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Epidemiological Studies of Smell: Discussion and Perspectives

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Abstract

The critical epidemiological data for estimating the prevalence of chemosensory disorders in the US are lacking. Several reasons for this will be discussed, including the time-consuming nature of many existing tests, stimulus delivery in a large-scale study, and the rationale for inclusion in a large-scale epidemiological study. The opportunity to include measures of chemosensory function in ongoing population-based studies has greatly facilitated the collection of recent data that establishes the high prevalence of olfactory impairment in older adults in the US population and the inability of self-report measures to capture this impairment. Epidemiological studies of the complete range of the population that involve chemosensory testing pose considerable challenges, but are critical to establishing prevalence rates. These studies have the potential to suggest prevention or intervention strategies for chemosensory impairment. Key issues, including cross-cultural issues in stimulus design, testing of special populations, cohort effects and optimal analyses of population-based chemosensory data, are considered.

Keywords

olfaction; olfactory impairment; smell; odor; prevalence; epidemiology; population studies

U.S. Epidemiologic data for estimating the prevalence of chemosensory disorders has been less available than such data for other modalities. A large-scale epidemiologic study of smell in the United States is crucial for estimating the public health burden of olfactory impairment in the general population and for identifying factors that may exacerbate or, conversely, mitigate smell problems, such as particular medications or co-morbidities.

The undertaking of such a project presents several challenges. First, a representative population sample, encompassing a wide variety of ages and ethnicities, must be recruited or be available for study. This requires a significant commitment of time and financial resources. Second, a rapid, reliable assessment of olfaction is required. Self-report alone is not sufficient, since this method has been demonstrated to significantly underestimate prevalence rates obtained by olfaction testing.[1] Ideally, the test should be easy to administer, inexpensive, and acceptable to participants. It should span cultural differences in odor familiarity, as well as lift language barriers, so that it can be used across a global population. Additionally, the needs of special populations, such as young children and subjects with cognitive impairment, must be taken into account.

Dr. Dalton's presentation highlights the special requirements involved in testing olfaction in children. In fact, many of the same issues that challenge epidemiological studies will challenge any study with small children: the need for rapid administration of tests that

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present stimuli that are familiar odors in a format that minimizes adaptation and maximizes reliability and validity in this population. A number of tests have been successfully used with children. Generally children aged five and above require some accommodation but can produce reliable, valid data. For example, the San Diego Odor ID test showed a test-retest reliability of .86 in children and in adults with Down syndrome.[2] Dr. Dalton's study in progress, designed to test the feasibility of an odor identification test for children beginning at age three, is a major undertaking and the results will be welcome and informative. It incorporates the features of earlier tests and is sensitive to the issues relevant to testing very young children.

Dr. Wysocki's presentation raises the important consideration of individual differences in olfactory function and specifically ethnic/racial differences. His research group has been focusing on a subset of olfactory receptor genes, that vary across individuals, known as segregating pseudogenes, and on specific anosmias. Such considerations become important in attempts to generalize the data from epidemiological studies in specific samples and they underscore the need for epidemiological studies that are broad in scope.

Recently conducted epidemiological studies of olfaction have focused upon specific subpopulations, such as the middle-aged and elderly population in the Beaver Dam study discussed by Ms. Schubert[1] and Japanese-American males in the Honolulu-Asia Aging Study.[3] In each case, brief olfaction tests were added to a pre-existing project that had been designed to acquire epidemiological data on other variables, such as hearing loss in the Beaver Dam study and cardiac disease in the Honolulu-Asia Aging Study. In both cases, chemosensory tests were administered after training existing project personnel. Such an arrangement allowed for the collection of valuable data with limited impact on financial and human resources. However, it does require collaboration between researchers from diverse training backgrounds, who may differ in their terminology and data analysis and sharing practices. The addition of chemosensory testing should avoid taxing the major study and maximize the application of new ideas.

The Epidemiology of Hearing Loss Study (EHLS), a longitudinal population-based study involving Beaver Dam, Wisconsin residents, has provided many significant insights into this field. The San Diego Odor Identification Test has been incorporated into this study, and subsequently, taste testing has been adopted. Ms. Schubert presented data from both the EHLS and BOSS, a study of offspring which spans a larger age range. In the EHLS Murphy et al.[1] found a mean prevalence of olfactory impairment of 24.5% among people older than 50 years of age, with rates rising exponentially with increasing age (See Figure in Hoffman, this volume). Among 80- to 97-year-olds, 62.5% had olfactory impairment on the San Diego Odor Identification Test. In contrast, self-reported olfactory impairment was low and this measure became less accurate with age. Table 1 compares the ability of older adults to accurately report olfactory loss with measured impairment, illustrating the low sensitivity of the self-report measure and thus, the need for sensory testing. The very high specificity suggests that older adults who do report loss of function do so accurately.

In this same population, Schubert et al.[4] recently reported that among 1,920 participants in the EHLS, olfactory impairment at baseline was associated with cognitive impairment (MMSE score) at five-year follow-up (Odds Ratio (OR) = 6.62, 95% CI 4.36–10.05). The association remained significant after adjusting for possible confounders, i.e., MMSE at baseline, age, sex, education, and occupation (OR = 3.33, 95% CI = 2.04–5.42). This result is particularly interesting since the population is younger (M = 67 at baseline) than in previous studies indicating an association of olfactory impairment with subsequent cognitive impairment, and thus the incidence of cognitive impairment in this population was low, and positive predictive value low. However, the negative predictive value was very high, 97.2%,

so that older adults without olfactory impairment were very likely to be free of cognitive impairment for five years.[4] Interestingly, preliminary data from the Beaver Dam Offspring Study (BOSS), which involves children of the original Beaver Dam study participants, indicate a lower prevalence of olfactory impairment in the BOSS cohort as compared to the EHLS cohort at similar ages.

Self or informant-reported data on smell disorders has also been gathered through the Disability Supplement to the National Health Interview Survey (NHIS), which was randomly distributed to 42,000 randomly selected households in 1994. Adjusted national estimates suggested a prevalence of 1.4% for self-reported olfactory disorders amongst U.S. adults. Approximately 40% of those who reported chronic smell problems were 65 years or older. Significant associations were found between rates of smell disorders and the individual's overall health status, functional limitations, depression, and trouble hearing.[5] The relatively low prevalence rates in this study are likely underestimates of actual prevalence, given the use of self-report only, with no opportunity for clinical testing of olfaction.

Epidemiological studies in which olfaction is assessed are critical for accurate determination of prevalence, determining potential cohort effects, as well as investigating the health implications of chemosensory disorders. Smell disorders have a significant impact on dietary habits and weight, and may also impact blood pressure and other risk factors for cardiovascular disease and diabetes. The prevalence of obesity has reached nearly epidemic levels, partially due to dietary modifications with higher intake of saturated fats and sugars. Obesity serves as a risk factor for many health problems, including heart disease, hypertension, stroke, and certain types of cancer. Obesity is also a significant risk factor for diabetes, with a three-fold increase in diabetes risk seen in moderately obese middle-aged men.[6] The prevalence of this disease has been accelerating rapidly since 1990;currently, over 18 million people in the U.S. have been diagnosed with diabetes.[7]

Increasing evidence indicates that cognitive status in old age is closely linked to health status in middle age. A recent study demonstrated that the risk of dementia is increased by 74% in obese middle-aged individuals, while this risk is increased 35% in overweight middle-aged individuals.[8] Strong evidence supports glucose dysregulation as a predictor for cognitive impairment. A nearly twofold increase in the risk of developing cognitive impairment has been shown in post-menopausal women with diabetes, as well as those with impaired fasting glucose.[9] Moreover, levels of glycosylated hemoglobin (HbA1c), a marker of long-term glucose control, have been linked to the risk of developing mild cognitive impairment or dementia.[10] Older patients with poor diabetes control have a high risk of undiagnosed cognitive dysfunction.[11] Some evidence of olfactory impairment has also been seen in diabetics.[12] An increased risk of Alzheimer's disease has been associated both with diabetes[13] and the metabolic syndrome, which is manifest by large waist circumference, elevated glucose levels, and lipid dysregulation.[14]

Olfactory loss has been closely linked to cognitive decline, particularly in neurodegenerative diseases such as Alzheimer's disease (AD)[15] and Parkinson disease (PD).[3] Some 4.5 million Americans suffer from AD and the number is projected to rise to 5.7 million by 2020. The disease is expected to quadruple by 2050, absent treatment or cure for AD. Estimates of the indirect and direct health costs of AD approach $150 billion. Parkinson's disease affects at least 500,000 Americans, or approximately 2 percent of those older than 65. Activity in the pharmaceutical sector to develop effective treatments has increased significantly. Because of its potential to serve as an early marker of prodromal AD or PD, population studies of olfactory function that assess the sensitivity and specificity of olfactory impairment combined with other measures of dementia may be very important in establishing the

potential for olfactory testing, in conjunction with other neuropsychological testing, to signal pre-clinical disease in those who are potential targets for pharmaceutical intervention. Recent results from a number of population studies are promising. Wilson et al.[16] reported that impaired olfaction at baseline predicted mild cognitive impairment at 5 year follow-up.Similarly, participants in the Beaver Dam population study showed a strong association between olfactory impairment at baseline and the 5-year incidence of cognitive impairment.[4]Ross et al.[3] reported that odor identification impairment at baseline was strongly associated with Parkinson's disease at 5 year follow. In all of these studies, specificity was high, sensitivity less so, suggesting the potential utility of combining olfactory assessment with other measures in a dementia battery. Novel population studies that assess the influence of environmental and genetic influences on the development of cognitive impairment and dementia may be very informative and suggest avenues for prevention.

The advent of specific medications may have positive cohort effects if their use protects against olfactory impairment. For instance, increased use of nasal steroids and oral antibiotics for nasal inflammation and paranasal sinus disease over recent decades could potentially reduce the insult of inflammatory diseases on the peripheral olfaction system, thereby lessening the risk of permanent olfactory impairment. The use of hormone replacement therapy (HRT) in post-menopausal women may also protect against olfactory loss, as has been demonstrated in individuals with the Apolipoprotein epsilon 4 allele.[17] The Beaver Dam study demonstrated a decreased risk of olfactory impairment in subjects taking oral steroids or statins, a widely used cholesterol-lowering medication. Olfactory impairment is common in aging and may serve as a useful marker for other age-related disorders. Opportunities may exist for both prevention and treatment of these diseases if modifiable risk factors can be identified. Cohort effects related to birth year, medication use, and co-morbidities such as obesity and diabetes are areas of particular interest for future research utilizing a large-scale epidemiological study.

In summary, self-report, cross-sectional studies and research on age-limited cohorts suggest that there is significantly high prevalence of olfactory impairment in the US population. The opportunity to include measures of chemosensory function in ongoing population-based studies has greatly facilitated the collection of recent data. Epidemiological studies of the complete range of the population pose considerable challenges, but are critical. Absent epidemiological studies focused on testing the chemical senses, incorporation of chemosensory assessment into existing large-scale cohort studies will advance knowledge and open opportunities for prevention.

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Table 1

Sensitivity and specificity of self-reported olfactory impairment in the US older adult population, shown as a function of age and gender, support the need for chemosensory testing.

	Sensitivity	Specificity
Women		
52–59 yrs	0.33	0.94
60–69	0.24	0.95
70–79	0.16	0.94
80–97	0.12	0.96
All	0.16	0.94
Men		
52–59 yrs	0.36	0.91
60–69	0.25	0.93
70–79	0.24	0.95
80–97	0.18	1.00
All	0.24	0.93
All	0.20	0.94

Data from Murphy et al., 2002, Journal of the American Medical Association[1]