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Neuroinflammation in Preclinical Alzheimer's Disease: A Review of Current Evidence

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Abstract

The pathology of sporadic Alzheimer's disease (AD) may be present at mid-life and precede the prodromal and clinical dementia syndromes associated with the disorder by decades. Few successful therapeutic treatments exist and, as a result, attention is turning to the preclinical stages of the disease for the development of future intervention strategies. The success of such strategies will rely on well-defined biomarkers of preclinical disease to identify and monitor changes earlier in the disease course. Here, we consider whether immune function changes are potentially useful markers of preclinical disease. We have selected studies spanning epidemiological, animal, clinical and imaging research pertaining to the earliest stages of AD pathogenesis, as well as studies of non-demented adults at high AD risk. We examine changes in inflammatory markers, alongside changes in established biomarkers, to highlight their suitability as disease indicators across preclinical and prodromal stages. We conclude that further work surrounding this topic is required, calling for larger prospective epidemiological studies of preclinical disease that incorporate serial assessment designs with a wider range of inflammatory mediators. We anticipate that future benefits of work in this area include improved disease detection and modification, as well as diagnostic accuracy of trial participants, leading to more cost-effective observation and intervention studies.

Keywords: Preclinical Alzheimer's disease; Neuroinflammation, Biomarkers

Introduction

Increasing evidence suggests sporadic Alzheimer's disease to be a clinically silent disease of mid-life, which remains undetected for decades until its terminal stage, characterized by dementia [1-4]. In light of multiple failures to develop an effective treatment for prodromal or clinical (dementia) AD, research efforts are now focusing on earlier stages of the disease process and clinical services are moving towards a similar model [5]. The development of therapeutic intervention strategies targeting the pre-clinical stages of the disorder currently relies, however, on our ability to identify biomarkers, which may be used to monitor change at this early stage. Within this context the focus is currently on neurological markers, notably neurodegeneration, amyloid and tau accumulation and pre-clinical cognitive markers [6,7]. Immune system changes on the other hand, although extensively studied in relation to prodromal AD and AD dementia, have to date been relatively neglected.

While considerable attention was given to early evidence of neuroinflammation in AD dementia, it fell out of favour as the amyloid cascade hypothesis [8] became the predominant aetiological model. In the last decade there has been a resurgence of interest in the potential role that neuroinflammation may play not only as pathological consequence of Aβ pathology, but also as a potential trigger and accelerator of amyloid plaque formation and tau-related neuronal injury [9-11]. Inflammatory reactions have been implicated in the pathogenesis of AD dementia in the form of glial cells, such as astrocytes and microglia, as well as inflammatory components, such as cytokines and chemokines [11,12]. Additional support comes from associations of AD dementia with genes implicated in immune responses, such as TREM2, CR1 and CD33 and chronic psychological stress [13-15]. An inflammatory contribution to disease pathogenies has also been observed in the prodromal stages of AD [16]. Given accumulating biological evidence that neuroinflammation may precede both Aβ and tau formation [11], it is of considerable interest as a potential pre-clinical marker.

The present review does not aim to describe the biological role of neuroinflammation within the disease process, but rather to consider whether inflammatory markers may have a potential use as a means of identifying persons with clinically silent AD for clinical intervention studies. Epidemiological, animal, clinical and imaging studies have been selected which have included data on the earliest stages of AD pathogenesis, as well as studies of normal persons at high AD risk. We examine changes in markers across time from the pre-clinical to the prodromal phases and also attempt to evaluate their utility alongside already established biomarkers. Finally, we make suggestions for future research design.

Epidemiological Studies

Due to the relatively recent advent of research in preclinical AD, there is little epidemiological evidence linking neuroinflammation to this specific AD population. However, associations of several inflammatory-related diseases, such as obesity, type 2 diabetes, rheumatoid arthritis and psoriasis [17-20] in the decades before AD dementia diagnosis have been consistently observed. Traumatic brain injury, with associated inflammation, has also been observed to significantly increase risk of AD dementia later in life [21]. Conversely, the use of non-steroidal anti-inflammatory drugs (NSAIDs) in mid-life has been associated with a reduced risk of developing AD dementia in some studies [22,23] but not others [24,25]. Episodes of acute systemic infections, accompanied by

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raised levels of cytokine TNF-α, have been found to correspond to an acceleration of cognitive decline in AD dementia patients [26], but the nature of inflammation's impact in the pre-clinical period has not been specifically examined within epidemiological studies.

A retrospective general population study of persons diagnosed with AD dementia observed that C-reactive Protein (CRP) levels were not significantly different ten years previously in individuals remaining cognitively healthy (i.e., controls) and those evolving towards AD dementia [4]. However, against expectation, levels of CRP in the AD dementia cases showed a significant downward slope closer to the time of diagnosis, while the control group showed a slightly raised curve towards the same time-point similar to the sigmoidal trajectories observed by Jack et al in relation to other biomarkers, notably amyloid and tau [27-29]. The study was limited by its restriction to a single inflammatory marker assessed at only one point in time and also limited by the older age of the population (over 65 at recruitment). The value of future epidemiological studies of inflammatory markers in the pre-clinical period will very much depend on their ability to examine a wider range of markers across time from mid-life, when exposure to many of the principal inflammation-related disorders also implicated in AD risk (notably obesity, diabetes and stroke) are currently postulated to have their principal impact.

Animal Studies

The occurrence of plaque-dependent inflammation has been robustly observed in animal models of AD [9,30], with microglia present in neutritic plaques [31,32] that are spatially related to dendritic spine loss [33]. Furthermore there is some evidence to suggest that a pro-inflammatory process may be initiated before plaque deposition. In transgenic mice overexpressing amyloid precursor protein, a microglial activation processes involving Il-1β and Il-6 was detected early at 3 months of age when amyloid plaques were not yet present [34]. Similarly, using a triple transgenic mice model (3xTg), Janelsins et al. [35] observed increased expressions of TNF-α and monocyte chemoattractant protein-1 (MCP-1) in the entorhinal cortex of three-month-old mice which coincided with the production and accumulation of intracellular amyloid but preceded extracellular plaque deposition, the latter of which occurred only at 12 months of age [35]. Another study found that exposure of a viral mimic (polyriboinosinic-polyribocytidilic acid) to wild-type and transgenic mice prenatally and again in adulthood corresponded to an emergence of AD-like pathology (amyloid and tau aggregates), microglia activation and reactive gliosis over the course of animal ageing [36].

Taken together, these studies suggest that pro-inflammatory processes may act as very early indicators of preclinical disease. However, their relevance to pre-clinical AD is limited by the difficulties inherent in defining 'pre-clinical' in animal models. This can only currently be estimated by reference to progression of amyloid and tau deposition. Although human and rodent amyloid plaques share morphological similarities, they are distinct in biochemical composition [37] and might interact differently with other pathological features, such as inflammatory agents. Moreover, animal models typically involve the manipulation of genetic markers associated with familial forms of AD and such models might not correspond to the relatively more prevalent sporadic form associated with humans. Therefore, while animal studies provide limited evidence of inflammation as an upstream marker of disease, prospective studies are required to monitor changes before and during the evolution of neurological changes within the human brain.

Clinical and Imaging Studies

Research on the role of brain inflammation in the evolution of the AD began in the mid-1980s [38]. Subsequently, the inflammatory profiles of prodromal AD and AD dementia are relatively well described but present a heterogenous picture; possibly as a result of discrepant methodological practices and patient characterisation between studies [39]. Inflammation has primarily been studied in the context of advanced AD pathology involving amyloid plaques. Therefore, the involvement of elevated inflammatory agents in evolution from prodromal changes to dementia remains unclear, with inconsistent evidence for a specific risk for AD dementia [40]. Relatively few studies have assessed inflammatory profiles in preclinical AD, so it is even less clear if or how neuroinflammation promotes AD-related cognitive and brain changes in the direction of prodromal and clinical AD. In addition, the initiation of the acute inflammatory response is counterbalanced by an active resolution and specialized pro-resolving mediators (SPMs) have been identified that drive resolution by diminishing inflammatory molecules, such as cytokines [41]. Thus it has been suggested that age-related deficits in resolution of inflammatory responses may contribute to the development of late onset AD dementia [42], including in humans [43]. Finally, while, preclinical evidence suggests that inflammation can induce tau hyperphosphorylation, a better understanding of whether this increases neurofibrillary tangles is needed [44].

Given that the preclinical phase of AD is, by definition, not observable in terms of everyday functioning, research participants with preclinical AD are likely to be included in studies of "healthy" or "normal" cohorts. Elevated levels of pro-inflammatory cytokines and markers, such as IL-1β, IL-6, TNF-α and CRP have been observed in some but not all persons over time and attributed to age [45]. It is, however, possible that such persons are manifesting pre-clinical AD, a proposition supported by studies of midlife and older normal adults showing elevated levels of inflammatory markers in association with cognitive deficits and brain changes (Table 1).

In healthy adults, elevated YKL-40 concentrations have been associated with poorer Mini-Mental State Exam (MMSE) performance [46,47] and PAI-1 has been negatively correlated with motor speed and coordination [48]. Serum CRP levels have been negatively associated with performance on executive function tasks [49], while composites of CRP with other inflammatory markers have correlated with visuospatial function (CRP+TNF-α [50]; CRP+IL-6 [51]), verbal proficiency and short-term memory (CRP+IL-6 [51]). Midlife inflammation levels may contribute to later-life cognitive performance, as one study found that inflammation composite scores created from immunoassays ascertained at mid-life (45-65 years old) were associated with reduced episodic performance 24 years later [52].

These relationships between raised inflammatory levels and cognitive scores are not always demonstrated [53,54], possibly due to heterogeneous cognitive ability within "healthy" aged samples. For example, in one study, participants' levels of inflammatory markers were classified into tertiles of high, middle and low values. Cognitive scores were adjusted for age, education-level and gender. At baseline, the highest tertiles of ACT and lowest tertiles of albumin were associated with delayed memory recall and MMSE performances, respectively. However, excluding participants with MMSE scores<21 at baseline, revealed a further linear relationship between ACT and information processing speed, while the association between MMSE performance and albumin disappeared. At follow-up both ACT and albumin tertiles were associated with decline in MMSE performance. Only the association between ACT and MMSE performance remained

Marker	Main Findings
YKL-40	Levels are significantly increased in preclinical and prodromal AD groups [46]. Levels are higher in preclinical stages 2-3 and SNAP stage compared to Stage 0, 1 [60]. Levels significantly correlate with t-tau and p-tau levels in preclinical AD [46], middle and older adults [62]. Levels correlated with MMSE and MAT performance for combined preclinical and prodromal AD groups [46] as well as change scores for global cognition in older adults [64]. Levels correlates with cortical thinning in middle and inferior temporal areas but only in individuals with low CSF Aß42 [65].
CRP	An association with cognitive performance is not always demonstrated [53, 54]. Nonetheless, higher levels are associated with worse performance in executive function [49], while individuals within the highest tertiles of CRP show significantly lower MMSE scores overtime [47]. CRP levels inversely related to white matter integrity in corticosubcortical pathways and association fibres of frontal and temporal lobes [48]; global and regional FA scores of the frontal lobes, the corona radiata and the corpus callosum [49] as well as regional gray matter volume in the posterior and lateral aspects of left temporal cortex [58].
PAI-1	Levels correlate with lower processing speed and motor coordination [48]. Higher levels associated with white matter integrity loss in corticosubcortical pathways and association fibres of frontal and temporal lobes [48].
ACT	Highest tertile of ACT was associated with lower delayed recall scores cross-sectionally and greater decline on MMSE longitudinally [54].
IL-6	As part of a composite with CRP, has been negatively associated with tests of spatial processing, short-term memory, verbal proficiency, verbal learning and memory, executive function [51] as well as episodic performance [52]. Higher levels associated with reduced cortical thickness in inferior occipital gyrus and sulcus, inferior temporal gyrus (both hemispheres) crossectionally. Higher levels associated with cortical thinning in: frontopolar gyri and sulci; right subcentral gyrus and sulci; inferior temporal poles (bilatreal) and left occipital pole and right calcarine sulcus cortex overtime [57].
TNF-a	As part of composite with CRP, has been associated with correlated with visual spatial ability. DA in the body and isthmus of the corpus callosum was shown to mediate this association [50].
Composites	Composite (fibrinogen, albumin, white blood cell count, von Willebrand factor, Factor VIII,) was negatively associated with episodic memory and was associated with greater ventricular degeneration, smaller hippocampal and occipital volumes [52]. Composite (cystatin C, VEGF, TRAIL-R3, PAI-1, PP, NT-proBNP, MMP-10, MIF, GRO-a, fibrinogen, FAS, eotaxin-3) significantly enhanced the ability of tau/Ab42 ratio, to discriminate CDR 0 from CDR 0.5 [67].

CSF: Cerebral Spinal Fluid; MMSE: Mini-Mental Status Exam; MAT: Memory Alteration Test; FA: Fractional Anisotropy; DA: Diffusion Anisotropy

Table 1: Summary of clinical and imaging studies for healthy participants and preclinical AD.

when participants with MMSE<21 at baseline were excluded from the longitudinal analyses [54]. These findings imply the possible sensitivity of different inflammatory markers to cognitive impairment at different stages along dementia continuums and underscore the importance of sub-group analyses in cognitively heterogeneous samples.

Where these relationships between cognitive performance and inflammation are present, they may be partially mediated by inflammation's influence on brain morphology [50,51]. Smaller hippocampal volumes have been found for individuals with higher levels of STNFR-1, STNFR-2; IL-6 and CRP [51,55,56]; these effects being strongest for individuals between 60-70 years [55]. In both middle and older healthy aged adults, higher CRP has been related to reduced global and regional fractional anisotropy in the frontal and temporal lobes, the cortico-subcortical tracts, and corpus callosum [48,49]. Higher IL-6 has been associated with smaller total brain volume, total and regional grey and white matter volumes as well as with reduced cortical thickness of the inferior occipital and temporal gyri [56-58]. The influence of prolonged inflammation on brain morphology is not yet clear, with one recent study finding that the presence of baseline inflammatory biomarkers did not modify the change of brain measures over time [59], but earlier reports indicating greater cortical thinning and white matter volume reduction at follow-up [56,57]. Age and race may mediate the relationship between inflammation and later-life brain integrity as younger and white participants with higher levels of systemic inflammation during midlife were more likely to show reduced brain volumes 24 years later [52].

Some studies of inflammation in healthy adult samples incorporate the assessment of established AD risk factors alongside immunoassay analyses but few studies have compared inflammatory mediators across the stages of preclinical dementia as defined by accepted research criteria [6]. These criteria propose a spectrum of stages pertaining to biomarker load within preclinical AD: stage 1 individuals show evidence of amyloid deposition only; stage 2 individuals possess both amyloid and neurodegeneration; while stage 3 individuals show subtle cognitive symptoms in addition to these biomarkers. In one study of cognitively normal individuals [60], those participants qualifying for stages 2 and 3 as well as those with suspected non-Alzheimer's pathophysiology (SNAP) showed higher levels of CSF YKL-40 than those in stages 1 and those without amyloid evidence. At the cohort level, YKL-40 concentrations correlated with t-tau and p-tau deposition, in keeping with other research [46,61,62]. This correlation remained significant when amyloid positive and amyloid negative participants were analysed separately, emphasising a possible role for YKL-40 in tau hyperphosphorylation and neuronal injury, which may be at least partially independent from amyloid plaque deposition. The overlap of elevated YKL-40 levels across preclinical and SNAP participants further suggests that neuroinflammation may emerge independent of amyloidios. More recently, an assessment with a broader range of inflammatory markers again found no correlation of any markers with AB41-42 levels. Instead, six CSF markers (IL-15, MCP-1, sFLT-1, siCAM-1 and sVCAM-1) were associated with tau pathology independent of age, gender, cognitive status and APOE-E4 status [63]. Alternatively, certain inflammatory agents may interact with amyloid and tau pathologies to alter brain structure in preclinical AD. In a cohort of mid and later life adults at risk for AD, higher MCP-1 in combination with lower CSF AB42 levels was associated with measures of neuronal injury in the bilateral frontal cortex and lateral temporal lobe, while higher MCP-1 in combination with higher CSF p-tau was related to altered microstructure in the precuneus. Elevated YKL-40 was directly associated with CSF levels of neurofilament light chain protein and t-tau, markers of neuronal injury [62]. Similarly, YKL-40 was associated with a change in global cognition over the course of two years in older adults, but only for those who were positive for amyloid pathology [64]. Previously, YKL40 had been associated with reduced cortical thickness in the middle and inferior temporal areas in a cross-sectional research, but this association was again only observed in participants with low CSF Aß42 [65]. In both studies, CSF YKL-40 and AB42 levels did not correlate in the positive AB42 group, suggesting that amyloid build-up and neuroinflammation may underlie distinct processes but may have additive effects on cognition and brain structure.

Inflammatory indicators may have diagnostic and prognostic value in preclinical AD. Cognitively normal participants with high ratios

of CSF YKL-40/Aβ42 have been found to progress faster to cognitive impairment compared to those with lower ratios [61]. A combination of markers (Table 1, Composites) was shown to enhance the ability of the tau/Aβ42 ratio to discriminate mild AD, prodromal AD and cognitively healthy individuals, as defined by the Clinical Dementia Rating scale [66,67]. More recently, the inclusion of certain of certain serum (cFGF, CRP, IL-16, sFLT-1, sICAM-1, Tie-2, VEGF-C and VEF-D) and CSF (IL-15, MCP-1 and sFLT-1) inflammatory markers significantly improved the accuracy of classification for AD pathology in cross-sectional samples of healthy older adults, prodromal AD and mild AD dementia patients [63].

Discussion and Conclusion

The evidence considered in this review largely suggests that inflammation is present in preclinical AD and is associated with AD pathogenesis. Some findings from animal and clinical studies propose that inflammatory processes might precede or be independent from amyloid deposition, suggesting that these markers constitute the earliest indicators of preclinical disease. Some studies demonstrate direct associations with tau pathology, cognitive performance and brain changes; others identified interaction effects, where the presence of inflammation in combination with amyloid and/or tau pathology influenced neurodegeneration.

It is unclear whether inflammatory markers are associated with particular clinico-pathological characteristics that may underlie heterogeneous outcomes within aging and preclinical cohorts; for example, individuals who subsequently develop prodromal and clinical dementia compared to those who do not. Nonetheless, there is some evidence that inflammatory markers may possess diagnostic or prognostic value for future AD symptomology. Additional studies focusing on impaired resolution of inflammation, especially on tau related neurofibrillary pathology are needed, as are studies that examine whether such responses are dose-dependent and relevant to AD in humans.

Large epidemiological studies of preclinical AD are notably absent. The use of animal models, while undoubtedly facilitate knowledge of the various molecular mechanisms of AD, may not be the optional paradigms to simulate the preclinical stages of the disease. While it appears that elevated levels of inflammation are associated with cognitive processing deficits and morphometric changes in "healthy" adults, there is a distinct lack of preclinical AD samples available to investigate similar relationships in these individuals. The range of inflammatory markers investigated in preclinical AD studies is narrow and it is not yet possible to infer which agents, acting alone or in combination, are relevant in the proposed inflammatory process, and if they may support or prevent AD development at different stages of disease. The majority of these studies are cross-sectional, limiting inferences regarding causality, and temporal relationships between inflammation, cognitive performance and neurodegeneration. Where longitudinal designs have been adopted, few studies have captured inflammatory measures serially, using only baseline data to predict future cognitive and brain changes at follow-up. Single clinical assessments may over- or under-estimate the level of inflammation chronicity for the individual at baseline and precludes investigations of the impact of changes in inflammation markers, or combinations thereof, on neurodegenerative and cognitive outcomes. Further clinical and imaging studies with longitudinal data and the ascertainment of inflammatory agents alongside neuropathological and cognitive markers earlier in the disease course and at predefined times throughout disease duration is needed to the determine the contribution of inflammation within the cascade of pathological and cognitive changes associated with AD.

Interest in inflammation and AD is building and there are numerous benefits of developing this area of research within preclinical AD. Delineating the role and timing of neuroinflammation in this population will help to reconcile conceptual debates surrounding AD aetiology. Relatedly, including inflammatory markers alongside established biomarkers in future research studies could improve diagnostic accuracy of participant samples and help stratify individuals according to greatest risk for cognitive impairment, leading to smaller and more cost-effective observational and clinical trials that promote earlier disease detection and targeted therapeutic intervention. At present, the immediate clinical application of these markers for diagnostic purposes remains elusive since research studies are only beginning to consider their use for extending current definitions of preclinical AD. Future work will be able to assess the impact of utilising inflammatory markers on diagnostic decision-making and patient management in clinical contexts.

References

1. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, et al. (2004) Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. Proc Natl Acad Sci U S A 101: 284-289.
2. Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, et al. (2013) Amyloid β deposition, neurodegeneration and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. Lancet Neurol 124: 357-367.
3. Ritchie K, Ritchie CW, Yaffe K, Skoog I, Scarmeas N (2015) Is late-onset Alzheimer's disease really a disease of midlife? Alzheimers Dement Transl Res Clin Intervent 12: 122-130.
4. Ritchie K, Carrière I, Berr C, Amieva H, Dartigues JF, et al. (2016) The clinical picture of Alzheimer's disease in the decade before diagnosis. J Clin Psychiatry 77: e305-e311.
5. Ritchie K, Ropacki M, Harrison J, Kaye J, Kramer J, et al. (2017) Recommended cognitive outcomes in preclinical Alzheimer's disease: Consensus statement from the European prevention of Alzheimer's dementia project. Alzheimers Dement 13: 186 -195.
6. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, et al. (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 73: 280-292.
7. Mortamais M, Ash JA, Harrison J, Kaye J, Kramer J, et al. (2017) Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility. Alzheimers Dement 13: 468-492.
8. Selkoe DJ, Hardy J (2016) The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 86: 595-608.
9. Strang F, Scheichl A, Chen YC, Wang X, Htun N-M, et al. (2012) Amyloid plaques dissociate pentameric to monomeric C-Reactive protein: A novel pathomechanism driving cortical inflammation in Alzheimer's disease? Brain Pathol 223: 337-346.
10. McGeer PL, McGeer EG (2013) The amyloid cascade-inflammatory hypothesis of Alzheimer disease: Implications for therapy. Acta Neuropathol 126: 479-497.
11. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, et al. (2015) Neuroinflammation in Alzheimer's disease. Lancet Neurol 14: 388-405.
12. Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, et al. (2010) A meta-analysis of cytokines in Alzheimer's disease. Biol Psychiatry 68: 930-941.
13. Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, et al. (2013) TREM2 variants in Alzheimer's disease. N Engl J Med 368: 117-127.
14. Bradshaw EM, Chibnik LB, Keenan BT, Ottoboni L, Raj T, et al. (2013) CD33 Alzheimer's disease locus: Altered monocyte function and amyloid biology. Nat Neurosci 16: 848-850.
15. Piirainen S, Youssef A, Song C, Kalueff AV, Landreth GE, et al. (2017) Psychological stress on neuroinflammation and cognitive dysfunctions in

Alzheimer's disease: The emerging role for microglia? Neurosci Biobehav Rev 77: 148-164.

16. Magalhães TNC, Weiler M, Teixeira CVL, Hayata T, Moraes AS, et al. (2017) Systemic inflammation and multimodal biomarkers in amnestic mild cognitive impairment and Alzheimer's disease. Mol Neurobiol.
17. Profenno LA, Porsteinsson AP, Faraone SV (2010) Meta-analysis of Alzheimer's disease risk with obesity, diabetes and related disorders. Biol Psychiatry 676: 505-512.
18. Zhang J, Chen C, Hua S, Liao H, Wang M, et al. (2017) An updated meta-analysis of cohort studies: Diabetes and risk of Alzheimer's disease. Diabetes Res Clin Pract 124: 41-47.
19. Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, et al. (2010) Cause-specific mortality in patients with severe psoriasis: A population-based cohort study in the U.K. Br J Dermatol 163: 586-592.
20. Wallin K, Solomon A, Kåreholt I, Tuomilehto J, Soininen H, et al. (2012) Midlife rheumatoid arthritis increases the risk of cognitive impairment two decades later: A population-based study. J Alzheimers Dis 31: 669-676.
21. Simvanandam TM, Thakur MK (2012) Traumatic brain injury: A risk factor for Alzheimer's disease. Neurosci Biobehav Rev 36: 1376-1381.
22. Breitner JCS, Gau BA, Welsh KA, Plassman BL, McDonald WM, et al. (1994) Inverse association of anti-inflammatory treatments and Alzheimer's disease: Initial results of a co-twin control study. Neurology 44: 227-232.
23. In t'Veld BA, Ruitenberg A, Hofman A, Launer LJ, van Duijn CM, et al. (2001) Nonsteroidal anti-inflammatory drugs and the risk of Alzheimer's disease. N Engl J Med 345: 1515-1521.
24. Wichmann MA, Cruickshanks KJ, Carlsson CM, Chappell R, Fischer ME, et al. (2015) NSAID use and incident cognitive impairment in a population-based cohort. Alzheimer Dis Assoc Disord 30: 105-112.
25. Breitner JCS, Haneuse SJPA, Walker R, Dublin S, Crane PK, et al. (2009) Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort. Neurology 72: 1899-1905.
26. Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, et al. (2009) Systemic inflammation and disease progression in Alzheimer disease. Neurology 73: 768-774.
27. Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, et al. (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 91: 119-128.
28. Jack CR, Bennett DA, Blennow K, Carrillo MC, Feldman HH, et al. (2016) A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 875: 539-547.
29. Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, et al. (2013) Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurol 122: 207-216.
30. Ferretti MT, Cuello AC (2011) Does a pro-Inflammatory process precede Alzheimer's disease and Mild Cognitive Impairment? Current Alzheimer Research 82: 164-174.
31. Frautschy SA, Yang F, Irrizarry M, Hyman B, Saido TC, et al. (1998) Microglial response to amyloid plaques in APPsw transgenic mice. Am J Pathol 1521: 307-317.
32. Stalder M, Phinney A, Probst A, Sommer B, Staufenbiel M, et al. (1999) Association of microglia with amyloid plaques in brains of APP23 transgenic mice. Am J Pathol 154: 1673-1684.
33. Spires-Jones TL, Meyer-Luehmann M, Osetek JD, Jones PB, Stern EA, et al. (2007) Impaired spine stability underlies plaque-related spine loss in an Alzheimer's disease mouse model. Am J Pathol 1714: 1304-1311.
34. Heneka MT, Sastre M, Dumitrescu-Ozimek L, Dewachter I, Walter J, et al. (2005) Focal glial activation coincides with increased BACE1 activation and precedes amyloid plaque deposition in APP[V717I] transgenic mice. J Neuroinflammation 2: 22.
35. Janelsins MC, Mastrangelo MA, Oddo S, LaFerla FM, Federoff HJ, et al. (2005) Early correlation of microglial activation with enhanced tumor necrosis factor-alpha and monocyte chemoattractant protein-1 expression specifically within the entorhinal cortex of triple transgenic Alzheimer's disease mice. J Neuroinflammation 2: 23.
36. Krstic D, Madhusudan A, Doehner J, Vogel P, Notter T, et al. (2012) Systemic immune challenges trigger and drive Alzheimer-like neuropathology in mice. J Neuroinflammation 9: 151.
37. Kalback W, Watson MD, Kokjohn TA, Kuo YM, Weiss N, et al. (2002) APP Transgenic mice Tg2576 accumulate Aß peptides that are distinct from the chemically modified and insoluble peptides deposited in Alzheimer's disease senile plaques. Biochemistry 413: 922-928.
38. Cuello AC (2017) Early and late CNS inflammation in Alzheimer's disease: Two extremes of a continuum? Trends Pharmacol Sci 38: 956-966.
39. Brosseron F, Krauthausen M, Kummer M, Heneka MT (2014) Body fluid cytokine levels in mild cognitive impairment and Alzheimer's disease: A comparative overview. Mol Neurobiol 502: 534-544.
40. Koyama A, O'Brien J, Weuve J, Blacker D, Metti AL, et al. (2013) The role of peripheral inflammatory markers in dementia and Alzheimer's disease: A meta-analysis. J Gerontol A Biol Sci Med Sci 684: 433-440.
41. Whittington RA, Planel E, Terrando N (2017) Impaired resolution of inflammation in Alzheimer's disease: A review. Front Immunol 8: 1464.
42. Franceschi C, Campisi J (2014) Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci 69: S4-S9.
43. Zhu M, Wang X, Hjorth E, Colas RA, Schroeder L, et al. (2016) Pro-resolving lipid mediators improve neuronal survival and increase Aβ42 phagocytosis. Mol Neurobiol 53: 2733-2749.
44. Barron M, Gartlon J, Dawson LA, Atkinson PJ, Pardon MC (2017) A state of delirium: Deciphering the effect of inflammation on tau pathology in Alzheimer's disease. Exp Gerontol 94: 103-107.
45. Álvarez-Rodríguez L, López-Hoyos M, Muñoz-Cacho P, Martínez-Taboada VM (2012) Aging is associated with circulating cytokine dysregulation. Cell Immunol 273: 124-132.
46. Antonell A, Mansilla A, Rami L, Lladó A, Iranzo A, et al. (2014) Cerebrospinal fluid level of YKL-40 protein in preclinical and prodromal Alzheimer's disease. J Alzheimers Dis 42: 901-908.
47. Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, et al. (2003) Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology 61: 76-80.
48. Miralbell J, Soriano JJ, Spulber G, López-Cancio E, Arenillas JF, et al. (2012) Structural brain changes and cognition in relation to markers of vascular dysfunction. Neurobiol Aging 33: 1003.e9-1003.e17.
49. Wersching H, Duning T, Lohmann H, Mohammadi S, Stehling C, et al. (2010) Serum C-reactive protein is linked to cerebral microstructural integrity and cognitive function. Neurology 74: 1022-1029.
50. Arfanakis K, Fleischman DA, Grisot G, Barth CM, Varentsova A, et al. (2013) Systemic inflammation in non-demented elderly human subjects: Brain microstructure and cognition. PLoS One 8: e73107.
51. Marsland AL, Gianaros PJ, Kuan DCH, Sheu LK, Krajina K, et al. (2015) Brain morphology links systemic inflammation to cognitive function in midlife adults. Brain Behav Immun 48: 195-204.
52. Walker KA, Hoogeveen RC, Folsom AR, Ballantyne CM, Knopman DS, et al. (2017) Midlife systemic inflammatory markers are associated with late-life brain volume. Neurology 89: 2262-2270.
53. Weuve J, Ridker PM, Cook NR, Buring JE, Grodstein F (2006) High-sensitivity C-reactive protein and cognitive function in older women. Epidemiology 172: 183-189.
54. Dik MG, Jonker C, Hack CE, Smit JH, Comijs HC, et al. (2005) Serum inflammatory proteins and cognitive decline in older persons. Neurology 64: 1371-1377.
55. Schmidt MF, Freeman KB, Windham BG, Griswold ME, Kullo IJ, et al. (2016) Associations between serum inflammatory markers and hippocampal volume in a community sample. J Am Geriatr Soc 64: 1823-1829.
56. Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C (2012) Circulating IL-6 and CRP are associated with MRI findings in the elderly: The 3C-Dijon study. Neurology 78: 720-727.
57. McCarrey AC, Pacheco J, Carlson OD, Egan JM, Thambisetty M, et al. (2014) Interleukin-6 is linked to longitudinal rates of cortical thinning in aging. Transl Neurosci 51: 1-7.

58. Taki Y, Thyreau B, Kinomura S, Sato K, Goto R, et al. (2013) Correlation between high-sensitivity C-reactive protein and brain gray matter volume in healthy elderly subjects. Hum Brain Mapp 34: 2418-2424.

59. Gu Y, Vorburger R, Scarmeas N, Luchsinger JA, Manly JJ, et al. (2017) Circulating inflammatory biomarkers in relation to brain structural measurements in a non-demented elderly population. Brain Behav Immun 65: 150-160.

60. Alcolea D, Martínez-Lage P, Sánchez-Juan P, Olazarán J, Antúnez C, et al. (2015) Amyloid precursor protein metabolism and inflammation markers in preclinical Alzheimer disease. Neurology 85: 626-633.

61. Craig-Schapiro R, Perrin RJ, Roe CM, Xiong C, Carter D, et al. (2010) YKL-40: A novel prognostic fluid biomarker for preclinical Alzheimer's disease. Biol Psychiatry 68: 903-912.

62. Melah KE, Lu SYF, Hoscheidt SM, Alexander AL, Adluru N, et al. (2016) CSF markers of Alzheimer's pathology and microglial activation are associated with altered white matter microstructure in asymptomatic adults at risk for Alzheimer's disease. J Alzheimers Dis 50: 873-886.

63. Popp J, Oikonomidi A, Tautvydaite D, Dayon L, Bacher M, et al. (2017) Markers of neuroinflammation associated with Alzheimer's disease pathology in older adults. Brain Behav Immun 62: 203-211.

64. Sala-Llonch R, Idland AV, Borza T, Watne LO, Wyller TB, et al. (2017) Inflammation, amyloid and atrophy in the aging brain: Relationships with longitudinal changes in cognition. J Alzheimers Dis 58: 829-840.

65. Alcolea D, Vilaplana E, Pegueroles J, Montal V, Sanchez-Juan P, et al. (2015) Relationship between cortical thickness and cerebrospinal fluid YKL-40 in predementia stages of Alzheimer's disease. Neurobiol Aging 36: 2018 -2023.

66. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL (1982) A new clinical scale for the staging of dementia. Br J Psychiatry 140: 566-572.

67. Craig-Schapiro R, Kuhn M, Xiong C, Pickering EH, Liu J, et al. (2011) Multiplexed immunoassay panel identifies novel CSF biomarkers for Alzheimer's disease diagnosis and prognosis. PLoS One 64: e18850.