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Peripheral Immune Function and Alzheimer's Disease: A Living Systematic Review and Critical Appraisal

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Abstract

Background—A growing body of literature examines the relationship between peripheral immune function and Alzheimer's Disease (AD) in human populations. Our living systematic review summarizes the characteristics and findings of these studies, appraises their quality, and formulates recommendations for future research.

Methods—We searched the electronic databases PubMed, PsycINFO, and Web of Science, and reviewed references of previous reviews and meta-analyses to identify human studies examining the relationship between any peripheral immune biomarkers and AD up to September 7th, 2023.

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Contributors

RCS, GAN, and AEA initiated the study. CL and CL were responsible for study design, data collection, analysis, and visualization. CL, RCS, GAN, and AEA interpreted the study findings. CL, RCS, and GAN wrote the first draft of the manuscript. AEA revised the manuscript. All authors have read, revised, and agreed to the published version of the manuscript.

Declaration of interests

We declare no competing interests.

We examined patterns of reported statistical associations (positive, negative, and null) between each biomarker and AD across studies. Evidence for each biomarker was categorized into four groups based on the proportion of studies reporting different associations: corroborating a positive association with AD, a negative association, a null association, and presenting contradictory findings. A modified Newcastle–Ottawa scale (NOS) was employed to assess the quality of the included studies.

Findings—In total, 286 studies were included in this review. The majority were cross-sectional (n=245, 85.7%) and hospital-based (n=248, 86.7%), examining relationships between 187 different peripheral immune biomarkers and AD. Cytokines were the most frequently studied group of peripheral immune biomarkers. Evidence supported a positive association with AD for six biomarkers, including IL-6, IL-1β, IFN-γ, ACT, IL-18, and IL-12, and a negative association for two biomarkers, including lymphocytes and IL-6R. Only a small proportion of included studies (n=22, 7.7%) were deemed to be of high quality based on quality assessment.

Interpretation—Existing research on peripheral immune function and AD exhibits substantial methodological variability and limitations, with a notable lack of longitudinal, population-based studies investigating a broad range of biomarkers with prospective AD outcomes. The extent and manner in which peripheral immune function can contribute to AD pathophysiology remain open questions. Given the biomarkers that we identified to be associated with AD, we posit that targeting peripheral immune dysregulation may present a promising intervention point to reduce the burden of AD.

Keywords

Peripheral immune function; Alzheimer’s Disease; systematic review; quality assessment

INTRODUCTION

Dementia is a growing global health crisis, with Alzheimer’s disease (AD) accounting for 60–70% of cases.[1,2] Peripheral immunosenescence is increasingly recognized as a risk factor for brain health and AD development.[3–6] Peripheral immunosenescence refers to a set of changes that occur in the peripheral immune system including increasing chronic-low inflammation (i.e., inflammaging), an inversion of the CD4+:CD8+ T cells ratios, a decrease in naïve T cells, and an accumulation of effector memory T cells with limited function. These changes are often observed as individuals age but can also be observed in response to a variety of social stressors.[7–10] It was previously thought that only immune dysfunction occurring in the central nervous system (CNS) was relevant to the etiology of AD.[11–18] This belief stemmed from the longstanding consideration of the peripheral and central immune systems being separated by the blood-brain barrier (BBB) and blood-cerebrospinal fluid (CSF) barrier, respectively. However, accumulating evidence suggests that peripheral immune function, defined as systemic immune signals originating outside the brain, also plays both direct and indirect roles in AD pathogenesis and progression.[19–22] For example, peripheral immune cells can reside at the boundaries of the brain and actively participate in brain homeostasis through immune surveillance; they can also enter the CNS especially when the BBB is perturbated or impaired—often related to pathogen exposure and other stressors.[23–34] These developments foster a growing awareness of viewing AD as a systemic

condition that involves dynamic and interactive processes in both central and peripheral immune systems (Figure 1).[19]

Several marked changes in peripheral immune function, occurring with aging, potentially contribute to the development of AD and are worth noting. In the innate immune system, decreased leukocyte production and function, reduced phagocytic capability of neutrophils, monocytes, and macrophages, a functional shift towards a proinflammatory phenotype in monocytes, and decreased cytotoxicity of natural killer cells are observed.[35] In the adaptive immune compartment, antigenic stimulation across the life course drives the expansion of memory and effector T cell subsets increasing the number of pathogen-specific, highly differentiated T cells, which also generate a heightened inflammatory response.[36,37] The thymus gland, key in the adaptive immune response, undergoes chronic involution after puberty, resulting in a continual decline in thymic output of naïve T cells with age.[38] These processes coalesce to form a phenotype of immunosenescence in older age and contribute to AD development.[24,39]

Despite the progress mentioned above, the importance of the peripheral immune-AD relationship remains underappreciated, and many important questions need to be answered.[19,24] For example, while some studies have reported evidence that patients with AD have signs of advanced peripheral immunosenescence compared to non-AD controls, it is unclear whether the advanced immunosenescence is a cause or consequence of AD, highlighting the need for longitudinal studies.[30,40] Furthermore, the lack of population-based studies makes it challenging to evaluate whether findings of clinically-based studies are generalizable to the broader population and to examine how major social determinants, including race/ethnicity, sex/gender, and socioeconomic status, may modify the peripheral immune-AD relationship.[41,42] Addressing these questions will contribute to understanding the development of AD, identifying diagnosis and treatment tools, and developing population-wide prevention strategies.

There are many reviews on peripheral immune function and AD. Some focus on animal and in vitro studies,[23,24,26,43–47] while others center on single or few peripheral immune biomarkers.[20,48–62] However, none have comprehensively documented and evaluated human studies on peripheral immune function and AD. To address these knowledge gaps, we conducted this review. Specifically, we summarize the characteristics and findings of human studies on peripheral immune biomarkers and AD and critically appraise these studies from the perspective of study designs and epidemiological principles. Furthermore, we have developed a publicly accessible online database, providing a living update of related studies to serve as a reference for researchers interested in the role of peripheral immune function in AD. The database can be accessed at the GitHub repository (https://github.com/Peripheral-immune-AD/Peripheral-immune-and-AD).

METHODS

A living systematic review (LSR) is an approach that aims to regularly update a review and incorporate new evidence as it becomes available.[63,64] This approach is particularly suitable for synthesizing literature related to the rapidly growing body of studies examining

the relationship between peripheral immune function and Alzheimer's Disease (AD) among human populations.

Accordingly, this review will undergo biannual updates to integrate emerging evidence.

The study protocol, registered on the Research Registry (**UIN reviewregistry1487**), is provided in Supplementary Text 1. The protocol aimed to synthesize human studies on peripheral immune function and Alzheimer's Disease and related dementias (ADRD), including both AD and non-AD dementia. However, given the substantial volume of eligible studies and the complexity of various dementia types, this review narrowed its focus primarily to AD, the most prevalent type of dementia. Studies concerning peripheral immune function and non-AD dementia will be synthesized in a separate review to delineate detailed findings. Therefore, the main outcome of interest in this review is AD. Studies on all-cause dementia are also included if the type of dementia was not specified because AD accounts for 60–70% of all dementia cases. The main exposure of interest is measurable indicators within the peripheral immune system that can provide information about immune function and inflammation. These include various direct and derived measures of cells, proteins, cytokines, and antibodies that play a role in immune responses. Reporting of this review followed the Preferred Reporting Items for Systematic Reviewers and Meta-analysis (PRISMA) guidelines (Supplementary Table 1). An institutional ethics review was not sought because the current review relied on the secondary use of reported data.

Search strategy and selection criteria

Our search strategy was designed to identify any studies relating peripheral immune function to AD. First, three electronic databases were searched, including PubMed, PsycINFO, and Web of Science. The following broad search terms were used: ((inflammation OR inflammatory OR interleukin OR lymphocyte OR acute phase protein OR cytokine OR immunity OR immune cell OR immune function OR immunosenescence OR immune dysregulation OR immune regulation) AND (cognition OR cognitive decline OR cognitive change OR cognitive aging OR dementia OR Alzheimer's disease OR Alzheimer's disease and related dementias OR ADRD)) AND human. The initial search was conducted in March 2018, and updated searches were performed in August 2019, September 2022, and September 2023. Second, 46 relevant reviews and/or meta-analyses were identified, and their reference lists and supplementary materials were screened for additional studies (Supplementary Table 2). Detailed search process and results can be found in Supplementary Text 2.

Eligibility criteria

Studies meeting the following criteria were included: (1) the study was an observational study based on human populations; (2) AD was the main outcome of interest; (3) peripheral immune function was the main or secondary risk factor of interest, which was measured by peripheral blood biomarkers participated in immune responses; (4) the study examined the relationship between peripheral immune biomarkers and AD; (5) the study was reported in English. Studies were excluded if: (1) the study was published as a conference abstract, commentary, protocol, or review article; (2) the study did not provide clear descriptions of

the study population, study design, and analytical method; (3) the study had a total sample size of fewer than 20 subjects; (4) the study reported stimulated levels of peripheral immune biomarkers in vitro. When several studies were based on the same or overlapping study participants and they studied the same peripheral immune biomarkers, the study that had the largest sample size will be used as a representative study. However, if these studies examined different peripheral immune biomarkers, each of them would be included as an independent study even though they used the same or overlapping study participants.

Screening process and data extraction

At least two reviewers independently screened the title and abstract of each study for full-text examination. Two reviewers further conducted the full-text examination to evaluate if the study met the eligibility criteria. Any disagreements among reviewers were resolved by reaching an agreement through group discussion. For articles meeting the eligibility criteria, the following information was extracted by a single reviewer and examined by another reviewer: (1) author and publication information (author names, publication year, and PMID if available); (2) study characteristics (study setting, follow-up time, total sample size, number of AD cases, AD diagnosis tool, control selection, assessment tool of peripheral immune biomarkers, covariate assessment, main analytical method); (3) study participants characteristics by comparison groups (age, sex, education, race/ethnicity, severity of AD); (4) study results (association estimates and measures of uncertainty if available).

Quality assessment

Following the method used in our previous studies, the Newcastle–Ottawa scale (NOS) was customized from the perspective of study designs and epidemiological principles to evaluate the quality of included studies (Supplementary Text 3).[65–67] Two reviewers appraised each study based on the NOS independently, and discrepancies were resolved through group discussion. The NOS had ten domains: sampling representativeness, sample size, follow-up, AD assessment, laboratory methods, biomarker assessment, comparison selection, statistical methods, confounding adjustment, and finding report. The quality of each domain was scored as ‘good’ (2), ‘fair’ (1), or ‘poor’ (0), and a total score was calculated for each study (range: 0–20). With this quality assessment tool, we aimed to identify studies with top total scores and examine whether any patterns of study quality by domains may exist. For ease of description, we further classified studies into three groups based on their total quality score. Cutoffs of classification were selected based on intervals of equal distance. A study with a total score of 14 and over was classified as of ‘high’ quality, a score of 7–13 was classified as of ‘medium’ quality, and a score of 0–6 was classified as of ‘low’ quality.

Synthesis of the evidence and data sharing

We summarized the characteristics of the included studies. We documented all peripheral immune biomarkers reported across studies. For each peripheral immune biomarker, we examined the pattern of reported findings by summarizing the number and proportion of studies reporting a positive, null, or negative association separately.

We selected the top 20 most examined peripheral immune biomarkers and classified the available evidence into the following four categories: **Category 1.** evidence corroborating a

positive association with AD: 25% or more of studies reported a positive association with AD and less than 10% of studies reported a negative association with AD; **Category 2.** evidence corroborating a negative association with AD: 25% or more of studies reported a negative association with AD and less than 10% of studies reported a positive association with AD; **Category 3.** little or no evidence of an association with AD: less than 25% of studies reported either a positive or negative association; **Category 4.** contradictory evidence of an association with AD: 25% or more of studies reported a positive association and more than 10% reported a negative association. We determined these cut-off points based on previous related reviews and meta-analyses, finding that a quarter and more of a body of research tends to be a strong driver of an association in meta-analyses.[20,50,53,54,56,68–71] We also classified the available evidence for other less-studied biomarkers. However, the results were less conclusive due to the limited number of studies for each. We deposited all data and code necessary to reproduce the findings of this study in the GitHub repository. The repository is publicly accessible and will be updated biannually together with this review.

RESULTS

The search of electronic databases and relevant reviews identified 15,670 records, and the removal of 7,984 duplicates yielded 7,686 unique records (Figure 2). After the screening of their titles and abstracts, 658 studies underwent full-text examination. In total, 286 studies examining the relationship between peripheral immune function and AD met eligibility criteria and were included in this living systematic review (LSR). Due to the large number of these studies, a full list of included studies with publication information was summarized in Supplementary Table 3.

Table 1 summarizes selected characteristics of the 286 included studies based on whether they had a follow-up of participants or not. Among them, 245 (85.7%) studies had no follow-up, and the remaining 41 (14.3%) studies did have a follow-up. The number of studies published in each decade increased from 8 studies in the 1980s to 117 studies in the 2010s, and there have been 49 studies published in the first few years of this decade. Studies were predominantly single-hospital (n=214, 74.8%) or multiple-hospital (n=34, 11.9%) studies. Over 90% of them were conducted in Europe, Asia, and North America. Most studies had a sample size of fewer than 100 participants (n=158, 55.2%) or between 100 and 999 participants (n=107, 37.4%). The most used AD diagnosis tools included NINCDS-ADRDA (n=207, 72.4%) and DSM-III/IV (n=89, 31.1%). Two hundred seventy-four studies specified the number of AD cases, while the remaining 12 studies included all-cause dementia without detailing the types or numbers of different dementia cases. Only 42 (14.7%) studies examined the severity of AD, and the evaluation criteria varied by study. Serum and/or plasma samples were both widely used, and 272 (95.1%) studies specified assays and procedures used to examine peripheral immune biomarkers. The three most widely reported sociodemographic characteristics included age, gender, and education. Most of these studies included participants aged 60 years and older, and only 36 (12.6%) studies included participants younger than 55 years old. Detailed characteristics of each study can be found in Supplementary Table 4.

In total, relationships between 187 different peripheral immune biomarkers and AD were examined across 286 studies. These biomarkers mainly included adaptive immune cells (e.g., T and B cells), cytokines, and complement proteins. Cytokines were the most frequently studied group of peripheral immune biomarkers in relation to AD, especially those involved in inflammatory responses. A list of full and abbreviated names of these biomarkers is presented in Supplementary Table 5. The number of peripheral immune biomarkers examined in each study varied, ranging from one to 38. Figure 3A shows that 154 (53.8%) out of 286 studies examined the relationship between one or two peripheral immune biomarkers and AD, 83 (29.0%) studies examined three to five biomarkers, and 49 (17.1%) studies examined more than five biomarkers.

Figure 3B shows the number of studies for the top 20 most examined peripheral immune biomarkers, ranging from around 10 to over 90 studies for each biomarker. It also shows the pattern of reported associations between each biomarker and AD. The proportion of positive, null, and negative associations varied substantially by biomarkers. Evidence corroborating a positive association with AD was observed for six biomarkers: IL-6, IL-1β, IFN-γ, ACT, IL-18, and IL-12 (Supplementary Table 6). For these six biomarkers, 25% or more of the included studies reported a positive association with AD and less than 10% of studies reported a negative association with AD. Evidence corroborating a negative association with AD was observed for lymphocyte and IL-6R, with 25% or more of included studies reporting a negative association with AD and less than 10% of studies reporting a positive association with AD. Reported results for these eight biomarkers corroborating either a positive or negative association with AD across included studies were summarized in Supplementary Table 7. Four biomarkers showed little or no evidence of an association with AD because less than 25% or more of studies reported either a positive or negative association for them. These included IL-8, IL-2, IL-7, and IL-15. Seven biomarkers, TNF-α, CRP, IL-10, MCP-1, IL-1α, IL-4, and TGF-β1, had contradictory evidence, which had over 25% of studies reporting a positive association and over 10% of studies reporting a negative association.

In addition, studies that reported a null association were less likely to provide effect estimates and measures of uncertainty compared to studies that reported statistically significant results of either a positive or negative association (Supplementary Table 8). For example, among 44 studies that reported either a significant positive or negative association between IL-6 and AD, 33 (75.0%) studies provided effect estimates and measures of uncertainty; in contrast, among 51 studies that reported a null association between IL-6 and AD, only 29 (56.9%) studies provided effect estimates and measures of uncertainty. Supplementary Figure 1 describes patterns of reported associations between AD and all 187 peripheral immune biomarkers as Figure 3B. A detailed summary of reported findings by peripheral immune biomarkers in each study can be found in the GitHub repository.

Figure 4A shows quality assessment results for each study by domain based on the customized NOS. It shows that only 22 (7.7%) out of 286 included studies received a total score of 14 and over, which were classified as high quality.[28,72–92] These 22 studies generally were scored as good in most domains. Figure 4B summarizes the number of studies by total quality score (score range: 0–20). The remainder of them

were either of medium quality (n=200, 69.9%) or low quality (n=64, 22.4%). Figure 4C further summarizes the proportion of studies scored as good (2), fair (1), and poor (0) for each domain. Most studies scored good or fair in four domains, including AD assessment, laboratory methods, statistical methods, and finding report. In contrast, over 55% to almost 90% of studies received a score of poor in the other six domains: sampling representativeness, sample size, follow-up, biomarker assessment, comparison selection, and confounding adjustment.

Discussion

Our living systematic review (LSR) provides, to date, the most comprehensive overview of human studies on the relationship between peripheral immune function and AD. As of September 2023, at least 286 human studies have examined the relationships between peripheral immune biomarkers and AD. These studies were predominantly single- or multiple-hospital-based, typically did not include participant follow-ups and investigated a limited number of biomarkers. They also had substantial methodological variability in other aspects, and only 7.7% of them were deemed of high quality based on the modified Newcastle–Ottawa scale. Nonetheless, we identified a select group of immune biomarkers that showed moderately strong evidence of an association with AD. This highlights the potential of targeting peripheral immune dysregulation to reduce the burden of AD.

We found that 187 peripheral immune biomarkers have been examined in relation to AD across the included studies. We identified the most frequently examined biomarkers and examined patterns of reported findings. While a majority of studies reported a null association, seven biomarkers showed a relatively consistent positive or negative association with AD, including IL-6, IL-1β, IFN-γ, ACT, IL-18, IL-12, lymphocyte, and IL-6R. These biomarkers represent promising targets for future research. Multiple previous systematic reviews and meta-analyses have claimed a significant relationship between many of the biomarkers reviewed here and AD.[20,49,50,52–54,56,68–71] However, there are also some discrepancies comparing our findings to previous reviews. For example, we found only 22.6% of studies on CRP showed a positive association with AD. In contrast, among studies included in previous meta-analyses, the proportion of studies reporting a positive association between CRP and AD is higher, ranging from 25% to 50%.[20,54,56,60,69,93]

The reason for our contrasting findings may be related to methodological differences and the comprehensiveness of our review compared to earlier systematic reviews and meta-analyses.[20,50,53,54,56,58–62,68–71] First, it may be that previous meta-analyses failed to conduct a comprehensive screening of the literature, especially those studies that reported a null association. For example, the four previous systematic reviews and meta-analyses that focused specifically on CRP and AD included only 10 or fewer studies.[20,54,56,69] However, we identified 62 original studies that examined the relationship between CRP and AD. Using the GitHub repository we created, many more studies that were overlooked by previous meta-analyses can be identified for CRP and other peripheral immune biomarkers. Second, most previous meta-analyses did not evaluate biases associated with the studies and data sources when generating summary estimates.[20,50,53,54,56,68–71] We found that studies reporting a null association between peripheral immune biomarkers and AD were

much less likely to provide effect estimates and/or measures of uncertainty than studies reporting a statistically significant association (Supplementary Table 8). This latter concern was observed not only for CRP but also for other peripheral immune biomarkers. Therefore, a large proportion of studies reporting a null association were not included in prior meta-analyses. Similar to our approach, future reviews should include a more comprehensive sampling of the literature, as opposed to focusing only on meta-analytical eligible studies with published effect estimates.

In the quality assessment of studies included in this review, we determined that less than 5% were of high quality. This demonstrates the urgent need to improve the quality of studies investigating the peripheral immune-AD relationship. One of the key reasons that most included studies were of medium or low quality is that they were predominantly based on small clinical samples that did not follow participants over time. While small clinical samples are useful to establish preliminary evidence of an association, they lack population representativeness and statistical power to make broader conclusions about the hypothesized relationships. Furthermore, cross-sectional studies (i.e. those that lack follow-up) cannot establish the temporality required to infer any causal relationship.

Across the ten domains of quality assessment, we identified six that are most in need of improvement: sampling representativeness, sample size, follow-up, biomarker assessment, comparison selection, and confounding adjustment. These domains and recommendations to address these methodological problems are specified in Table 2. First, it is important to recruit a study sample that is representative of the broader target population (i.e., the researcher's target population, whatever that might be based on the research question), follow these recruited participants over time, and collect data on a broad range of peripheral immune biomarkers. Additionally, recruiting participants in early or mid-adulthood and tracking them longitudinally is essential. This approach will illuminate the timing of changes in these biomarkers and how they contribute to AD development. These design improvements will help answer many important research questions and establish the temporal sequence of the exposure-outcome relationship. For example, it remains unclear to what extent peripheral immunosenescence reflects normal aging or progression of AD. Ongoing studies in the U.S., such as the Health and Retirement Study (HRS) and the National Longitudinal Study of Adolescent to Adult Health (AddHealth), are particularly suited for this exploration. They possess the longitudinal framework to study dementia risk and a repository of biospecimens for testing multiple peripheral immune biomarkers.[9,94,95] There are myriad additional research questions that could be explored and answered once the research community embraces these opportunities for the improvement of data sources in this area.

In contrast, small clinical samples often hinder the interpretation of study findings, the generalizability of results to the target population, and the transportability of the results to other populations. For example, small clinically-based samples often differ from the broader population on several sociodemographic characteristics including age, sex, racial and ethnic makeup, and socioeconomic status.[96,97] Differences in the relative proportions of these groups within the sample and target population can lead to estimates that are not true to the target population, particularly in the case where these sociodemographic characteristics may

be modifiers of the exposure-outcome relationship in question. Designs of small clinical studies also made it challenging to have appropriate comparison selections and confounding adjustments.

Second, most of the included studies predominantly focused on a few inflammatory cytokines widely examined in social science research. It is important to look beyond these few biomarkers of inflammatory immune function, and we can do so by including comprehensive assays for other biomarkers of the peripheral immune compartment, such as T cell surface markers, in large, population-based studies. In the analysis stage, studies of the etiology of AD need to incorporate a more comprehensive mechanistic understanding of peripheral immune function. Immune dynamics are complex and our understanding of them is ever in flux. For example, while previous studies typically interpreted IL-6 and CRP as inflammatory biomarkers, this is not always the truth because they both can also be elevated in the absence of a wider inflammatory response, suggesting the complex role that these biomarkers play in a range of biological processes and different chronic conditions.[57,98] Therefore, one or two biomarkers cannot sufficiently represent the dynamic nature of immune function. Indeed, peripheral immune function might best be captured by employing a systems-wide approach.

Furthermore, the majority of the existing literature focuses on biomarkers of innate immunity. However, the adaptive system, particularly the T cell compartment, undergoes critical changes as individuals age and in response to a number of social, environmental, and biological stressors.[8] Antigenic stimulation across the life course drives the expansion of memory and effector T cell subsets, increasing the number of pathogen-specific, highly differentiated T cells which then generate a greater inflammatory response.[36,37] Studies comparing the immune profile of individuals with AD to those of healthy controls have found evidence of advanced immunosenescence, particularly in the adaptive immune compartment, in the blood of individuals with AD, specifically decreases in naïve T cells and increases in memory T cells.[30,40] This suggests that changes in the adaptive peripheral immune compartment may be critical biological intermediaries in the etiology of AD. As such, with the increasing ease of measuring these biomarkers, future studies should endeavor to include measures related to the adaptive immune system as well as the innate.

Additionally, while this review does not focus on viral pathogens, their potential role in the etiology of AD warrants further investigation. This is because multiple viral pathogens can burden the immune system and contribute to AD development. For example, emerging studies examining immune response to viral infections offer compelling evidence suggestive of a role of latent viral infections including CMV[99] and HSV-1[100–102] in AD, though a 2021 paper found no relationship between several latent infections and all-cause dementia incidence.[88] A more recent extensive human study revealed a significant and meaningful association between the Epstein-Barr Virus (EBV) and Multiple Sclerosis (MS).[103] This additional evidence highlights that the peripheral immune system and infections can have profound downstream clinical consequences on the central nervous system. Future studies should examine both the impact of having a latent viral infection and individuals' immunological responses to such infections.

The strengths of our LSR are the comprehensive coverage of the body of existing studies, the careful synthesis of their reported findings and identification of related patterns, and the systematic evaluation of their study quality. Our publicly accessible database on GitHub will serve as a reference for clinicians and medical researchers who are interested in studying the peripheral immune-AD relationship. We also plan to update this LSR and related data online biannually as new information becomes available and expand our databases to include different types of non-AD dementias.

However, our study does have several limitations warranting careful consideration. First, we did not conduct any meta-analyses to produce summary estimates of the relationships between specific peripheral immune biomarkers and AD. We are exploring ways to quantify reported findings of included studies and address two main problems that were overlooked or poorly addressed in previous meta-analyses: selective reporting of findings and large heterogeneity across studies on peripheral immune function and AD. Second, our review included studies on both AD and all-cause dementia. Out of 286 studies, 12 reported findings on all-cause dementia without specifying the type, leading to potential misclassification of the outcome of interest. However, excluding these 12 studies would not alter our study's main findings. Third, we focused on patterns of reported associations between peripheral immune biomarkers and AD across studies without considering their overall quality. Ideally, evaluations of reported findings across studies should weigh high-quality studies more than medium- and low-quality ones. However, due to the small number of high-quality studies, we observed no specific patterns when we stratified our analyses. We intend to update our analysis with emerging high-quality studies in the future. Fourth, our LSR included only studies published in English, and we identified 10 studies in other languages. Given the limited number of studies in other languages, we do not anticipate that including them would alter our main findings. We plan to incorporate these studies in future biannual updates.

In conclusion, we have identified the most extensively examined peripheral immune biomarkers in relation to AD. We found relatively consistent evidence of an association with AD for eight biomarkers: IL-6, IL-1β, IFN-γ, ACT, IL-18, IL-12, lymphocyte, and IL-6R. This suggests that these may be integral biomarkers associated with the development or pathology of AD. However, other biomarkers demonstrated less consistent associations with AD and even yielded contradictory evidence in the existing literature, suggesting that these biomarkers may not play a significant role in AD risk. Our review also highlights key methodological limitations in existing studies, the majority of which are clinical studies featuring small sample sizes and lacking longitudinal follow-up of participants. This work is timely given the rapidly growing interest in the peripheral immune system as a target for AD therapeutics. A deeper understanding of the causal roles that these consistently identified peripheral immune biomarkers have with AD may pave the way for the development of new diagnostic tools and medications for AD and other related neurogenerative diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing

The data used in this study are all presented in the main tables or supplementary materials. Additional data and code to generate findings reported in this study are available from the GitHub repository (https://github.com/Peripheral-immune-AD/Peripheral-immune-and-AD).

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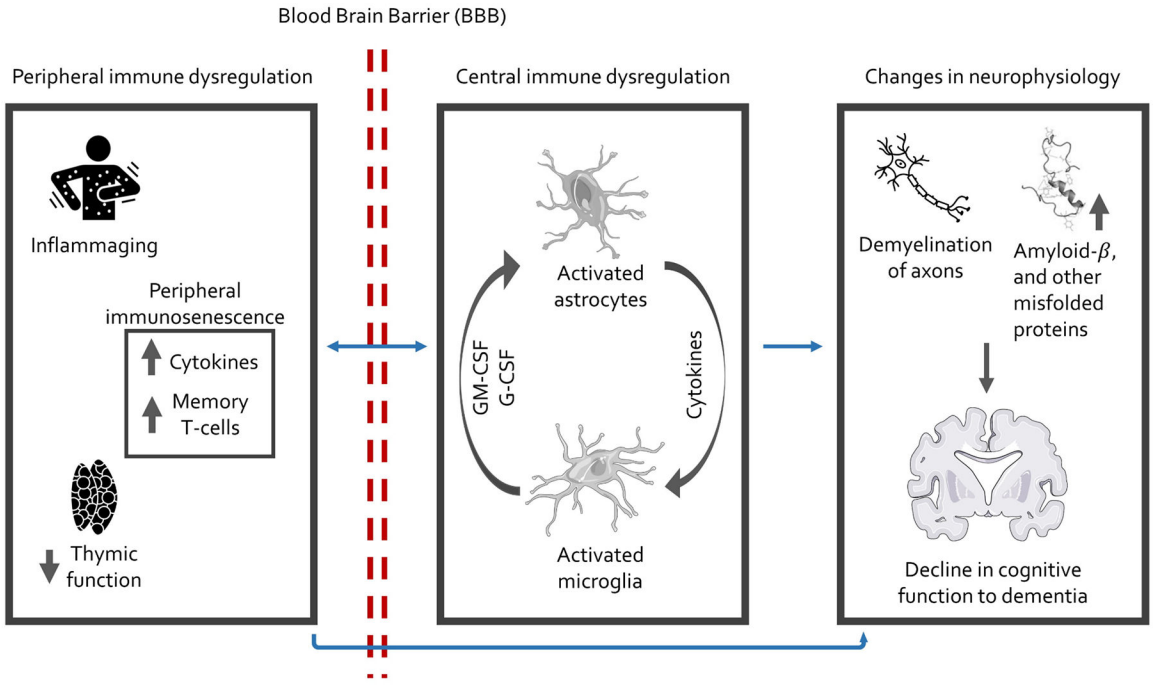

Figure 1. Theoretical mechanistic framework depicting the hypothesized relationship between peripheral and central immune dysregulation and neurophysiology

Inflammaging refers to the changes that take place in the innate immune system, distinct from the adaptive immune system, due to the aging process. This typically manifests as a rise in the levels of circulating pro-inflammatory cytokines as individuals age.

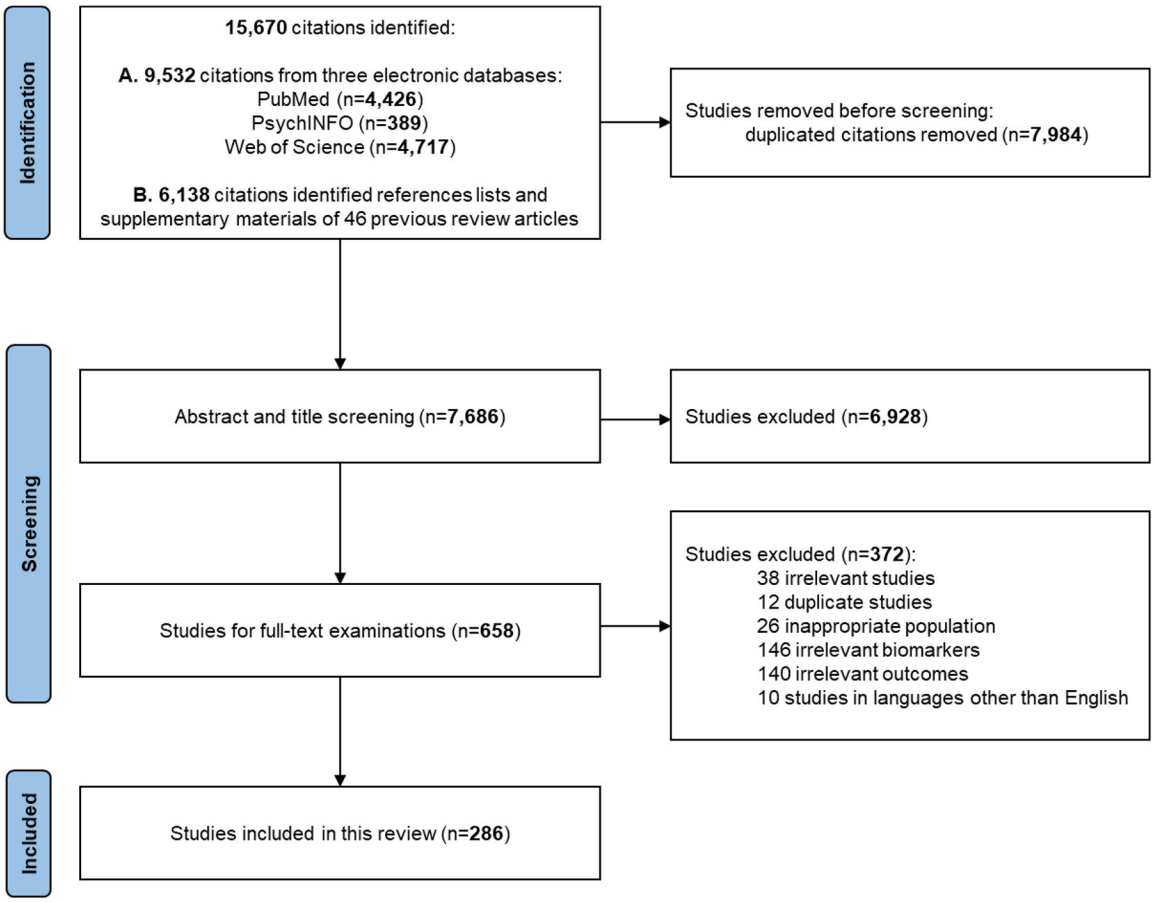

Figure 2.
Study selection

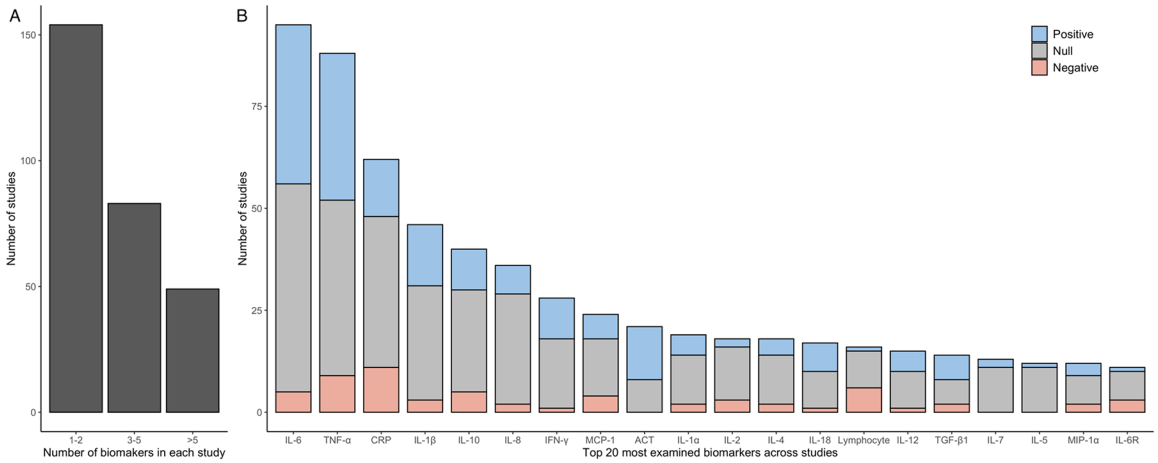

Figure 3. Summary of reported findings across included studies

Panel A displays the number of studies that examined between one and two, three and five, or more than five peripheral immune biomarkers, underscoring that most existing studies have only investigated a limited number of such biomarkers. Panel B depicts the number of studies and their reported associations for the top 20 most frequently examined peripheral immune biomarkers. Different colors were used for studies based on their reported statistical associations with AD. Evidence supports either a positive or a negative association with AD for eight of these biomarkers, including IL-6, IL-1β, IFN-γ, ACT, IL-18, IL-12, lymphocyte, and IL-6R.

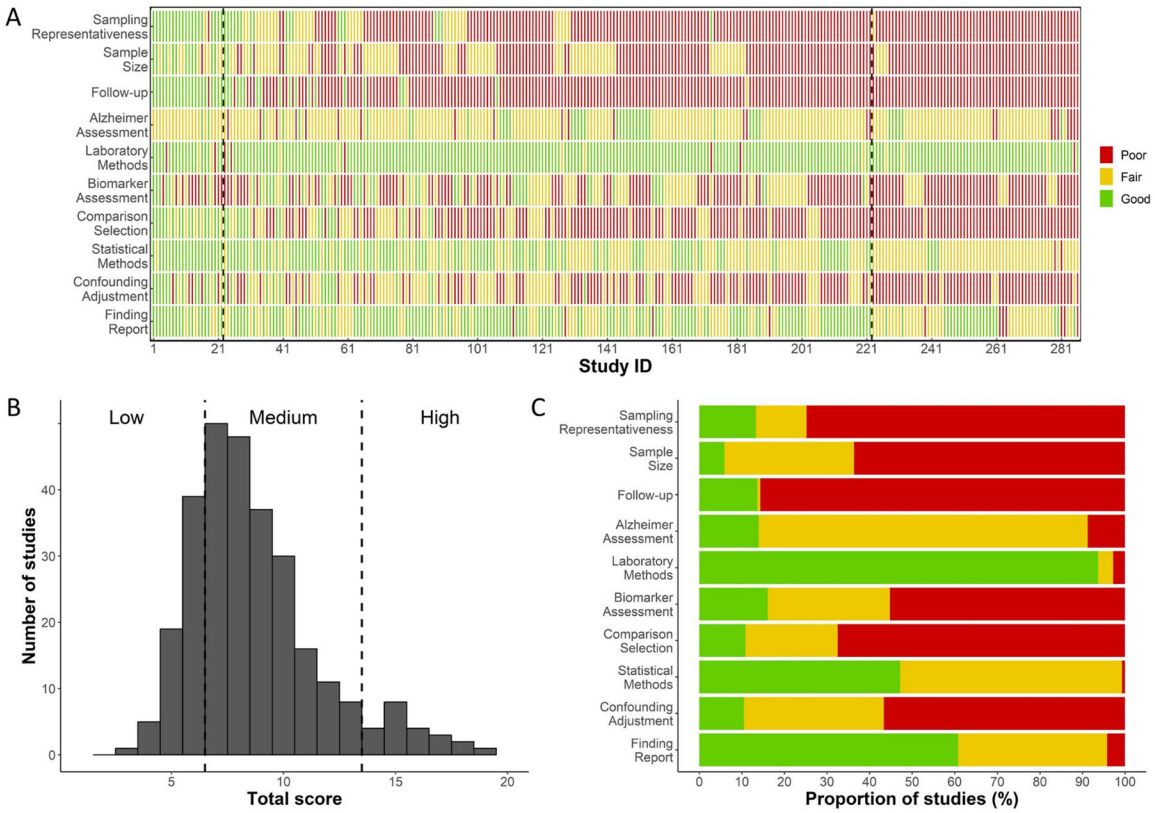

Figure 4. Quality assessment of included studies on peripheral immunity and AD

Panel A presents the detailed quality assessment results for all included studies. Studies are arranged based on their total quality assessment score, following the order documented in Supplementary Tables 3 and 4. Dashed vertical lines demarcate studies of low, medium, and high quality. This panel illustrates clusters of studies that have been scored as good, fair, or poor across different quality assessment domains. Panel B showcases the number of studies by their total quality assessment score, emphasizing the limited number of high-quality studies (n=22, 7.7%). Panel C outlines the proportion of studies that received scores of good, fair, or poor in each domain. Notably, sampling representativeness and follow-up are the two domains where the majority of studies received a score of poor.

Table 1.

Selected characteristics of included studies

	No. of studies by study designs		
	All	**Without follow-up**	**With follow-up**
N	286	245	41
Peripheral immune biomarkers as primary exposure of interest, n (%)			
Yes	258 (90.2)	224 (91.4)	34 (82.9)
No	28 (9.8)	21 (8.6)	7 (17.1)
Publication period, n (%)			
1980s and before	8 (2.8)	8 (3.3)	0 (0.0)
1990–1999	31 (10.8)	31 (12.7)	0 (0.0)
2000–2009	81 (28.3)	72 (29.4)	9 (22.0)
2010–2019	117 (40.9)	102 (41.6)	15 (36.6)
2020 and after	49 (17.1)	32 (13.1)	17 (41.5)
Sampling representativeness, n (%)			
Single-hospital	214 (74.8)	206 (84.1)	8 (19.5)
Multi-hospital	34 (11.9)	28 (11.4)	6 (14.6)
Regional	33 (11.5)	8 (3.3)	25 (61.0)
National	5 (1.7)	3 (1.2)	2 (4.9)
Study population by region, n (%)			
Asia	53 (18.5)	47 (19.2)	6 (14.6)
Europe	152 (53.1)	135 (55.1)	17 (41.5)
North America	54 (18.9)	38 (15.5)	16 (39.0)
Others *	27 (9.4)	25 (10.2)	2 (4.9)
Total sample size, n (%)			
20–99	158 (55.2)	152 (62.0)	6 (14.6)
100–999	107 (37.4)	90 (36.7)	17 (41.5)
1000 and over	21 (7.3)	3 (1.2)	18 (43.9)
AD assessment # **, n (%)**			
NINCDS-ADRDA	207 (72.4)	186 (75.9)	21 (51.2)
DSM-III or IV	89 (31.1)	76 (31.0)	13 (31.7)
ICD-9 or 10	11 (3.8)	3 (1.2)	8 (19.5)
Others	25 (8.7)	21 (8.6)	4 (9.8)
Not reported	25 (8.7)	21 (8.6)	4 (9.8)
AD severity examined, n (%)			
Yes	42 (14.7)	40 (16.3)	2 (4.9)

	No. of studies by study designs		
	All	**Without follow-up**	**With follow-up**
No	244 (85.3)	205 (83.7)	39 (95.1)
Biomarker sample source, n (%)			
Serum	121 (42.3)	108 (44.1)	13 (31.7)
Plasma	113 (39.5)	101 (41.2)	12 (29.3)
Serum and plasma	46 (16.1)	32 (13.1)	14 (34.1)
Not reported	6 (2.1)	4 (1.6)	2 (4.9)
Assay type reported, n (%)			
Yes	272 (95.1)	238 (97.1)	34 (82.9)
No	14 (4.9)	7 (2.9)	7 (17.1)
Mean age of AD cases, n (%)			
Middle-aged (<65 years)	12 (4.2)	10 (4.1)	2 (4.9)
Youngest-old (65–74 years)	112 (39.2)	103 (42.0)	9 (22.0)
Middle-old (75–84 years)	117 (40.9)	106 (43.3)	11 (26.8)
Oldest-old (85 years)	2 (0.7)	2 (0.8)	0 (0.0)
Not reported	43 (15.0)	24 (9.8)	19 (46.3)
Other sociodemographic characteristics examined, n (%)			
Gender	236 (82.5)	205 (83.7)	31 (75.6)
Education	93 (32.5)	68 (27.8)	25 (61.0)
Race/ethnicity	31 (10.8)	22 (9.0)	9 (22.0)
None reported	39 (13.6)	35 (14.3)	4 (9.8)

[*] Others include Africa, Australia, and South America

[#] Some studies used more than one AD assessment tool

Table 2.

Key domains for improvement and recommendations for future research

Quality assessment domain	Recommendation for future research	Rationale
Sampling representativeness	Conduct systematic sampling resulting in a study sample that is representative of a well-defined population	To be able to generalize results to the population and make inferences that will be borne out in real-world scenarios
Sample size	Prioritize larger study samples	To reduce random error in study results and to ensure representation of the wide range of biomarker levels in the population; to provide statistical power for investigation of biological and social interactions and effect modification
Follow-up	Invest in longitudinal studies that allow for investigation of trends in exposures and outcomes over time; invest in studies that enroll younger participants, thus allowing researchers to capture the onset of disease	Cross-sectional studies limit our ability to understand causal relationships and short-term or later-in-life cohorts are limited in the ability to detect the onset of dementia
Biomarker assessment	Employ a systems-wide approach to biomarker assessment and analysis; increase the number of biomarkers measured	The immune system is complex, and no single biomarker of immunity captures the dynamic processes underlying immune aging
Confounding adjustment	Craft a precise research question and select the appropriate covariate adjustment set based on a strong theoretical understanding of how the variables may relate to one another	Controlling for potential colliders and/or mediators can generate biased results