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Could Early Identification of Changes in Olfactory Function Be an Indicator of Preclinical Neurodegenerative Disease? A Systematic Review

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Introduction

Alzheimer's disease (AD) is a debilitating neurodegenerative disease that currently affects 850,000 individuals in the UK with estimates continuing to rise. Diagnosis is only available in the presence of significant neuronal pathology and apparent cognitive decline, meaning that treatment avenues are often limited and carry little to no effect on prognosis. Olfactory function has been shown to have a direct correlation with cognitive function and therefore may serve as a potential diagnostic tool for the detection of preclinical disease. Despite this, olfactory testing is not a clinical tool used routinely, which may represent a missed opportunity.

The aim of this review is to critically appraise relevant literature to establish whether olfactory testing provides a suitably accurate preclinical biomarker of Alzheimer's disease for clinical use, and if so, to make recommendations for future research to increase its accuracy.

Methods

A systematic review was performed using the search terms and Boolean operators 'Dementia OR Alzheimer's AND olfaction AND cognitive impairment' yielding 111 results. Articles were assessed via the inclusion/exclusion criteria alongside a PICO strategy (shown below).

Acronym	Definition	Determinants
P	Patient/population	Patient's with Alzheimer's Disease
I	Intervention	Preclinical detection of olfactory disturbance by the olfactory assessment tools: University of Pennsylvania Smell Identification Test (UPSIT) and Sniffin' Sticks
C	Control/comparison	Adult participants without AD or mild cognitive impairment
O	Outcome	How preclinical olfactory changes correlate with diagnosis/progression of cognitive decline

Table 1: PICO Framework used to guide research question
AD was selected due to being the most prevalent neurodegenerative disease and therefore an increased understanding of pathogenesis has the potential to benefit the greatest number of patients. UPSIT and Sniffin' Sticks were selected due to being the most commonly used olfactory tests in the literature and providing the widest amount of data for critical appraisal.

Articles were excluded based on age (>5 years old) (n = 37), review articles (n = 13), if the predominant neurodegenerative disease being investigated was not AD (n = 8), if participants had co-morbidity (n = 1) if not performed on humans (n = 1), or were unable to be readily attained (n = 4). 47 full text articles were assessed for eligibility, and further excluded based on ineligible study design or no comparable group (n = 25) incorrect olfactory assessment tool being used (n = 13). 9 studies met this criteria with a total of 14,760 participants for inclusion in this systematic review. Therse articles were then critically appraised using the AXIS tool for cross-sectional studies and the CASP tool for longitudinal studies.

Results

Despite different study designs, all studies included in this review found a correlation between OI and cognitive decline. This aligns with previous evidence. However, this review highlights novel limitations that may strengthen future work and result in the ability to use olfactory testing with greater accuracy in future.

Medication use

Only considered in 3 of 9 articles, and stated as a limitation in another, despite its proven effect on olfactory function.

Covariates

Smoking — 4
APOE ε4 — 3
Education — 9
Sex — 9
Age — 9
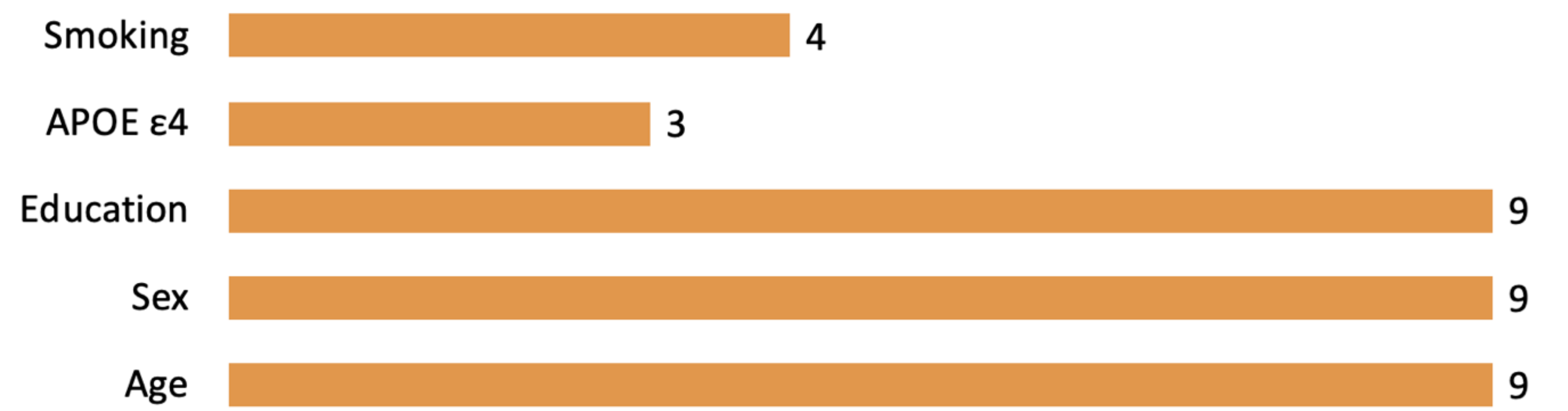
- Age, sex and education considered in all studies
- APOE E4 only considered in 3/9 studies
- Smoking only considered in 4/9 studies

Bias

Cultural — 5
Sampling — 4
Selection — 5

- **Cultural:** the use of an olfactory test on a population it was not designed for (5/9 studies)
- **Sampling:** not considering factors such as head trauma, sinonasal disease and infection (4/9 studies)
- **Selection:** recruitment from a specialist service (5/9 studies)

Discussion

The findings of this review align with current literature in demonstrating the correlation between olfactory and cognitive function. However, the strength of this review lies in the highlighting of multiple limitations that, if addressed in future work, may increase the accuracy of olfactory testing, and therefore its utilisation in clinical practise.

Recommendations for future work include:

- Modifying olfactory tests for individual cultures. This review highlights studies in which a test designed for one culture is used on another. This creates an inherent bias as each culture has an increased prevalence of certain odours, and lack of identification may be due to lack of recognition, not due to dysfunction.

- Including a consistent set of inclusion/exclusion criteria which covers factors that can influence olfaction outside of neurodegenerative disease, such as head trauma, infection and sinonasal disease.

- Considering a consistent set of covariates such as smoking and APOE E4 to increase the accuracy of association.

If these recommendations are utilised in future work, there is the potential to use olfactory testing as a regular clinical tool with the aim of providing earlier diagnosis and prompting therapeutic intervention with may slow or halt disease progression.

Conclusion

This systematic review aligns with the current literature; there is a connection between ofaction and cognition. However, the strength of this paper is in identifying limitations that may be preventing increasingly accurate conclusions to be found, which may facilitate regular clinicial use, and the possibility of designing new therapeutic targets.

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