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White matter integrity changes in mild cognitive impairment associated with Aspirin use

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Abstract

Objectives: Alzheimer's disease (AD) represents a significant public health challenge, particularly as its prevalence is projected to rise sharply. Aspirin, known for its anti-inflammatory and antiplatelet properties, has been hypothesized to affect AD progression, although findings from observational studies and clinical trials remain inconsistent.

Methods: This study utilized data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to investigate the potential association between aspirin use and white matter (WM) microstructural changes in a cohort of 148 mild cognitive impairment (MCI) subjects. Diffusion tensor imaging (DTI) was employed to assess WM integrity, with fractional anisotropy (FA) and diffusivity metrics serving as primary outcomes. Statistical analyses were conducted using ANCOVA, adjusting for age, sex, APOE ε4 genotype, and MMSE score.

Results: Aspirin users exhibited significantly higher FA values in the anterior corona radiata and left external capsule, alongside lower axial and radial diffusivity values in the right cingulum, indicating better-preserved WM microstructure compared to non-users.

Conclusion: These findings suggest that aspirin may confer neuroprotective effects on WM in early AD, potentially delaying cognitive decline. Further research is warranted to confirm these results and explore the underlying mechanisms. Aspirin is widely prescribed to millions of adults, yet its impact on WM regions in the brain remains largely unclear. Further research is necessary to replicate these findings and to assess whether the effects of aspirin on WM structure could contribute to delaying or preventing cognitive decline.

Keywords: Alzheimer's disease, Aspirin, DTI, white matter

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Introduction

In 2021, an estimated 6.2 million Americans aged 65 and older were affected by Alzheimer's disease (AD), contributing to $355 billion in total healthcare expenditures for individuals with dementia, as reported by the Alzheimer's Association. Projections suggest that by 2060, AD will impact 13.8 million Americans, underscoring its status as a significant public health

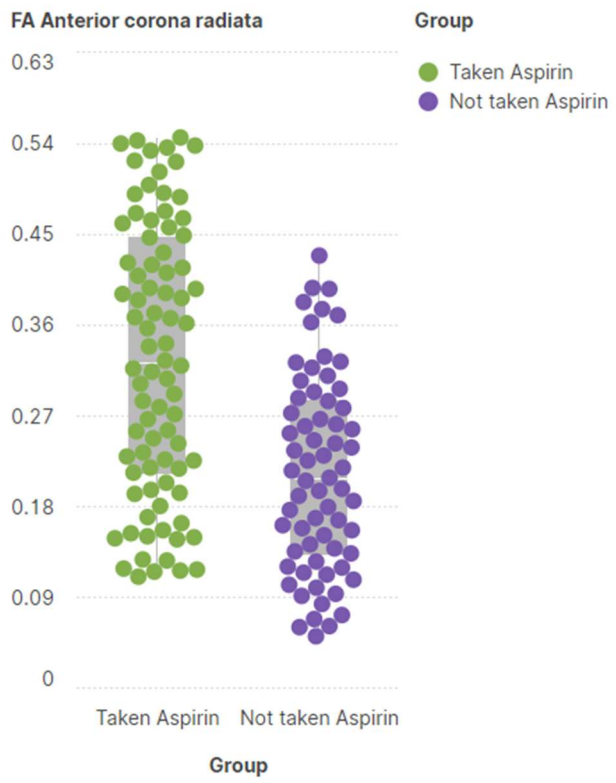

Figure1. Box plot of FA values

challenge in the United States (1, 2). In June 2021, the U.S. Food and Drug Administration (FDA) approved aducanumab, a monoclonal antibody, marking it as the first disease-modifying treatment for AD (3). While aducanumab has demonstrated efficacy in reducing amyloid plaques (4), there remains considerable debate regarding whether amyloid clearance effectively mitigates cognitive and functional decline in patients (5). In light of these uncertainties, focusing on modifiable risk factors presents a promising approach to AD prevention. Increasing evidence suggests that neuroinflammation and blood clot formation are critical contributors to AD progression (6). Aspirin, or acetylsalicylic acid, is a widely utilized drug with anti-inflammatory and antiplatelet properties, making it a potential candidate for addressing these aspects of AD pathology (7).

The potential association between aspirin use and a reduced risk of AD may be attributed to its anti-inflammatory and cardioprotective effects (http://www.alzdiscovery.org). However, findings from observational studies and clinical trials have been inconsistent and, at times, contradictory. Etminan et al. (8), in a meta-analysis of three case-control and five cohort studies, found no significant association between aspirin use and the risk of developing AD. Conversely, Nilsson et al. (9), in a cross-sectional analysis, reported that high-dose aspirin significantly reduced the risk of AD in individuals aged 80 years and older. Similarly, Szekely et al. (10) combined data from six prospective studies and observed a reduced risk of AD among aspirin users. Subsequent large-scale prospective studies, however, have yielded mixed results, with reports indicating no effect (11, 12), an increased risk (13, 14), or a decreased risk (15, 16) of aspirin on AD development. The ASPREE (ASPirin in Reducing Events in the Elderly) clinical trial (17) found that low-dose aspirin was not associated with a reduced risk of developing AD in healthy elderly individuals. A recent observational study suggested that long-term low-dose aspirin use may slow the progression of AD in patients with coronary heart disease (CHD) but not in other populations. Additionally, a retrospective cohort study indicated that aspirin use may help prevent AD in patients with ischemic stroke (17). These divergent findings underscore the inherent limitations of observational studies, the heterogeneity of AD, and the possibility that aspirin may be associated with a decreased risk of AD in specific subpopulations that are not adequately represented in existing clinical trials.

Diffusion tensor imaging (DTI) is a widely utilized in vivo neuroimaging technique for investigating white matter (WM) microstructure (18). By quantifying the diffusion of water molecules within tissues, DTI offers valuable insights into changes in WM integrity, such as axonal and myelin damage. In this study, we aimed to investigate the potential association between Aspirin use and WM microstructural changes quantified by DTI in a cohort of mild cognitive impairment (MCI) subjects.

Materials and Methods

Data Acquisition

Data were sourced from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Established in 2003, the ADNI is a public–private partnership led by Principal Investigator Michael W. Weiner, MD. The primary objective of ADNI is to evaluate whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can effectively monitor the progression of MCI and early AD.

For this study, participants from the Alzheimer's Disease Neuroimaging Initiative phases ADNI2, ADNI3, and ADNIGO, who had baseline DTI measurements along with available demographic data, were initially selected. Due to the low number of cases, individuals with subjective memory concerns (SMC) were excluded. The final cohort included 148 MCI participants. All MCI participants were diagnosed with amnestic MCI based on the following criteria: a Mini-Mental State Examination (MMSE) score between 24 and 30, the presence of a memory complaint, objective memory impairment determined by education-adjusted scores on the Wechsler Memory Scale Logical Memory II, a Clinical Dementia Rating (CDR) of 0.5, no significant deficits in other cognitive domains, preservation of activities of daily living, and the absence of dementia.

Data regarding statin use were extracted from the ADNI concurrent medication file, which documents the longitudinal medication usage of participants. Individuals who had used Aspirin for a minimum of three years were aspirin users. The

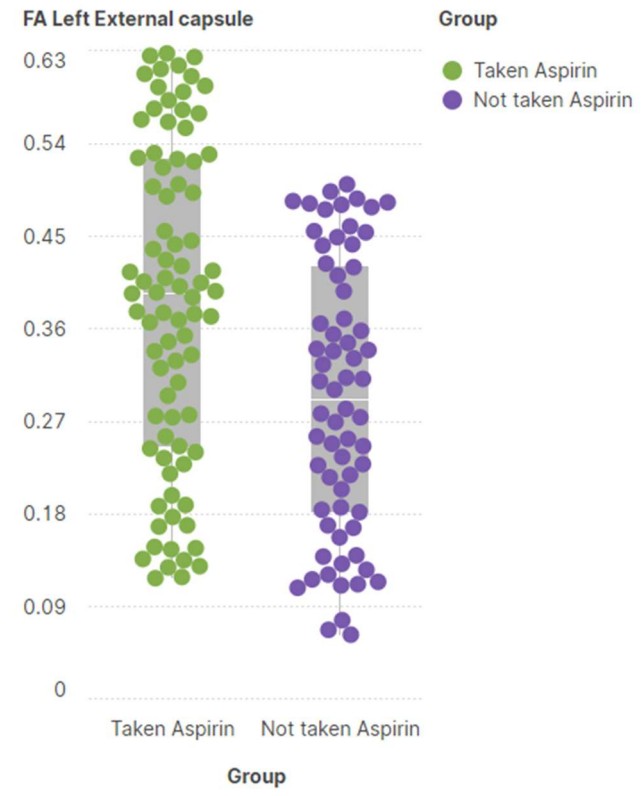

Figure2. Box plot of FA values

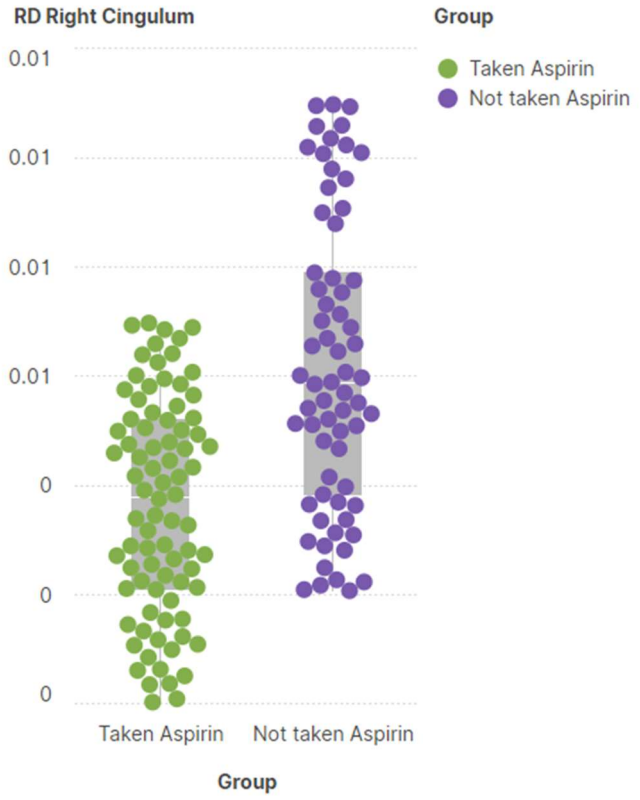

Figure3. Box plot of RD values

duration of statin use was calculated by determining the interval between the start date of aspirin therapy and the date of the baseline visit.

DTI Processing and Image Analysis

The analysis of DTI regions of interest (ROI) was conducted using data from the ADNI cohort. DTI scans were standardized using the Montreal Neurological Institute and Hospital (MNI) nu_correct tool (www.bic.mni.mcgill.ca/software/). Non-brain tissues were excluded using the Brain Extraction Tool (BET) from FSL. The T1-weighted images were aligned to a modified version of the Colin27 brain template using FSL's FLIRT [18]. The Colin27 brain was zero-padded to create a cubic isotropic image size (220 x 220 x 220 mm^3), which was then down-sampled to 110 x 110 x 110 mm^3 to match the resolution of the diffusion-weighted imaging (DWI). A single diffusion tensor was modeled at each voxel within the brain, generating scalar anisotropy and diffusivity maps from the diffusion tensor eigenvalues (λ1, λ2, λ3). Fractional anisotropy (FA), representing the directional dependence of water diffusion, and mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AxD), reflecting the extent of diffusion, were computed. Decreased FA and increased RD, AxD, and MD values suggest demyelination and white matter degeneration.

A shared information-based elastic registration algorithm, as previously described, was utilized to align the FA images from the Johns Hopkins University (JHU) DTI atlas to each participant's brain. Nearest-neighbor interpolation was employed to apply deformation to the stereotaxic JHU "Eve" white matter atlas labels (http://cmrm.med.jhmi.edu/cmrm/atlas/human_data/file/AtlasExplanation2.htm), thereby ensuring accurate placement of atlas ROIs within the same coordinate space as the DTI maps. Subsequently, average FA and MD values were computed within the boundaries of each ROI mask for each participant.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 16 (IBM Corp., Armonk, NY). Comparisons of clinical and demographic variables between groups stratified by aspirin exposure were conducted using the t-test for continuous variables and the chi-square test for categorical variables. Neuroimaging variables were log-transformed to ensure they met the criteria for normal distribution prior to analysis. The relationship between aspirin exposure and neuroimaging parameters was assessed using an analysis of covariance (ANCOVA) model, adjusted for age, sex, APOE ε4 genotype, and Mini-Mental State Examination (MMSE) score. To control for type I errors resulting from multiple comparisons, the Benjamini-Hochberg correction was applied.

Results

Patient demographic

This study comprised 148 MCI participants with a mean age of 75.2 (±7.6) years, of whom 82 were identified as aspirin users. There were no significant differences in clinical or

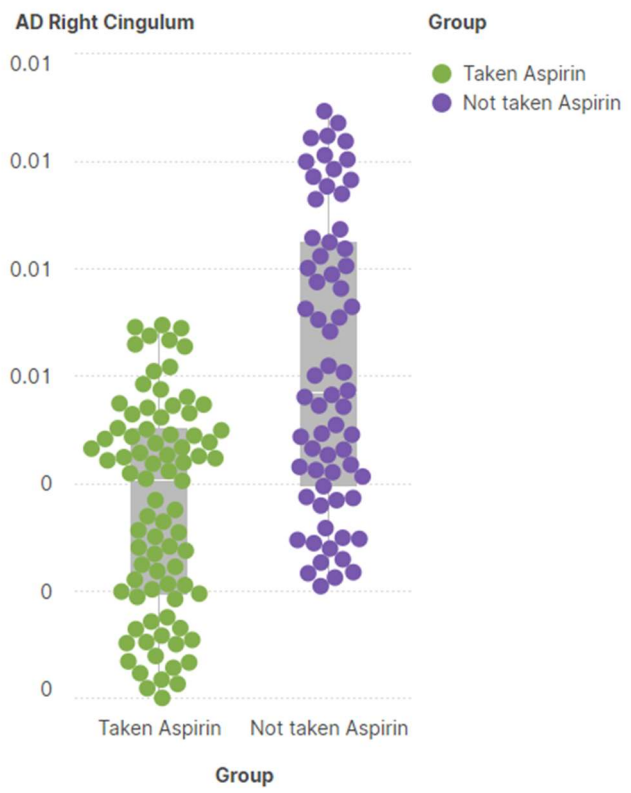

Figure4. Box plot of AD values

demographic characteristics between aspirin users and non-users.

A univariate linear model was utilized to compare hippocampal and cortical volumes between aspirin users and non-users, adjusting for age, sex, and APOE ε4 genotype. The results from the univariate model revealed that aspirin users had significantly higher FA values in the anterior corona radiata ($p < 0.001$) (Figure 1) and the left external capsule ($p = 0.003$) (Figure 2). Moreover, the AD and RD values of the right cingulum were significantly lower in aspirin users compared to non-users ($p < 0.001$)(Figures 3 and 4).

Discussion

Although the precise etiology of AD remains largely undetermined, the "amyloid hypothesis" posits that impaired clearance of amyloid-beta protein plaques plays a key role in AD pathogenesis (19). Consequently, enhancing the brain's cellular pathways responsible for waste disposal may represent a promising approach to slowing or delaying the progression of AD. Transcription factor EB (TFEB) is known to regulate the expression of the brain's debris-clearing mechanisms. A previous study demonstrated that aspirin use upregulated TFEB, increased lysosome production, and reduced amyloid plaque pathology in AD model mice (20).

Epidemiological and clinical trial studies have produced inconsistent and often contradictory findings regarding the relationship between aspirin use and AD risk. These observational studies are vulnerable to residual confounding and bias. Moreover, the potential protective effects of aspirin on AD may be confined to specific subpopulations. For instance, previous observational studies have suggested that aspirin is associated with reduced cognitive decline in patients with stroke or coronary heart disease (CHD) in intensive care unit (ICU) (16, 21, 22). The ASPREE trial, which focused on healthy elderly participants (17), may have failed to detect the protective effects of aspirin on reducing AD risk in certain high-risk populations. Our study, utilizing summary genetic data from large-scale genome-wide association studies (GWAS), provides evidence that aspirin use may be causally linked to a decreased risk of AD, potentially mediated by factors such as CHD, blood pressure, and lipid levels. This suggests that aspirin could offer a more substantial protective effect in individuals at higher risk for CHD, depression, abnormal blood pressure, or lipid dysregulation (23).

White matter, primarily composed of myelinated axons, plays a crucial role in maintaining cognitive function by facilitating communication between different regions of the brain (24). Inflammation, cancer and microvascular pathology are key contributors to white matter damage, leading to conditions such as white matter hyperintensities, which are associated with cognitive decline and neurodegenerative diseases, including AD (25, 26). White matter brain changes in Alzheimer's disease are pathologically associated with impairments in visual dual-task performance, reflecting the disruption of neural networks critical for multitasking and cognitive-motor integration (27). Emerging research suggests a potential association between tranexamic acid, Vitamin C, and Zinc and an increased risk of AD, although the underlying mechanisms and clinical significance of this relationship require further investigation (28, 29). Also, COVID-19 infection may be associated with white matter brain changes, including microstructural alterations and potential long-term impacts on cognitive function, though further research is needed to fully understand the extent and mechanisms of these changes (30-32). However, recent evidence suggests white matter damage due to the COVID-19 and other viral infections (33, 34). Pathological changes in white matter have been implicated in autism spectrum disorder, suggesting that disruptions in white matter integrity may underlie the atypical neural connectivity and cognitive impairments characteristic of the condition (35). Furthermore, other techniques such as quantitative ultrasound which has been explored as a non-invasive tool to detect pathological changes in brain white matter, with studies suggesting it may be sensitive to microstructural alterations linked to various neurodegenerative conditions (36, 37).

Aspirin, due to its anti-inflammatory and antithrombotic properties, has been investigated for its potential protective effects on white matter integrity. Some studies have suggested that aspirin may help preserve white matter health by reducing inflammation and preventing microvascular injury, which are critical factors in the development of white matter lesions. For instance, Bowman et al. found that aspirin use was associated with a reduction in the progression of white matter hyperintensities in elderly individuals (38). However, the results are not universally consistent, and further research is necessary to clarify aspirin's role in white matter health.

Conclusion

Aspirin is widely prescribed to millions of adults, yet its impact on WM regions in the brain remains largely unclear. In this study, we demonstrate that aspirin preserves WM microstructure in early AD. Although aspirin has been suggested as a potential therapeutic agent for neurodegenerative diseases, including AD, clinical trials have generally yielded negative results, likely due to the insufficient duration of therapy or the initiation of treatment after cognitive impairment has already developed. Further research is necessary to replicate these findings and to assess whether the effects of aspirin on WM structure could contribute to delaying or preventing cognitive decline.

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Declarations

Funding

We do not have any financial support for this study.

Conflict of interest

The authors have no conflicts of interest to disclose.

Availability of data

The datasets analyzed during the current study are available upon request with no restriction.

Code availability

Not applicable

Ethical approval

The data in this paper were obtained from the ADNI database (adni.loni.usc.edu). It does not include any examination of human or animal subjects.

Consent for publication

This manuscript has been approved for publication by all authors.

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