future studies should consider design elements related to the adequacy of follow up, including the rate of age-specific cognitive decline, and should use a core minimum data set of neuropsychological tests and follow up durations that could be used for reliable assessment of cognitive decline. Although many assessment tools are well established in the field of AD disease (e.g., MMSE, ADAS-Cog), they may not be sensitive enough to track cognitive decline in participants without dementia. To this end, the NIH established the NIH Toolbox® for the assessment of neurological and behavioral function, with the goal of providing the clinical research community a set of brief, psychometrically sound measures to assess neurological and behavioral function in community-based populations (Gershon et al., 2013). However, none of the studies included in the current review used the NIH Toolbox. Cognitive biomarkers are limited to research with no clinical implications. Translations to practice will likely occur once research evidence has accumulated to an extent to warrant a practice adoption.

CONCLUSION

Emerging evidence suggests peripheral inflammation in general may contribute to the pathological process of AD. The relationship between inflammatory biomarkers and cognitive decline is complex, with some components associated with better global cognition and others with domain-specific cognitive decline. Future studies are needed to unveil these relationships and identify novel therapeutic targets for AD.

REFERENCES


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Table A. Characteristics of the 9 studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study location</th>
<th>Year</th>
<th>Biomarkers measured</th>
<th>Sample size</th>
<th>Age at baseline</th>
<th>Male/Female or %Male</th>
<th>Education (years)</th>
<th>APOE4 positive</th>
<th>Assessment of cognition</th>
<th>Followup duration/frequency</th>
<th>Followup rate</th>
<th>NOSG score</th>
<th>Missing data addressed</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blasko et al</td>
<td>Austria</td>
<td>2007</td>
<td>Neopterin, CPR</td>
<td>43</td>
<td>75.1 (7.2)</td>
<td>13/30 or 30%</td>
<td>6.2 (0.4)</td>
<td>63%</td>
<td>CERAD 7 tests</td>
<td>14.5 (0.5) months/once</td>
<td>35/43 or 84%</td>
<td>8/9</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Holmes et al</td>
<td>UK</td>
<td>2009</td>
<td>CRP, TNF, alpha</td>
<td>275</td>
<td>82.7 (7.4)</td>
<td>99/170 or 36%</td>
<td>Not available</td>
<td>Not available</td>
<td>ADAS-COG</td>
<td>6 months/every 2 months</td>
<td>222/275 or 81% rate at 2, 4, and 6 months</td>
<td>8/9</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Jordanova et al</td>
<td>UK</td>
<td>2007</td>
<td>IL-6, CRP, and SAA</td>
<td>205</td>
<td>55-75</td>
<td>89/118 or 43%</td>
<td>Not available</td>
<td>Not available</td>
<td>CERAD, MMSE</td>
<td>34 (2.2) months/once</td>
<td>216/290 or 75%</td>
<td>7/0</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Marioni et al</td>
<td>UK</td>
<td>2009</td>
<td>CRP, Fibrinogen</td>
<td>504</td>
<td>63 (5.83)</td>
<td>135/359 or 27%</td>
<td>Not available</td>
<td>Not available</td>
<td>AVLT, RAVENS, VFT, DST, TMT1</td>
<td>5 years/once</td>
<td>Not available</td>
<td>6/9</td>
<td>No</td>
<td>Unclear</td>
</tr>
<tr>
<td>Economos et al</td>
<td>USA</td>
<td>2013</td>
<td>CRP and IL-6</td>
<td>1224</td>
<td>71 (7.3)</td>
<td>441/783 or 36%</td>
<td>Not available</td>
<td>Not available</td>
<td>Modified Telephone Interview for Cognitive Status (TICS-m)</td>
<td>Median 3.0 years/every year</td>
<td>1224/3298 or 37%</td>
<td>8/9</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Beeri et al</td>
<td>USA</td>
<td>2011</td>
<td>sMG</td>
<td>267</td>
<td>83.5 (5.3)</td>
<td>67/200 or 75%</td>
<td>14.3 (3.1)</td>
<td>20%</td>
<td>MMSE</td>
<td>35.7 (15.7) months/once</td>
<td>267/443 or 60%</td>
<td>8/9</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Lima et al</td>
<td>UK</td>
<td>2014</td>
<td>CRP</td>
<td>286</td>
<td>77.1 (5.5)</td>
<td>117/149 or 44%</td>
<td>9.5 (1.7)</td>
<td>21%</td>
<td>MMSE</td>
<td>4.1 years/once</td>
<td>268/273 or 95%</td>
<td>8/9</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sharma et al</td>
<td>USA</td>
<td>2016</td>
<td>IL2, IL6, IL10, PTX3 and SAP, PAI-1, Adiponectin, Resistin, RAGE, Endothelin 1</td>
<td>1258</td>
<td>73.0 (3.4)</td>
<td>712/686 or 55%</td>
<td>54% with advanced studies after high school</td>
<td>20%</td>
<td>MMSE</td>
<td>7 years/every 6 months</td>
<td>82/1298 or 93.7%</td>
<td>9/9</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Chi et al</td>
<td>USA</td>
<td>2016</td>
<td>IL2, IL6, IL10, PTX3 and SAP, PAI-1, Adiponectin, Resistin, RAGE, Endothelin 1</td>
<td>1182</td>
<td>73.9 (3.4)</td>
<td>651/534 or 56%</td>
<td>14.3 (3.0)</td>
<td>25.10%</td>
<td>CVLT, BD, BNT, TMTA and S12</td>
<td>7 years/every 6 months</td>
<td>1182/1319 or 90%</td>
<td>9/9</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
1 AVLT: Auditory Verbal Learning Task; RAVENS: Raven's Standard Progressive Matrices; VFT: Verbal Fluency Test; DST: Digit Symbol Test; TMT: Trial Making Test

2 CVLT: California Verbal Learning Test Long Delayed Recall; BD: Block Design; BNT: Boston Naming Test; TMTA: Trail Making Test A; ST: Stroop Task