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Featured Article

Olfactory function and neurocognitive outcomes in old age: The Atherosclerosis Risk in Communities Neurocognitive Study

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Abstract

Introduction: We tested the hypothesis that poor sense of smell is associated with lower cognitive function and higher mild cognitive impairment (MCI) prevalence.

Methods: Olfaction, measured by the Sniffin' Sticks test, was categorized as olfactory impairment (OI) (score ≤6) or no OI (score >6). MCI was adjudicated based on review of a neuropsychological examination. Linear regression estimated the mean difference in cognitive factor scores, and log-binomial regression quantified MCI prevalence among participants with versus without OI.

Results: Participants with OI had lower mean factor scores (memory: −0.27 standard deviation [SD], 95% confidence interval [CI]: −0.35 to −0.19; language: −0.24 SD, 95% CI: −0.30 to −0.17; executive function/processing speed: −0.09 SD, 95% CI: −0.12 to −0.06; and general cognitive performance: −0.25 SD, 95% CI: −0.30 to −0.20). OI was also associated with MCI (n = 204; prevalence ratio = 1.56, 95% CI: 1.37, 1.78).

Discussion: An impaired sense of smell may serve as a readily accessible early marker of neurodegeneration and improve upon the prevailing delayed diagnoses and underascertainment of MCI/dementia.

Keywords: Cognition; Mild cognitive impairment; Olfaction

1. Background

The prevalence of olfactory impairment (OI) is almost 25% in individuals aged 53 years or older, rising to 60% at ages 80–97 years [1]. OI can lead to reduced quality of life (i.e., loss of pleasure in food [2]) and increased health hazards (i.e., inability to detect spoiled food and gas leaks [3]), and it is a strong and independent risk factor for mortality [4,5]. The most salient predictor of OI among healthy adults is age [6]. Other predictors include race, sex, inflammation of the nasal passages, upper respiratory infections, viral infections, exposure to toxins, and head trauma [1].

Impaired olfaction is an early symptom of neurodegenerative pathogeneses due to Alzheimer's disease (AD), as well as Parkinson's disease [7]. Autopsy data show that a greater loss in the sense of smell is associated with plaques and tangles in the central olfactory region of the brain [8] that connects to the hippocampal region. More specifically, damage due to Braak neurofibrillary tangle stage I of AD occurs preferentially in areas including the olfactory cortex [9–11]. Recent data suggest OI is associated with reduced cognitive performance, incident mild cognitive impairment (MCI), and rate of progression from MCI to dementia due to AD [12]. Additional population-based studies are needed

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both for confirmation and to examine cognitive decline and individual cognitive domains.

Differences by race and sex also warrant investigation. Preliminary data suggest that African Americans and Hispanics have worse olfactory function than individuals of European ancestry [13], with greater differences than by sex [14]. Few studies have examined differences by race in the associations between olfaction and neurocognitive outcomes. Nondemented community-dwelling older adults from the Health, Aging, and Body Composition study with poorer odor identification had a three-fold greater risk of dementia compared to those with good odor identification; this association was stronger in whites compared to blacks [15]. In a multiethnic cohort of 1037 participants from Northern Manhattan, those in the lowest quartile of a smell test score had a higher risk of transitioning to Alzheimer's dementia compared to participants in the highest quartile [16].

Our objective was to examine the associations of olfactory function with cognitive function in the absence of dementia. Here we add to the literature by testing the hypothesis that poor sense of smell is associated with (1) lower domain-specific cognitive function, specifically in the domain of memory; (2) greater prior cognitive decline; and (3) increased prevalence of MCI.

2. Methods

2.1. Study population and design

The Atherosclerosis Risk in Communities (ARIC) Study is a community-based prospective cohort study that recruited 15,792 participants aged 45 to 64 years between 1987–1989 from four US communities (Washington County, Maryland; Forsyth County, North Carolina; Minneapolis, Minnesota; and Jackson, Mississippi). ARIC was designed to investigate the etiology of atherosclerosis and its clinical sequelae. Detailed information about the ARIC Study has been described [17]. The present study is based on the fifth cohort examination (2011–2013, n = 6538), the ARIC Neurocognitive Study (NCS). The primary aim of ARIC-NCS was to evaluate the contribution of mid-life vascular risk factors to cognitive decline and risk of MCI and dementia. ARIC-NCS participants completed a smell identification test and comprehensive neuropsychological battery. Neurologists and neuropsychologists adjudicated MCI and dementia [18]. Owing to small numbers, we excluded non-black/non-white participants (n = 18); blacks from Minneapolis, Minnesota, and Washington County, Maryland (n = 25); and participants who were missing the smell test data (n = 440). Participants without smell test data (Supplementary Table 1) were older, more often blacks, and had lower educational attainment and a higher prevalence of hypertension and stroke. Given our interest in examining associations of olfaction with early impairments, and to avoid the artifact of poor smell test performance in persons with dementia, participants with diagnosed dementia (n = 247) were excluded from the analysis. We excluded an additional 787 participants due to incomplete covariate/outcome data. Our analytic sample included 5021 older adults. Institutional review boards at each study site approved the study.

2.2. Exposure: Olfactory function

The sense of smell identification was measured by the 12-item Sniffin' Sticks screening test at ARIC visit 5 [19]. Participants were asked to smell 12 common odorants in a felt-tip pen (orange, leather, cinnamon, peppermint, banana, lemon, licorice, coffee, cloves, pineapple, rose, and fish), one at a time, and asked to identify each using a multiple-choice format of four possible answer choices. One point was assigned to each correctly identified odorant, yielding a total possible score of 12. The smell test score was dichotomized according to a conventional cut point for OI (score $\leq$ 6) [20]. We also examined associations of interest across the continuous values of the smell test score (0–12, higher score = better olfactory function). The Sniffin' Sticks test is comparable to other brief olfactory screening tests, including the Brief Smell Identification Test, and has been widely used in both clinical and epidemiologic studies [20,21].

2.3. Outcomes: Cognitive function and MCI

Cognitive function was assessed with a comprehensive neuropsychological battery administered at ARIC visit 5. The following domains and cognitive tests were examined: memory (delayed word recall, logical memory, and incidental learning), executive functioning/processing speed (Trail Making Tests, Parts A and B; Digit Symbol Substitution Test), and language (semantic and phonemic fluency, Boston Naming Test). Using data from these tests in a factor analysis, factor scores for general cognitive performance, executive functioning/processing speed, memory, and language were derived [22]. Briefly, the factor analysis is a structured approach for identifying common covariation between specific indicators, in this case the cognitive tests, to reduce measurement error when combining data across multiple cognitive tests. The interpretations of factor scores are similar to that for z scores because they were scaled to have a mean of 0 and variance of 1 at ARIC visit 2 when the participant's cognitive function was first tested.

Algorithms based on the National Institute of Aging–Alzheimer's Association workgroups [23,24] and Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [25], were used to determine a diagnosis of MCI. An MCI diagnosis was assigned to participants if they met the following criteria: (1) performing worse than −1.5 standard deviations on at least one cognitive domain; (2) scored >0.5 and ≤3 on the Clinical Dementia Rating Score sum of boxes; (3) scored ≤5 on the Functional Assessment Questionnaire; and (4) declined below the 10th percentile on one test or below the 20th percentile on two tests in a serial ARIC cognitive battery first administered at