# INPLASY PROTOCOL

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**Corresponding author:**
**Mingwan Su**

**sebastiamerald@gmail.com**

**Author Affiliation:**
**Beijing University of Chinese Medicine**

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**None declared.**

# The correlation between olfactory test and hippocampal volume in AD and MCI patients: a meta-analysis

Su, M[1]; Ni, J[2]; Cao, T[3]; Wang, S[4]; Shi, J[5]; Tian, J[6].

**Review question / Objective:** **This meta-analysis determines to quantify the correlation between odor identification test score and hippocampal volume in AD.**
**Eligibility criteria:** **Studies were included if they meet the following criteria: (1) subjects of AD or MCI patients were involved, with or without health control; (2) both olfactory testing and hippocampal volumetric counting from MRI image were conducted; (3) the correlation coefficient could be extracted directly or through calculation from raw data; (4) English studies published in peer- reviewed journals not before 2003; (5) study type should be cohort study, case-control or cross-sectional study. Results were filtered to include only English-written studies on living humans.**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 April 2021 and was last updated on 17 April 2021 (registration number INPLASY202140088).

## INTRODUCTION

**Review question / Objective:** **This meta-analysis determines to quantify the correlation between odor identification test score and hippocampal volume in AD.**

**Condition being studied:** **Alzheimer's disease (AD) is an insidiously onset, progressive neurodegenerative disease that primarily causes dementia. It's estimated that 44 million people live with dementia worldwide currently. Mild cognitive impairment (MCI) is a transitional stage between normal cognitive function and dementia. Approximately 15% to 20% of people have MCI in age≥65 yrs and are**

susceptible to dementia with a higher conversion rate. AD is characterized by memory decline that relates to premature atrophy of hippocampus, entorhinal cortex and other medial temporal lobe structures. Alteration in olfactory function often coincides with clinical symptoms or even precede it. Olfactory dysfunction (OD) occurs in the prodromal stage of AD and could progress with the disease. Since early detection of AD is crucial to preventing and slowing the progress, OD has been considered as a potential clinical marker for AD prediction, severity and progression. Olfactory structures such as entorhinal cortex, amygdala, hippocampus, caudate and other medial temporal lobe, have been discovered to contain classic pathological features, such as neurofibrillary tangles and amyloid-βplaques, which are as well observed in olfactory regions in early stage AD and MCI patients including olfactory bulb and tract, anterior olfactory nucleus. Studies have suggested that aggregation of Aβ and tau protein occurs in olfactory neuro-epithelium. Nevertheless, central olfactory structures play a more important part in olfactory dysfunction. Impaired odor identification during life was discovered to be robustly related to increased density of tangles in the entorhinal cortex and CA1/subiculum region of the hippocampus but unrelated in other cortical sites after death[11]. Hippocampal atrophy and volumetric measurement are included among the biomarkers of neuronal injuries for MCI and AD diagnosis. Over the recent years, the link between olfactory identification performance and hippocampal atrophy has been recognized in some cross-sectional and longitudinal researches. The positive results implicate that olfactory deficits may become a potential biomarker for hippocampal function. The aim of this systematic review and meta-analysis was to examine whether olfactory deficits correlate with hippocampal atrophy quantitatively, and provide a comprehensive overview on under what circumstances the correlation may prominent due to different moderation factors.

## METHODS

**Participant or population:** subjects of AD or MCI patients were involved, with or without health control.

**Intervention:** Both olfactory testing and hippocampal volumetric counting from MRI image were conducted.

**Comparator:** The correlation coefficient could be extracted directly or through calculation from raw data.

**Study designs to be included:** Study type should be cohort study, case-control or cross-sectional study. Results were filtered to include only English-written studies on living humans.

**Eligibility criteria:** Studies were included if they meet the following criteria: (1) subjects of AD or MCI patients were involved, with or without health control; (2) both olfactory testing and hippocampal volumetric counting from MRI image were conducted; (3) the correlation coefficient could be extracted directly or through calculation from raw data; (4) English studies published in peer- reviewed journals not before 2003; (5) study type should be cohort study, case-control or cross-sectional study. Results were filtered to include only English-written studies on living humans.

**Information sources:** Papers from "PUBMED, EMBASE, WEBOFSCIENCE" database up to Jan.2003.

**Main outcome(s):** 7 of 627 original studies on AD/MCI with olfactory identification test were included in the meta-analysis. In the mixed population, a positive correlation was found between hippocampal volume and olfactory test score Egger's regression test revealed an overall reporting bias . A trim-and-fill funnel plot adjusted a rather weak positive correlation . The contour-enhanced funnel plot revealed a low risk of publication bias. Moderator analysis showed that AD and MCI patients were more profoundly in correlation than normal control. Age difference and patient type are

the main heterogeneity sources in this analysis.

**Quality assessment / Risk of bias analysis:** Not coming yet.

**Strategy of data synthesis:** Meta-analysis was proceeded in R language with "meta" package in R-studio Version 1.3.959 (https://rstudio.com/), where random and fixed effect model were applied according to the heterogeneity test. The $I^2$ statistic was calculated to assess the heterogeneity between studies. We attempt to fit a fixed effect model when $I^2$ value 50% or P-value <0.05 suggests a rather heavy inconsistency and high heterogeneity, we'd chose sensitivity and subgroup analysis to render it and to further discuss the potential sources. Subgroups were divided in categories of: (1) subjects, patients/normal; (2) sides, left/right/both; (3) age groups in difference of 5 years old. Publication bias was graphically demonstrated with a funnel plot. Deviation of funnel shape indicates an evidence of publication bias. If asymmetry arises, the trim-and-fill method[17] would detect and adjust for publication bias. Counter-enhanced funnel plot is further induced to confirm the sources of bias.

**Subgroup analysis:** Subgroups were divided in categories of: (1) subjects, patients/normal; (2) sides, left/right/both; (3) age groups in difference of 5 years old.

**Sensitivity analysis:** The $I^2$ statistic was calculated to assess the heterogeneity between studies. We attempt to fit a fixed effect model when $I^2$ value 50% or P-value <0.05 suggests a rather heavy inconsistency and high heterogeneity, we'd chose sensitivity and subgroup analysis to render it and to further discuss the potential sources.

**Language:** English.

**Country(ies) involved:** China.

**Keywords:** Olfactory deficits, hippocampus, mild cognitive impairment, Alzheimer's disease.

**Contributions of each author:**

Author 1 - Mingwan Su - The author drafted the manuscript.
Email: sebastiamerald@gmail.com
Author 2 - Jingnian ni.
Author 3 - Tianyu Cao.
Author 4 - Shuoshi Wang.
Author 5 - Jing Shi.
Author 6 - Jinzhou Tian.
Email: jztian@hotmail.com