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How predictive of dementia are peripheral inflammatory markers in the elderly?

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SUMMARY

Dementia is a huge public health concern today owing to the exponentially increasing number of older adults it affects each year, and there has been a large number of investigators looking at potential biomarkers of dementia. Peripheral inflammatory markers have emerged as one potential class of markers that may be useful in predicting those individuals at a greater risk of developing dementia, or in expounding the underlying mechanisms or pathways of this complex disease. Although some evidence has been promising, indicating that peripheral inflammatory markers are indeed crucial in brain changes that occur in both normal aging and in dementia, results have been mixed on their usefulness for predicting dementia or cognitive decline in older adults. Here, the authors present a review of existing studies investigating inflammatory markers as potential biomarkers of dementia, highlighting some strengths and limitations of the current research and discuss the future directions for this field.

Nearly 34 million older adults are living with dementia worldwide (including all subtypes; i.e., Alzheimer's disease [AD] and vascular dementia), and the prevalence is expected to increase exponentially in the coming years to reach 81 million adults by the year 2040 [1,2]. There are several underlying factors contributing to such staggering statistics: an increased life expectancy, an increase in the elderly population and no currently available treatment that effectively prevents or delays the onset of or treats dementia [1-3]. The result is a huge impact on public health systems. Given the exponential increase in the prevalence of dementia, we can only expect the public health burden to also increase. Thus, there has been a rush to identify reliable biomarkers that can be used to predict those individuals at an increased risk of dementia, and that may aid in understanding the physiological progression of the disease. Inflammatory markers have been identified as one such category of potentially useful markers in predicting and monitoring progression of dementia and cognitive decline [4,5]. In this article, the state of the current literature investigating inflammatory cytokines as biomarkers of dementia will be reviewed, and the limitations, strengths and future directions of this area of interest will be discussed.

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Epidemiologic evidence

Several peripheral markers of inflammation, evaluated in both blood plasma and serum, have been investigated as potential dementia biomarkers, but results are still unclear. In terms of dementia, the most widely investigated inflammatory markers have been CRP, IL-6 and TNF- α (Table 1). Individual studies have found that a high level of CRP, IL-6 or TNF- α is associated with an increased risk of AD and cognitive decline [6-8]. For example, in a prospective study of AD patients looking at both CRP and TNF- α with performance on a cognitive test over time, there were significant baseline and longitudinal associations between high levels of TNF- α and poorer performance on the Alzheimer's Disease Assessment Scale-Cognitive subscale, but no significant associations were found with CRP [9]. However, these patients already had diagnosed dementia, so these results may reflect a consequence of the dementia process rather than a predecessor [9].

In two longitudinal studies with follow-up times of approximately 2 years, there were significant associations between inflammatory markers and cognitive outcomes. In the Health, Aging and Body Composition (Health ABC) study, among those with the highest serum IL-6 or CRP tertile, Modified Mini-Mental Status Examination scores were an average of two points lower at baseline, compared with those who were in the lowest IL-6 or CRP tertile ($p < 0.001$ for both IL-6 and CRP) [10]. Furthermore, those in the highest IL-6 tertile had a one-point decline over 2 years, compared with those in the lowest tertile ($p = 0.01$), and the relationship over time was similar when comparing those in the high versus the low CRP tertile ($p = 0.04$) [10]. However, there were no significant differences at baseline or over time between TNF- α and cognitive function [10]. A strength of this study is that participants were free of cognitive impairment at baseline; however, because dementia pathology likely starts years before the disease is clinically apparent, it cannot be assumed the participants were free of early pathological changes. In the Rotterdam Study, high IL-6 and α -1-antichymotrypsin levels were significantly associated with an increased risk for dementia (rate ratio [RR]: 1.28; 95% CI: 1.06, 1.55; and RR: 1.49; 95% CI: 1.23, 1.81, respectively), and there was a trend for higher CRP to be associated with increased risk of dementia (RR: 1.12; 95% CI: 0.99, 1.25) [11]. There are several strengths to these two studies, including the fairly diverse population in the Health ABC study, and the complete dementia adjudication in the Rotterdam Study [10,11]. Furthermore, a large number of potential confounders were assessed in both studies [10,11]. However, both studies were limited in having only 2 years of follow-up visits completed; as dementia is a disease that progresses over a long period of time, having a longer follow-up is critical to assess the development of the disease.

Several longitudinal studies have reported a slightly longer follow-up when investigating the association between inflammation and dementia. In the MacArthur Study of Successful Aging, the association between plasma IL-6 and cognitive function was assessed longitudinally over follow-up periods of 2.5 and 7 years [12]. Those in the high, compared with those in the low, IL-6 tertile were significantly more likely to experience cognitive decline over 2.5 years (odds ratio: 2.21; 95% CI: 1.44, 3.42), and over 7 years (odds ratio: 1.90; 95% CI: 1.14, 3.18) [12]. These relationships were only significant when cognitive function was dichotomized, and not when a continuous measure of cognitive function was used [12]. Investigators hypothesize that this could be due to inflammation not being related to a full range of cognitive performance (i.e., only associated with the worst outcomes, hence the significant dichotomous association) [12]. This may be due to the fact that these large changes in cognitive function are more clinically meaningful [12]. One weakness of this study is that investigators measured inflammation at only one time point, so change in inflammation was not assessed [12]. In the Framingham Study, with an average follow-up of 7 years among participants, investigators reported a significant association between the

highest tertile of TNF- α and an increased risk of developing AD (hazard ratio [HR]: 2.59; 95% CI: 1.09, 6.12), but not among several other inflammatory markers including IL-1, the IL-1 receptor antagonist, CRP or IL-6 [13]. This study was strengthened by having extensive measurement of covariates, which were adjusted for in all statistical models. However, one weakness is that all of the cytokines, with the exception of CRP, were measured relatively close to the time of outcome adjudication, so again, there may not have been enough time for the development of dementia. While CRP was measured earlier than the other inflammatory markers, investigators found no significant association between CRP and an increased risk of AD [13].

In a recent meta-analysis of seven longitudinal studies, pooled HRs were calculated to determine the association between peripheral inflammatory markers and the risk of all-cause dementia or AD [14]. With a total of 5717 pooled participants, investigators reported a significant association between high CRP and an increased risk of AD and all-cause dementia (HR: 1.21; 95% CI: 1.03, 1.42; and HR: 1.45; 95% CI: 1.10, 1.91, respectively) (Figure 1) [14]. When looking at high IL-6, there was a significant increased risk of all-cause dementia (HR: 1.32; 95% CI: 1.06, 1.64), but not of AD alone (HR: 1.06; 95% CI: 0.83, 1.35) [14]. This finding highlights the possibility that inflammatory markers may be contributing to other types of dementia, such as vascular dementia, rather than just AD alone. Several cautionary notes should be made, however, when drawing this conclusion: it should be noted that cerebrovascular disease often contributes to many different types of dementia, including AD [15]; AD is the most commonly diagnosed form of dementia [16]; and it is difficult to interpret from many studies what exact definition of dementia was used, and many causes are often grouped together.

While these results have been promising, some studies have found no association between dementia or AD and inflammation, or have found associations in the opposite direction. For example, in a prospective study of approximately 2000 men, there was no significant association between IL-6 (HR: 0.66; 95% CI: 0.32, 1.35) and CRP (HR: 0.79; 95% CI: 0.42, 1.44) for the risk of dementia [17]. One weakness of this study is that the male participants were quite young (45–59 years of age) when inflammatory markers were measured, so the markers may not have been indicative of cognitive status years later when cognitive function was assessed (65–84 years of age), and some of these men may have still been too young for the onset of clinically detectable dementia symptoms when outcomes were assessed [17]. Another cross-sectional study found that high IL-6 and IL-12 tertiles were associated with decreased processing speed and executive function, but not with other domains of cognitive function, such as memory, language or spatial ability [18]. In another cross-sectional study of the oldest old (all 90 years and older), high serum CRP was associated with an increased risk of allcause dementia, and this association remained significant only among women when stratifying by sex [19]. However, in a prospective study of the same participants, with CRP measurements at multiple time points over 4.5 years, there was no association between elevated CRP and allcause dementia, even after stratifying by APOE ϵ 4 and sex [20]. Interestingly, at least one study has reported a protective effect of higher CRP levels on cognitive function in this age group, suggesting that inflammatory markers may be pleiotropic with different age cut-offs [21].

Potential mechanisms

One critical component of a successful predictor of dementia is that the biomarker in question should contribute to the etiologic process of dementia [22]. Thus, inflammatory markers are intriguing because they may, in fact, be large contributors to the underlying pathology and mechanisms of dementia [23,24]. It has been hypothesized that inflammation is a precursor to the development of neurofibrillary tangles, amyloid plaques and

neurodegeneration – hallmarks of AD [24]. Additionally, IL-6 is intimately involved in other pathophysiological processes of the nervous system, such as demyelination, which could contribute to white matter changes, and neurodegeneration [24,25]. If IL-6 production is upregulated or induced by the general aging process or by other conditions that occur in aging, it is possible that these changes begin the pathological process of dementia. High levels of serum CRP and IL-6 and plasma TNF- α have been associated with decreased total brain volume ($p < 0.001$) in a group of approximately 1900 Framingham offspring [26]. High serum CRP has also been associated with markers indicative of decreased neuronal function and decreased brain metabolism in middle-aged adults, suggesting CRP may play a role in cognitive decline or dementia in later life [27]. Finally, in middle-aged adults, higher levels of IL-6 have also been shown to be related to decreased hippocampal volume – a structure critical in the formation of long-term memory, which is also associated with dementia [28].

Another way that inflammation could contribute to the underlying etiologic process of AD is through the development of other dementia risk factors. For example, elevated IL-6 affects lipid metabolism and triglyceride production, and stimulates the hypothalamic–pituitary–adrenal axis, which is associated with central obesity, hypertension and insulin resistance; all of these factors are associated with an increased risk of dementia [29–31]. Higher levels of inflammation are also associated with cardiovascular disease, which is indeed a risk factor for dementia [32].

Another possible mechanism linking inflammation and dementia is depression. Depression is a major risk factor for dementia, and a number of studies have shown an association between higher peripheral circulating levels of IL-6, CRP and TNF- α with prevalent depressive symptoms and major depression in older adults [33,34]. One potential problem is that depression is often both a precursor and a result of dementia, so it is a possibility that the results are confounded. In a prospective study of the oldest old adults who were dementia and depression free at baseline, the association between circulating levels of CRP, IL-6, TNF- α and IL-1 β and the development of depressive symptoms and cognitive impairment was investigated with the objective of trying to shed some light on the highly intertwined associations [34]. Results indicated that depressive symptoms (Geriatric Depression Scale scores) attenuated the relationship between Mini-Mental State Examination scores and inflammation to a greater extent than how cognitive function was demonstrated to attenuate the association between depressive symptoms and inflammation [34]. This suggested that inflammation plays a larger role in the development of depressive symptoms [34]. However, this association was limited to the oldest old adults, and as has been previously discussed, there could be something unique about inflammation in this population.

Genetic components may also underlie an association between inflammation and AD. For example, *APOE* $\epsilon 4$ was investigated in a cross-sectional study comparing 206 middle-aged off-spring with and without parental history of late-onset AD; those with a parental history of AD were significantly more likely to have at least one *APOE* $\epsilon 4$ allele ($p < 0.001$), and to have higher *ex vivo* circulating levels of IL-1 β ($p < 0.001$), IL-6 ($p = 0.04$) and TNF- α ($p = 0.008$) [35]. However, when compared with those with no parental history of AD, those with a history were also significantly more likely to have a higher systolic blood pressure and a higher diastolic blood pressure, which could independently affect inflammatory markers [35]. Circulating levels of serum CRP have also been previously associated with the *APOE* $\epsilon 4$ allele, where it was reported that 2–5% of the variability in circulating CRP may be due to *APOE* $\epsilon 4$ allele status [36]. Similarly, in a microarray study of immune- and inflammation-related genes, investigators showed that there was a significant upregulation of immune- or inflammatory-related gene expression in the aging brain [37]. Furthermore, in

a recent genome-wide association study from the Religious Orders Study, investigators identified a variant (rs10808746) associated with the rate of cognitive decline, which influences two genes (*PDE7A* and *MTFR1*) that affect oxidative stress and inflammation; this again supports the notion that inflammation is an important contributor to the underlying pathways of cognitive decline and dementia [38]. Similarly, in a genomewide association study of cognitively normal older adults, another variant (rs17178006), influencing the *MSRB3* gene, which plays a role in regulating oxidative stress, was associated with decreased hippocampal volume [39].

Finally, infection or systemic inflammation may also underlie an association between inflammation and dementia [40]. It has been hypothesized that microglia, or the innate immune cells of the CNS, are changed in older adults after a lifetime of insults due to infection and acute inflammatory response [40]. This is important because it has been proposed that one way peripheral inflammation affects the brain is by inflammatory mediators in the blood communicating with macrophages – which lack a blood-brain barrier (BBB) – which then go on to communicate with microglia, triggering an inflammatory response in the brain. Thus, changes in the microglia associated with aging are quite pernicious, because rather than triggering a protective or anti-inflammatory response in the brain, a heightened inflammatory response is initiated in the brain after infection or systemic inflammation occurs, which contributes to increased neurodegeneration [40].

One aspect that would strengthen the argument for using inflammatory markers to predict dementia in older adults is sensitivity to the effects of anti-inflammatory therapies that modify the progression of dementia [22]. However, thus far, clinical trials with nonsteroidal anti-inflammatory drugs (NSAIDs) have not been promising [6,41,42]. For example, in ADAPT, there was no difference in the risk of developing AD in celecoxib or naproxen sodium groups, compared with a placebo group after 3 years; similar results were found in the Alzheimer's Disease Cooperative Study (n = 351), which found no difference in cognitive test scores in naproxen or rofecoxib groups compared with a placebo group [6,41]. It should be noted that, in an extended 2-year follow-up of ADAPT participants, it was concluded that NSAIDs may have pleiotropic effects, such that when given to cognitively normal participants, NSAIDs reduced the risk of AD after 2–3 years of administration, but when given to AD participants, NSAIDs had unfavorable effects on disease pathology [43]. However, in a recent comprehensive review of all randomized controlled trials of aspirin, NSAIDs and steroids in the treatment of AD, investigators found no sufficient evidence that any of these treatments are effective in the treatment of AD [44]. It is possible that more studies are needed to follow-up participants for longer time periods, as shown with the extended results from ADAPT. Furthermore, it could be that special attention needs to be paid when classifying trial participants and analyzing data because if there is a pleio tropic effect at differing disease stages, then this would weaken any reported associations when participants are misclassified. Finally, perhaps there is a need to investigate more specific treatments targeted toward particular inflammatory markers that have been shown to have an effect on cognitive function (similar to anti-TNF drugs used in rheumatoid arthritis [45]).

One major question that must be addressed is whether peripheral inflammatory markers reflect direct changes in the brain. It has been previously reported that cytokines readily cross the BBB, suggesting that peripheral measures do reflect direct brain changes [46]. Previous studies of mice have linked the inflammatory response in the periphery with inflammation in the brain, especially for IL-6, TNF- α and IL-1 β [47,48]. Previous studies have also demonstrated that TNF- α and IL-6 can be transported across the BBB via saturable systems [46,49]. The ability to cross the BBB may differ by type of inflammatory marker (i.e., inflammatory cytokine vs soluble receptors). In mice, binding of TNF- α to its soluble receptor completely inhibited travel across the BBB, but unbound TNF- α could

cross the BBB [46]. Furthermore, the soluble form of the receptor itself could not cross the BBB [46]. Peripheral inflammatory markers may also set off a cascade of events, for example, upregulating lipid mediators or communicating with peripheral macrophages, which ultimately leads to an inflammatory response in the brain [4,50]. Thus, there seems to be evidence supporting the peripheral inflammatory markers' ability to cross the BBB via multiple pathways, but as most studies so far have been conducted in animals, more work is needed to determine how peripheral inflammatory markers are crossing the BBB in humans.

On the other hand, if inflammatory markers do not cross the BBB, there are other means by which a peripheral inflammatory response may affect inflammation in the brain. As described previously, altered microglia in older adults, which communicate with macrophages after systemic inflammation or injury, may lead to increased inflammatory cytokine production in the brain [40]. Another proposed pathway of peripheral inflammatory markers to influence inflammatory response in the brain is via the vagus nerve [40,51]. Sensory nerve fibers in the vagus nerve, activated in the abdomen and chest by peripheral inflammatory markers, relay information very rapidly to the brain, triggering an inflammatory response in the brain [40,51].

Conclusion & future perspective

An important limitation to understanding the association between inflammation and dementia is that it is not completely clear if the inflammation precedes the symptoms of dementia, or if the inflammation is a result [24]. Abnormal materials in the periphery are a common cause of inflammation, so it is not strange to consider that plaques or tangles in the brain are a cause of inflammation [24]. Furthermore, the process of aging is associated with chronic, low-grade inflammation, which makes it even more difficult to determine if, how and when inflammation may be important in the pathway of dementia [24]. Other limitations to understanding the role of inflammatory markers in predicting dementia include relatively new and not well validated or standardized methodology across studies, and highly mixed epidemiological and trial results. Furthermore, many studies investigating these markers only measure inflammation at one time point [20,21,34,52], and it is extremely difficult to conclude if the inflammation measured is the result of some acute event, such as infection or injury, or is an indicator of a consistently elevated level of inflammation. Thus, more studies are needed to assess if change in inflammation over time is associated with dementia. Furthermore, the current gold standard of living biomarkers for distinguishing AD from other types of dementia is cerebrospinal fluid-derived amyloid- β and tau [53,54]; if considered as useful biomarkers for dementia, peripheral inflammatory markers should be compared against this gold standard, and achieve a good predictive ability, either alone or in combination with other markers. It is unclear if these markers would be as useful in distinguishing AD, or perhaps some other subtype of dementia, but certainly more work is needed in this area.

In spite of these weaknesses, there are important strengths in using peripheral inflammatory markers as potential predictors of dementia. For example, blood can be collected relatively easily, making it a viable option for large, population-based epidemiological studies. Furthermore, methods used to quantify multiple inflammatory markers or inflammation-related genes, such as proteomics or microarray studies, are emerging and may strengthen the current research. For example, one study using proteomics found that a panel of approximately 22 serum-derived proteins could be used to identify AD patients from normal controls with a sensitivity of 0.80 and a specificity of 0.91; interestingly, a large number of these proteins were, in fact, inflammatory markers [55]. Similar studies have also reported panels of plasma-derived proteins that contain a number of inflammatory proteins, and can distinguish AD patients from normal controls with fairly high accuracy [56,57]. However,

one study comparing cerebrospinal fluid and plasma proteomes found that the cerebrospinal fluid proteome was much better at distinguishing AD patients from normal controls, and in order for the plasma proteome to successfully distinguish these two groups, APOE and age had to be added to the models [58].

As we know, dementia is an extremely complex disease with a wide range of presentations and severities, and with many underlying contributing causes, so caution should be exercised when trying to use any single marker as a predictor for the disease. Because of this, multipronged approaches, such as proteomics or microarray studies, may prove to be the most useful in the end. With such a mix of results reported, it seems that, at this time, peripheral inflammatory markers have limited use as predictors of dementia. However, because of the aggregate of evidence directly linking inflammation to the numerous pathological changes of dementia, perhaps they could be used to indicate an increased susceptibility for neurodegeneration or cognitive decline, and then a more complete risk profile could be obtained.

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Practice Points

- ❑ Several peripheral inflammatory markers, especially CRP, IL-6 and TNF- α , have been widely investigated as potentially useful biomarkers in predicting cognitive decline or dementia in older adults, but results have been highly mixed.
- ❑ There are several potential underlying mechanisms linking peripheral inflammatory markers to brain changes, providing support for these markers being useful as biomarkers of dementia.
- ❑ Thus far, clinical trials investigating the effects of drugs with anti-inflammatory properties on dementia or Alzheimer's disease have demonstrated no beneficial effects.
- ❑ Emerging proteomics or microarray techniques may greatly add to this research, as they allow researchers to investigate an entire panel of peripheral markers at one time.

CRP and incident all-cause dementia **CRP and incident all-cause Alzheimer's disease**

Figure 1. Pooled hazard ratios for CRP and incident all-cause dementia and Alzheimer's disease
 HR: Hazard ratio.

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Table 1
Summary of studies investigating plasma- and serum-derived CRP, IL-6 and TNF- α as potential predictors of dementia or Alzheimer's disease

Author (year)	Source	Outcome	Significant association?	Sample size (n)	Mean age	Adjusted covariates	Ref
CRP							
Engelhart <i>et al.</i> (2004) Cohort from the Rotterdam Study	Plasma	Risk of AD 1 year	No	727	71.7 years at baseline	Age, sex, education, smoking, BMI, diabetes, anti-inflammatory medication use and atherosclerosis	[11]
Eriksson <i>et al.</i> (2011)	Serum	Prevalent and incident all-cause dementia and AD	Prevalent cases: no Incident cases: no	3937	77.7 years for controls; 75.3 years for dementia cases	APOE ϵ 4, BMI, smoking, blood pressure, education, diabetes, coronary heart disease and stroke	[59]
Gallacher <i>et al.</i> (2010)	Plasma	Risk of dementia 20 years	No	865	65–84 years at cognitive status determination; 45–59 years at measurement of inflammatory markers	Age, social class, systolic blood pressure, BMI, smoking, total cholesterol and alcohol use	[17]
Holmes <i>et al.</i> (2009)	Serum	Cognitive performance on the ADAS-COG, and change in ADAS-COG 1 year	No	300	82.7 years at baseline	Not stated	[9]
Kravitz <i>et al.</i> (2009) Cohort from the Leiden 90+ Study	Serum	Risk of developing dementia 1 year	No	227	93.9 years	Age, sex, education, APOE ϵ 4, hypertension, coronary artery disease, congestive heart failure and transient ischemic attack	[20]
Ravaglia <i>et al.</i> (2007)	Serum	Incident all-cause dementia, AD and vascular dementia	All-cause: no AD: no Vascular: no When analyzed together, having a high level of both CRP and IL-6 was significantly associated with an increased risk of vascular dementia; high CRP was not individually associated with an increased risk of vascular dementia (HR: 2.56; 95% CI: 1.21, 5.50)	804	73.6 years at baseline	Age, sex, education, APOE ϵ 4, stroke, cardiovascular disease, physical activity, BMI, total plasma homocysteine, serum creatinine, serum folate and serum vitamin B12	[60]
Schmidt <i>et al.</i> (2002) Cohort from the Honolulu-Asia Aging Study	Serum	All-cause dementia, AD, AD with cardiovascular disease and vascular dementia	All-cause: yes (HR: 2.8; 95% CI: 1.6, 5.1) AD: no (HR: 2.2; 95% CI: 0.9, 5.1) AD with cardiovascular disease: yes (HR: 4.7; 95% CI: 1.2, 17.9) Vascular dementia: yes (HR: 5.1; 95% CI: 1.8, 14.8) All reported HRs are comparing the highest quartile of CRP with the lowest quartile reference group	1050	Not reported for entire cohort	Education, midlife smoking status, midlife average cholesterol, midlife blood pressure, age, years of follow-up, APOE ϵ 4 and BMI	[61]
Schram <i>et al.</i> (2007) Cohort from the	Plasma	Cognitive function (test scores) and decline 4.5 years	Cross-sectional: yes; higher CRP was associated with poorer global cognitive function and executive function ($p < 0.001$ for both)	3874	72.1 years	Age, sex and education	[52]

Author (year)	Source	Outcome	Significant association?	Sample size (n)	Mean age	Adjusted covariates	Ref
Rotterdam Study							
Schram <i>et al.</i> (2007) Cohort from the Leiden 85+ Study	Plasma	Cognitive function (test scores) and decline 5 years	Cross-sectional: no Longitudinal: no	491	85 years	Sex and education	[52]
Silverman <i>et al.</i> (2009)	Plasma	Performance (scores) on a neuropsychological test battery	Yes: those in the lowest CRP tertile had significantly worse memory scores than those in the other two tertiles ($p < 0.0001$)	176	85 years	Age, sex, education and APOE $\epsilon 4$	[21]
Sundelof <i>et al.</i> (2009)	Serum	Risk of all-cause dementia, AD and non-AD dementia 11.3 years	All-cause: no (for both cohorts) AD: no (for both cohorts) Non-AD: no (for both cohorts)	Age 70 years cohort: 1062 Age 77 years cohort: 749	Age 70 years cohort: 71.0 years at baseline Age 77 years cohort: 77.5 years at baseline	Age, APOE $\epsilon 4$, diabetes, NSAID use, aspirin treatment and smoking status BMI, hypertension, serum cholesterol, stroke and education	[62]
Tan <i>et al.</i> (2007) Cohort from the Framingham Study	Serum	Risk of developing AD	No	691	79 years	Age, sex, APOE $\epsilon 4$, stroke, education, homocysteine levels, smoking history, BMI and anti-inflammatory drug use	[13]
Yaffe <i>et al.</i> (2003)	Serum	Cognitive function (3MS) and clinically significant cognitive decline (5 point decline 2 years)	Yes: those in the highest CRP tertile had significantly worse scores on the 3MS compared with those in the lowest tertile (88.7 vs 90.4 points; $p < 0.001$). Those in the highest CRP tertile experienced significantly greater cognitive decline 2 years (-1.7 vs -1.1 points; $p = 0.05$). CRP was not significantly associated with clinically significant cognitive decline after adjustment (OR: 1.24; 95% CI: 0.96,1.63)	3031	74 years at baseline	Age, education, race, sex, smoking, alcohol use, BMI, self-reported health, depression, MI, diabetes, hypertension, stroke, NSAID use and estrogen use (for women)	[10]
IL-6							
Engelhart <i>et al.</i> (2004) Cohort from the Rotterdam Study	Plasma	Risk of AD 1 year	Yes: high IL-6 was significantly associated with increased risk for AD (rate ratio per SD increase in IL-6:1.28; 95% CI: 1.06,1.55)	727	71.7 years	Age, sex, education, smoking, BMI, diabetes, anti-inflammatory medication use and atherosclerosis	[11]
Eriksson <i>et al.</i> (2011)	Serum	Prevalent and incident all-cause dementia and AD	Prevalent: yes: when compared with controls, those with all-cause dementia and AD had significantly elevated levels of IL-6 Incident: no	3937	77.7 years for controls; 75.3 years for dementia cases	APOE $\epsilon 4$, BMI, smoking, blood pressure, education, diabetes, coronary heart disease and stroke	[59]
Gallacher <i>et al.</i> (2010)	Plasma	Risk of dementia 20 years	No	865	65–84 years at cognitive status determination; 45–59 years at measure of inflammatory markers	Age, social class, systolic blood pressure, BMI, smoking, total cholesterol and alcohol use	[17]

Author (year)	Source	Outcome	Significant association?	Sample size (n)	Mean age	Adjusted covariates	Ref
Licastro <i>et al.</i> (2000)	Plasma	Cross-sectional comparison of IL-6 level in AD patients and normal controls	Yes: levels of IL-6 were increased in patients with AD compared with normal controls ($p < 0.001$)	196	78 years for AD; 75 years for controls	None stated	[63]
Ravaglia <i>et al.</i> (2007)	Serum	Incident all-cause dementia, AD and vascular dementia	All-cause: no AD: no Vascular: no When analyzed together, having a high level of both CRP and IL-6 was significantly associated with an increased risk of vascular dementia; high IL-6 was not individually associated with an increased risk of vascular dementia (HR: 2.56; 95% CI: 1.21, 5.50)	804	73.6 years at baseline	Age, sex, education, APOE e4, stroke, cardiovascular disease, physical activity, BMI, homocysteine, creatinine, folate and vitamin B12	[60]
Schram <i>et al.</i> (2007) Cohort from the Rotterdam Study	Plasma	Cognitive function (test scores) and decline (4.5 years in the Rotterdam Study and 5 years in the Leiden 85+ Study)	Cross-sectional: yes: higher IL-6 (per SD) was associated cross-sectionally with lower 3MS scores, poorer global cognitive function and poorer executive function ($p = 0.03$; 0.009 and 0.008, respectively) Longitudinal: no	3874	72.1 years	Age, sex and education	[52]
Schram <i>et al.</i> (2007) Cohort from the Leiden 85+ Study	Plasma		Cross-sectional: no Longitudinal: yes: those with higher IL-6 had greater decline overtime on delayed recall tasks ($p = 0.03$). Associations were modified by the APOE e4 allele, such that they were stronger among those with at least one allele	491	85 years	Sex and education	[52]
Sundelof <i>et al.</i> (2009)	Serum	Riskofall-cause dementia, AD, and non-AD dementia 11.3 years	All-cause: Age 70years cohort:yes (HR: 1.45; 95% CI: 1.06, 2.07) Age 77 years cohort: no AD: no (for both cohorts) Non-AD: Age 70years cohort:yes (HR: 2.21; 95% CI: 1.23, 3.95) Age 77 years cohort: no	Age 70 years cohort: 1062 Age 77 years cohort: 749	Age 70 years cohort: 70 years Age 77 years cohort: 77 years	Age, APOE e4, diabetes, NSAID treatment, aspirin treatment and smoking status, BMI, hypertension, serum cholesterol, stroke and education	[62]
Tan <i>et al.</i> (2007) Cohort from the Framingham Study	Serum	Risk of developing AD	No	691	79 years	Age, sex, APOE e4, stroke, education, homocysteine levels, smoking history, BMI and anti-inflammatory drug use	[13]
Weaver <i>et al.</i> (2002)	Plasma	Baseline cognitive function and cognitive decline 2.5 and 7 years Measured with five tasks assessing verbal memory, naming, recall, language and spatial ability, with a combined score	Cross-sectional: no Longitudinal: yes: after 2.5 years, those in the highest tertile were significantly more likely to experience cognitive decline than those in the lower tertile (OR: 2.03; 95% CI: 1.30, 3.19). After 7 years, those in the highest tertile were significantly more likely to experience cognitive decline than those in the lower tertile (OR: 1.90; 95% CI: 1.14, 3.18)	779	74 years at baseline	Age, race, sex, education, alcohol use, activity level, BMI, history of cancer, diabetes and fasting blood glucose levels	[12]

Author (year)	Source	Outcome	Significant association?	Sample size (n)	Mean age	Adjusted covariates	Ref
Yaffe <i>et al.</i> (2003) Cohort from the Health ABC Study	Plasma	Cross-sectional cognitive function (3MS), change in 3MS over time and clinically significant cognitive decline (5 point decline 2 years)	Cross-sectional: yes: those in the highest IL-6 tertile had significantly worse scores on the 3MS, compared with those in the lowest tertile (88.9 vs 90.6 points; $p < 0.001$) Longitudinal: yes: those in the highest IL-6 tertile experienced significantly greater cognitive decline 2 years (-2.0 vs -1.2 points; $p = 0.01$). IL-6 was not significantly associated with clinically significant cognitive decline after adjustment (OR: 1.23; 95% CI: 0.96,1.59)	3031	74 years at baseline	Age, education, race, sex, smoking, alcohol use, BMI, self-reported health, depression, MI, diabetes, hypertension, stroke, NSAID use and estrogen use (for women)	[10]
TNF-α							
Holmes <i>et al.</i> (2009)	Serum	Cognitive performance on the ADAS-COG, and change in ADAS-COG 1 year	Cross-sectional: yes: those in the lowest TNF- α quartile had significantly better ADAS-COG scores compared with those in the highest quartile ($p = 0.02$) Longitudinal: yes: worsening in ADAS-COG scores was significantly greater among those in the highest serum TNF- α quartile compared with those in the lower quartile ($p = 0.02$)	300	82.7 years at baseline	Not stated	[9]
Yaffe <i>et al.</i> (2003) Cohort from the Health ABC Study	Plasma	Cross-sectional cognitive function (3MS), change in 3MS over time and clinically significant cognitive decline (>5 point decline 2 years)	Cross-sectional: no Longitudinal: no	3031	74 years at baseline	Age, education, race, sex, smoking, alcohol use, BMI, self-reported health, depression, MI, diabetes, hypertension, stroke, NSAID use and estrogen use (for women)	[10]

3MS: Modified Mini-Mental Status Exam; AD: Alzheimer's disease; ADAS-COG: Alzheimer's Disease Assessment Scale-Cognitive subscale; Health ABC: Health, Aging and Body Composition; HR: Hazard ratio; MI: Myocardial infarction; OR: Odds ratio; SD: Standard deviation.

[†]All inflammatory markers (CRP, IL-6 and TNF- α) selected to be summarized here were published in manuscripts during or after the year 2000 and included humans (not animal models).