INPLASY PROTOCOL

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None declared.

A systematic review and meta-analysis of cerebrospinal fluid amyloid and tau levels in patients progressing from Mild Cognitive Impairment to Alzheimer's Disease

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Review question / Objective: **Reported levels of amyloid-beta and tau in human cerebrospinal fluid (CSF) are evaluated to discover if these biochemical markers can predict the transition from Mild Cognitive Impairment (MCI) to Alzheimer's disease (AD). A systematic review and quantitative meta-analyses are performed to test relationships between three potential biomarkers in CSF (Aβ(1-42), T-tau, and P-tau181) and the evolution of AD in longitudinal evaluations of levels relative to baseline, using prior-published experimental data. The primary focus of the analysis is on the period describing the transition of a patient from MCI to AD, where it is critical to discover the main biomarker characteristics that differentiate patient outcomes for those who have a stable form of MCI, and those who progress to a confirmed diagnosis of AD. A secondary purpose of the review was to examine the status of iron in CSF as a function of disease status.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 July 2022 and was last updated on 05 July 2022 (registration number INPLASY202270020).

INTRODUCTION

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where it is critical to discover the main biomarker characteristics that differentiate patient outcomes for those who have a stable form of MCI, and those who progress to a confirmed diagnosis of AD. A secondary purpose of the review was to examine the status of iron in CSF as a function of disease status.

Condition being studied: Alzheimer's Disease (AD) is the most common cause of dementia. Clinically observable characteristics of this disorder include memory loss, decline in cognitive function, and changes in behavioural patterns. Further, AD is identified as the greatest cause of death without an effective disease-modifying therapy. Efforts to develop drugs to treat AD have had a high failure rate. The analysis in this study focusses on progression to AD from a normal cognitive status and from mild cognitive impairment (MCI) classified as either stable (non-progressive MCI throughout the period of clinical follow-up), or those with MCI who will progress to a diagnosis of AD during the period of clinical follow-up.

METHODS

Search strategy: The following search query terms were used in PubMed ('Title') and Web of Science ('Topic') respectively, with the search being completed in April 2021: ((((Alzheimer) OR (AD) OR (MCI) OR (mild cognitive impairment)) AND ((CSF) OR (Cerebrospinal fluid)) AND ((biomarker) OR (iron) OR (metal)) AND ((longitudinal) OR (follow-up))) NOT (Review)) NOT (Parkinson).

Participant or population: Subjects (individuals with Alzheimer's disease, MCI, and healthy controls) participating in clinical studies where CSF measures of the target analytes were obtained. This study only focuses on Alzheimer's Disease, so progression from MCI to disorders other than Alzheimer's (including Parkinson's related disorders) is excluded. The clinical diagnoses reported according to recognized criteria were accepted for the purposes of this analysis, rather than requiring validation in the form of neuropathological assessment at autopsy.

Intervention: Not applicable.

Comparator: Not applicable.

Study designs to be included: The review specifically focuses on longitudinal (instead of cross-sectional) studies that included measurements repeated after baseline at one or more timepoints, so that levels can be tracked in a cohort.

Eligibility criteria: Studies measuring CSF levels of Aβ(1-42) and/or tau (T-tau, and/or P-tau181) were included. It was also necessary for the studies to include the values for these analytes at baseline (initial visit) and then at one or more subsequent time points for the healthy controls and the patients along with their diagnostic status (MCI, AD or an-other form of dementia). To be included, the studies also needed to state which criteria were used for the diagnosis of MCI and AD. For CSF analyte levels, the study needed to document not only the average values but also the standard deviation or interquartile range for each measurement. The study population also needed to be stated for each diagnostic group. Studies that did not meet these criteria were excluded: for example, if analyte concentration data were reported with 95% confidence interval and therefore did not include the necessary statistical information to be included in the present analysis. Where multiple independent studies were performed with a cohort, all studies except for the latest available study were excluded on the basis that the latest study should contain the most up-to-date information and methods. The methods used to assess cognitive function (e.g. MMSE), were not taken into account in the inclusion/exclusion criteria, but the analytical methods for the measurement of the analytes were examined to determine which were valid for inclusion. Studies of MCI patients progressing to forms of dementia that were not explicitly classified as AD were excluded. Studies that did not include measures of CSF T-tau, P-Tau, or Aβ(1-42) were also excluded. Additionally,

studies were excluded where the data were reported providing the confidence interval of the median, which prevented inclusion because those data could not then be transformed into the mean and standard deviation.

Information sources: Electronic databases (PubMed and Web of Science).

Main outcome(s): Reported levels of amyloid-beta and tau in human cerebrospinal fluid (CSF) were evaluated to discover if these biochemical markers can predict the transition from Mild Cognitive Impairment (MCI) to Alzheimer's disease (AD). A systematic review of the literature in PubMed and Web of Science (April 2021) was performed by a single researcher to identify studies reporting immuno-logically-based (xMAP or ELISA) measures of CSF analytes Aβ(1-42) and/or P-tau and/or T-tau in clinical studies with at least two timepoints, and statement of diagnostic criteria. Of 1137 screened publications, 22 met the inclusion criteria for CSF Aβ(1-42) measures, 20 studies included T-tau, and 17 included P-tau. Six meta-analyses were conducted to compare the analytes for HC versus progressive MCI (MCI_AD) and for non-progressive MCI (Stable_MCI) versus MCI_AD; effect sizes were determined using random effects models. Heterogeneity of effect sizes across studies was confirmed with very high significance ($p<0.0001$) for all meta-analyses except HC versus MCI_AD T-tau ($p<0.05$) and P-tau (non-significant). Standard mean difference (SMD) was highly significant ($p<0.0001$) for all comparisons (Stable_MCI versus MCI_AD: SMD[95%-CI] Aβ(1-42)= 1.19[0.96,1.42]; T-tau= -1.03[-1.24,-0.82]; P-tau= -1.03[-1.47,-0.59]; HC versus MCI_AD: SMD Aβ(1-42)= 1.73[1.39,2.07]; T-tau= -1.13[-1.33,-0.93]; P-tau= -1.10[-1.23,-0.96]). Follow-up interval in longitudinal evaluations was a critical factor in clinical study design, and the Aβ(1-42)/P-tau ratio most robustly differentiated progressive from non-progressive MCI. The value of amyloid-beta and tau as markers of patient outcome are supported by these findings.

Additional outcome(s): At the time of submission, the secondary analysis (of iron status as a CSF marker) has not been completed; the primary analytical focus has been on the amyloid and tau levels.

Quality assessment / Risk of bias analysis: The review was performed by a single operator and followed the PRISMA guidelines. Study design for each report selected for inclusion had to meet the criteria detailed above, and study size was also considered (>30 participants required). For each of the comparisons between groups, a separate meta-analysis was conducted for the three different analytes. Effect sizes were determined using random effects models ensuring somewhat balanced weights across studies despite the inclusion of one individual studies with much larger sample size than all others and considering differences in the populations of the individual studies. Roughly symmetric funnel plots confirmed that there is no clear evidence of bias in any of the comparisons. Heterogeneity of effect sizes across studies was confirmed with very high significance for all three meta-analyses comparing Stable_MCI versus MCI_AD ($p<0.0001$), as well as for amyloid in the HC versus MCI_AD comparison ($p<0.0001$), and a statistically significant difference was also observed for T-tau for HC versus MCI_AD ($p<0.05$) although not for P-tau. Hence, random effects are used for all but the last comparison. Note that the small number of studies in the last condition means that we can only draw limited conclusions from this. Effect sizes are given in standard units. In most of the comparisons, the absolute magnitude of the effect is between 1 and 1.2 standard error difference, except for amyloid in HC vs MCI_AD, where it is even higher with 1.73. The direction of the effects also confirm the trends observed: amyloid is increased in both non-AD conditions (Stable_MCI and HC) versus MCI_AD, while the other two analytes (T-tau, P-tau) are decreased. Normality assumptions were checked in each of the six settings and turned out to be sufficiently satisfied (supported by the histogram plots showing the distribution of effect sizes for each

analysis), while the symmetry of the funnel plots created for each of the conditions confirmed no clear evidence for bias.

Strategy of data synthesis: Summary measures for amyloid (concentration of Aβ1-42 in CSF), tau (T-tau and P-tau181 in CSF) from all studies are saved into an Excel spreadsheet for all conditions (stable MCI (MCI_St), MCI progressing to Alzheimer's disease (MCI_AD), and healthy control (HC)). After reading in the data we conduct separate meta-analyses comparing MCI_AD to each of the other two conditions. The analysis is performed using the open source freely available software R and the 'meta' package (version 4.20-2), which supports the book 'Meta-Analysis with R' by Schwarzer, Carpenter, and Rücker, Springer, Cham, 2015, first edition. We use the methods detailed in Part II Chapter 2 and Part III Chapter 5.1. of 'Meta-Analysis with R' first edition, which follows the Cochrane Handbook for Systematic Reviews of Interventions. All measurements of interest are continuous. To accommodate different measurement technologies or analytical protocols potentially resulting in incompatible scales across the studies, a standardised mean difference is chosen to measure the effect. We use Hedges' g, which is based on pooled sample variance and very similar to Cohen's d but more appropriate to the group sizes in the present analysis. We conduct the meta-analyses using both a fixed effect model and a random effects model. The fixed effects model assumes that the individual studies included in the meta-analysis are sampled from the same population, so their observed means are the effect size, give or take an error term. To accommodate for differences in precision, weights in-verse to the individual studies' variances are used in the construction of the overall effect estimator. The random effects model assumes the individual studies' effects are normally distributed with variance tau^2. While the fixed effects model attributes differences between observed effects entirely to sampling error, the random effects model attributes some of them to true differences between effect sizes across the studies. Significance tests for the overall effects are based on inverse variance methods.

Subgroup analysis: The format of the data, as provided in the source papers, sometimes gave direct access to the average and standard deviation values for the analytes, but in other cases it was in the form of the median and accompanying range, or median with 1st and 3rd quartile values. In the latter cases, the method previously published by D. Luo and X. Wan was used to estimate the average and standard deviation to align the datasets to enable a meta-analysis. Where the source data were available as the median and inter-quartile range, they were assumed to follow a normal distribution with standard deviation equal to the inter-quartile range divided by 1.35. Hedge's G values were calculated to determine the effect size for the datasets included in this study, using random effect size model. In this context, the Hedge's G value was defined as positive for the scenario where patients with progressive MCI had a higher CSF baseline measurement than the other groups with which they were compared (non-progressive MCI or health control) for each selected biomarker. To detect publication or other biases, funnel plots were used. Heterogeneity across studies was primarily accessed by Higgins' I^2.

Sensitivity analysis: For this study, forest plots provide a graphical and numerical summary of the results of a meta-analysis and have become a common part of the Cochrane review framework. They list the individual studies with their sample sizes, study means, and SDs, and the meta-analysis' effect size with confidence interval, both numerically and visually, together with the random and fixed effect model estimates. Because of the structure of the datasets used from prior-published reports it was not viable to perform an analysis that determines how sensitive the analyte levels are to the diagnostic status of the individual.

Language: Only reports providing access to findings in English were included.

Country(ies) involved: UK.

Keywords: Alzheimer's Disease; Cerebrospinal Fluid; Tau; Amyloid Beta; Mild Cognitive Impairment; Biomarker; Systematic Review; Meta-analysis.

Dissemination plans: It is intended to publish the results of this study in Biomedicines in 2022 where the work is under review at the time of this registration, and the findings will also be presented in due course as part of Yunxing Ma's PhD thesis.

Contributions of each author:

Author 1 - Yunxing Ma - Y.M. initiated the study, performed the systematic review and initial analysis, and drafted the manuscript.
Email: y.ma.17@warwick.co.uk
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