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The Epidemiology of Olfactory Disorders

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Abstract

Insights into risk factors for olfactory decline are needed, because knowledge about its origin is limited. This impairment has important implications for human health. Several epidemiologic studies of olfaction provide insight into the prevalence of olfactory disorders.

Here, we review the major population studies carried out on this topic to date. Our purpose is to characterize knowledge about olfactory disorders from human studies. We also describe the existing methods for measuring the sense of smell in population studies, present recent insights into the epidemiology of smell disorders, and discuss the risk factors identified to date. Synthesis of these data shows that olfactory dysfunction increases as people age and is worse in men. Further study of olfaction is warranted for gaining better information on the etiologies affecting its impairment, research that will have a large public health impact.

Keywords

Olfaction; Olfactory Dysfunction; Epidemiology; Smell; Risk Factors

Introduction

Olfaction plays a major role in human daily life. The key role of this ancient sensory system is to provide information on chemicals in the environment [1]. Olfaction plays a role in the detection of dangerous compounds, maintaining of nutrition, interpersonal behavior, neurologic health, and sensation of pleasure, among other functions. Consequently, olfactory dysfunction can lead to a risk of injury (especially regarding dangerous chemicals, exposure to smoke, and putrid food), malnutrition, social isolation, and a poor quality of life. Indeed,

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Jingpu Yang and Dr. Jayant M. Pinto declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Note

We have included a table summarizing the major studies of olfaction in humans to date (Table 1), along with risk factors for olfactory loss that have come out of this work (Table 2). These are provided for reference for readers interested in this field of study.

olfactory decline has been shown to presage neurologic disease and to predict death itself [2]. Understanding the risk factors that underlie this important sensory condition, therefore, is of great interest. Analysis of existing data from human cohorts could identify interventions that would prevent, mitigate, or potentially reverse olfactory loss. Such information would have an enormous public health impact.

This epidemiologic review summarizes the definition of, characteristics that mark, and assessment of olfactory disorders in population studies. Using existing data, we describe their prevalence and discuss our knowledge of factors that underlie susceptibility to these disorders.

Types of olfactory disorders: definitions and characteristics

There are two major categories of olfactory disorders: the loss of olfactory ability and qualitative changes in olfactory perception. Diminished smell function is defined as hyposmia, and complete smell loss is defined as anosmia. These loses can be general to all odors, or they can be restricted to particular odorants (specific anosmias). Qualitative olfactory impairment is referred to as dysosmia, and may be divided into parosmia and phantosmia. Parosmia is defined by distorted odor perception in the presence of an odor source, usually unpleasant odors described as ‘foul’, ‘rotten’, ‘sewage’, or ‘burning’ smells, and often labeled as gasoline, chemical, tobacco, or coffee odors[3]. Phantosmia is defined by odor perception in the absence of an actual odor [4]. Leopold[5]defines phantosmia as “a sensation in either one or both nostrils that cannot be masked by foods.”

Assessment of olfactory disorders in population studies

There are many tests used for evaluation of olfactory function. In a recent review, 27 olfactory tests that are currently used clinically throughout the planet were discussed in detail, along with advantages and disadvantages of each [6].

The olfactory assessment most often used in the United States (US) for both clinical and research purposes is the University of Pennsylvania Smell Identification Test (UPSIT) [7]. This UPSIT is comprised by a booklet with 40 individual sheets that have microencapsulated beads impregnated with specific odors. The person being tested scratches a spot with a pencil to release the odor and then identifies the odor from a list of four options. The result is scored as number gotten correct. This type of smell assessment measures the ability to recognize and identify in words a particular odor, but does not measure the threshold (or sensitivity) to certain smells. Thus, this test relies on cognitive function for completion of the assessment. Screening versions of this test are often employed in large-scale studies; these contain 3 and 12 items, respectively, and the latter has been validated cross culturally in the USA, Europe, and Scandinavian countries [8, 9].

A cross-culturally modified original UPSIT, the Japanese version of the UPSIT (UPSIT-J) is also composed of 40 test odorants and 10 distractors; however, 11 test odorants and 5 distractors were replaced from the original version with those considered to be more familiar to the Japanese population. The UPSIT-J is effective in assessing olfactory function in the

Japanese population [10]. Researchers in other countries have made efforts to utilize or adapt the UPSIT for use in their cultural contexts[11], and age and gender norms are available.

Another commonly used olfactory test is the Sniffin' Sticks (SS)[12] test. The test battery includes assessment of odor identification, odor threshold, and odor discrimination, and is scored on a scale of 1 to 48. The odor identification portion consists of 16 common odorants, a multiple forced choice from four verbal choices per odorant, scored as number correct. The odor discrimination consists of 16 pairs of odorants presented with a third odor in a forced choice format where the participant has to select the different odor, also scored as number correct. The odor threshold component consists of 16 distinct dilutions typically administered by use of the staircase method, scored in reverse from 1 to 16. The test commences at one of the two weakest dilutions, chosen randomly, for determining the lowest concentration that the patient can reliably detect.

An alternative testing method is dynamic. Here, the interviewer modifies the concentrations that are presented tailored to the subject's previous responses. However, these processes are relatively complex and require some technician training. Also, the duration of this procedure can be long, limiting its use in population studies. The test is scored with age and gender norms.

The San Diego Odor Identification Test (SDOIT) is an odor identification test with eight common odors [13–15]. A picture array with the 8 test odorants and 12 distracters is used to aid the participant with identification. This also lets the respondent the opportunity to give nonverbal response to overcome any issues related to naming. If the respondent does not correctly identify an odorant, they are given the correct name of the odorant, and it is presented again, later in the test. The SDOIT score is the number of odorants correctly identified (0–8) after two trials. Olfactory impairment is defined as identifying fewer than 6 odorants correctly [13].

The Scandinavian Odor-Identification Test (SOIT) consists of 16 odors with 4 response choices each. Developed for Scandinavians, it has good test-retest and split-half reliability [16, 17]. This test is scored as number correct, and impairment is defined as10 to 12 for hyposmia and 9 or less for anosmia.

Recently, a fast, easy, and reliable method of assessing olfactory thresholds was reported for use in field studies. Kern et al. designed a 5-minute, in-home assessment of older adults (National Social Life, Health and Aging Project, NSHAP) and used it in to study a nationally representative sample of US home-dwelling older adults [18]. This test selected the 6 dilutions of n-butanol to target the expected distribution of thresholds in this age group: 0.13%, 0.25%, 0.50%, 2.0%, 4.0% and 8.0% (dilution steps 6, 5, 4, 2, 1 and 0 of the Sniffin' Sticks) (SS) threshold test, with comparable reliability.

Finally, the combined olfactory test (COT) is a feasible method for assessing the sense of smell in the Hong Kong Chinese population [19]. This test consists of an odor identification test involving nine odors and a threshold test for 1-butanol.

Unlike hearing or vision tests, which are reproducible across cultures and populations, there are no standard, internationally accepted procedures for assessing olfaction (other than of electrophysiologic methods-see below). A representative population sample may encompass a wide variety of ages and ethnicities, requiring a rapid, reliable assessment and a significant amount of time and financial resources. The tests we described above have been used for assessment of smell loss in different well-designed epidemiologic research studies in population-based samples. Nevertheless, comparison of studies is challenging because of the differences in methodology.

As an alternative to objective testing, assessment of olfaction by self-report has been used in some studies. These include questionnaires [20] or simple yes/no responses to a question such as “Do you have problems with your sense of smell?”[13]. A visual analog scale is also used in some studies to provide information on the magnitude of the problem the participant has with their sense of smell [21]. However, the correlation of self-reported olfactory function and objective measures is generally poor [22]. The factors that influence this disconnect are unknown. Ratings of intensity of odors and pleasantness have also been performed.

Finally, electrophysiologic measures are often used in the research setting [23]. These are logistically and technically challenging and are not suitable for population research and therefore will not be discussed here.

Available major epidemiologic studies of olfaction

We will now briefly review major population studies of the epidemiology of olfactory disorders.

The prevalence of olfactory disorders

The prevalence of olfactory disorders has been measured in several studies. The prevalence of self-reported smell loss varies between 1.4% and 15.3% across these studies. Based on objective olfactory assessment, population-based studies of olfactory loss indicate that the prevalence of smell dysfunction varies between 2.7 and 24.5% (depending on age range and other study differences). These data suggest that there is a relatively high prevalence of olfactory impairment. Differences in prevalence across these studies may have several reasons:

1. Self-report generally underestimates olfactory impairment[13]. In population-based studies, the prevalence of self-reported smell impairment is lower than the prevalence determined using testing. Self-reported smell function may not be a sensitive indicator of objectively measured olfactory impairment, something that might be especially true in mild cases [24]. People may tune their self-rated assessment to reflect age-adjusted perception of where they think they should be performing. Also, older adults often ignore a slow, gradual decline in odor sensitivity. On the other hand, previously reported low sensitivities of self-reported smell alterations might due to the fact that some studies used a single question, which simply asked participants to rate their current smell ability [13]. As previously demonstrated, self-reported measures that as the question in terms

of age context show a better correspondence with measured moderate to severe dysfunction [24]. These current National Health and Nutrition Examination Survey (NHANES) prevalence estimates are higher than 1994 National Health Interview Survey (NHIS) estimates—the latter queried only about "chronic" taste or smell problems (lasting ≥3 months) during the preceding year. In the most recent NHANES study, asking about smell loss with age produced a higher prevalence (17%) than asking about a problem within the past year [25]. Either way, self-report does get at perceived smell loss, a phenotype that remains useful.

2. Unlike hearing or vision tests, the tests for measuring smell and taste loss are not based upon standard, accepted procedures. A standard method used across global populations is very difficult to achieve. Such a test would need to span cultural differences in familiarity of smells as well as language barriers. Additionally, the needs of young children those who are cognitively impaired, must be taken into account. Thus, the literature is full alternative methods for measuring smell and taste loss.

3. Population differences in olfaction may have many inputs. Differences in exposures, activity, diet, and many other factors may explain why some epidemiologic studies have identified differences in ability among specific subpopulations (e.g., middle age and up populations in the Beaver Dam study and Japanese-American males in the Honolulu Asia Aging Study (HAAS), or African Americans in the NSHAP). Some epidemiologic studies are motivated by a need to understand a current illness or chronic condition, such as the Blue Mountains Eye Study and the Memory and Aging Project. This may color their findings as they apply to specific groups. Also, genetic diversity may explain some population differences in olfaction. Finally, the variable distribution of key differences in age range, gender, comorbidity, smoking, mental health, and other covariates (across a lifetime) may vary by country or region.

Major population studies

Skövde (Sweden)

The Skövde population study examined a random sample of 1900 adult inhabitants from the city population records of Skövde, Sweden, who were stratified by age and gender. Notably, the characteristics of this sample match the overall population of Sweden. In the olfaction component of the study, 1387 volunteers (73% of the full sample) were examined concerning their self-evaluation of their odor detection sensitivity (age range 20~80+ years, 51.77% women). The prevalence of self-reported worse-than normal odor detection sensitivity was 15.3%, and the prevalence of better-than normal odor detection sensitivity 17.4% [26]. Using the SOIT as an objective measure, the prevalence of olfactory dysfunction was 19.1%; 13.3% had hyposmia, and 5.8% suffered from anosmia [27]. In 2007, the study added 401 teenage inhabitants and assessed qualitative olfactory disorders. In this follow up study, 1,713 individuals (age range 13~80+ years, 52.13% women) agreed to participate, and the prevalence of parosmia (defined as a qualitative odor distortion, and often described as a foul, rotten, or burnt sensation, almost always unpleasant) was 3.9% (4.0% in adults and

3.4% in teenagers) by means of either a structured interview (adults) or a questionnaire (teenagers)[28]. These are some of the only data on the prevalence of this type of olfactory condition.

Beaver Dam (US)

The first large population-based study to report the prevalence of objective olfactory impairment in the US was performed on 2491 adults living in Beaver Dam, Wisconsin, and participating in the 5-year follow-up examination (1998–2000) of the Epidemiology of Hearing Loss Study (EHLS), an ongoing (1993 to present) population-based longitudinal study. Subjects comprised a middle-aged and elderly population (aged 53 to 97 years, 58% women). The mean (SD) prevalence of impaired olfaction was 24.5% (1.7%) assessed by the SDOIT, a figure that was much higher than that for self-reported smell impairment (9.5%). The prevalence increased with age: 62.5% of those over the age of 80 years had objective olfactory impairment. This study was perhaps the best-designed study of olfaction to date. However, the participants were primarily of non-Hispanic white race and homogenous in other ways, which may limit the generalizability of these data to minorities [13].

In a follow up investigation, the Beaver Dam Offspring Study (BOSS) (ages 21 to 84, 54.4% women) was a study of age-related sensory disorders in the adult children of participants in the EHLS. It examined the prevalence of olfactory impairment across spectrum of age in the general adult population. In this study, the prevalence of olfactory impairment was low at 3.8% in this primarily middle-aged cohort; increased with age (from 0.6% in those <35 years to 13.9% among those ≥65 years), but was more common in men than in women, similar to findings in older adults [29].

The National Health Interview Survey (NHIS) (US)

The National Health Interview Survey (NHIS) was administered to approximately 42,000 randomly selected households in 1994 (corresponding to 80,000 adults above 18 years of age). The NHIS assessed olfactory function by questionnaire. Adjusted estimates derived from this survey showed that 1.4% of US adults complained of an olfactory problem. The prevalence rates increased rapidly with age: almost 40% of those who reported a chemosensory problem were 65 years of age or older [30]. The relatively low prevalence rates are probably underestimate the actual prevalence, given the lack of objective testing.

Korea National Health and Nutrition Examination Survey (KNHANES) (South Korea)

Data from the 2009 Korea National Health and Nutrition Examination Survey (KNHANES) (ages 20–95 years, 56.7% women) showed that the prevalence of subjective olfactory disorders was 4.5% based on a self-reported olfactory questionnaire. This prevalence increased with age for both men and women. This was the first large population-based study to provide a clinical association between olfactory dysfunction and mental health [31]. To analyze the association between olfactory dysfunction and mental health such as depressive symptoms and suicidal thoughts in South Korea, using data from the 2010–2011 KNHANES, Joo et al. found that the prevalence of olfactory dysfunction was 5.0% (ages ≥ 19 years)[32].

The National Social Life, Health and Aging Project (NSHAP) (US)

The National Social Life, Health and Aging Project (NSHAP) is a nationally representative sample of older U.S. adults, with 3,005 community-dwelling adults aged 57–85, 56.7% women, studied in 2005–6 (Wave 1) and the same participants and their cohabiting partners studied again in 2010–11 (Wave 2) (n=2918) (http://www.norc.org/Research/Projects/Pages/national-social-life-health-and-aging-project.aspx). Olfaction was measured with a 5-item version of the SS (0–5 correct) in both Waves 1 and 2, and the olfactory threshold to n-butanol was measured by use of a modified method (described above) in Wave 2. NSHAP Wave 1 analyses showed that the prevalence of severe olfactory dysfunction was 2.7%[33]. Dysfunction was associated with increased age and in men, despite adjustment for differences in psychosocial and health conditions. Interestingly, African Americans were more likely than to experience olfactory impairment in adjusted analyses [34]. Perhaps the most striking information to come out of this work is that odor identification is one of the strongest predictors of 5-year mortality and that it may serve as a bellwether for slowed agig physiological processes or as a marker of environmental exposures [1].

Olfaction in Catalonia (OLFACAT) (Spain)

Using a creative method similar to a historic study of olfaction performed by National Geographic Magazine [35], the OLFACAT (Olfaction in Catalonia) survey studied the general population of Catalonia in Spain. Questionnaires on olfaction and health and a set of four microencapsulated odorants (rose, banana, musk, and gas) were distributed to the general population through a bilingual (Catalan, Spanish) newspaper in Catalonia in December 2003. From this, 9348 surveys were analyzed from the 10,783 returned. The respondents were aged 5 to 91 years, and 65.7% were women. Normosmia, hyposmia, and anosmia were defined as when participants detected, recognized, or identified all four, one to three, or none of the odors, respectively. For problems with detection, the overall prevalence of dysfunction was 19.4%, with anosmia being 0.3%. Olfaction was worse in men than in women across all ages. There was a significant age-related decline in odor detection; however smell recognition and identification increased up to the 30s and then declined in the 50s. Risk factors in this study for anosmia were: being a man, history of smell loss, and worse olfactory self-perception for detection; less education, poor self-perception and pregnancy for olfactory recognition; and older age, worse self perception, history of sustained head trauma, and smell loss for identification [36].

Honolulu-Asia Aging Study (HAAS) (US)

Recent neuropathologic advances suggest that the olfactory system may be one of the earliest brain regions involved in Parkinson's disease (PD) [37]. Olfactory deficits have been associated with the presence of incidental Lewy bodies in the brains of decedents without Parkinson's or dementia during life [38].

For examining the association of olfactory dysfunction with future development of PD, olfaction was assessed by use of the Cross-Cultural Smell Identification Test (CCSIT, 12-item modified UPSIT) in subjects who did not have clinical PD and dementia at baseline in the population-based, longitudinal HAAS (ages 71 to 95 years, all men). The odor identification scores were (0~5) 24.2%, (6~7) 22.7%, (8~9) 27.4%, and (10~12) 25.6%.

Approximately 75% of participants had scores of less than 10, indicative of impaired odor identification. Participants were followed for incidence of PD. HAAS showed that, after adjustment, the odds ratios for PD in the lowest quartile was 5.2 compared with the top two quartiles. Impaired olfaction predated clinical PD in men by at least 4 years and may be a method by which we could identify those at high risk for later development of PD[39].

Memory and Aging Project (MAP) (US)

The Rush Memory and Aging Project aimed to identify risk factors for Alzheimer's disease (AD) in a longitudinal cohort of older adults living in Northern Illinois [40]. Notable aspects of the study design include a detailed neuropsychological testing, collection of biomeasures including olfaction measured by use of the CC SIT, and requirement for participation of autopsy at death, with collection of brain specimens, allowing for neuropathologic analyses [41]. At the time, 481 participants completed at least one follow-up evaluation (mean age 80.6 ± 7.0 years, 72.6% women, 94.6% white and non-Hispanic); the prevalence of olfactory impairment in MAP was 55.3%[42], which is comparable to the rate of impaired odor identification performance (45.7%) described in prior research on olfaction in older adults without dementia [43]. MAP showed that difficulty in identifying familiar odors was highly correlated with AD pathology score in autopsied cases, and this effect was primarily due to the accumulation of neurofibrillar pathology in the central olfactory regions [44]. The authors also concluded that impaired olfactory performance might aid in the detection of underlying Lewy-body disease [45].

Blue Mountains Eye Study (Australia)

Olfaction was measured with the San Diego Odor Identification Test (SDOIT) among 1636 participants (age ≥60 years, 58.1% female) residing in and around Sydney, Australia, as part of the Blue Mountains Eye Study (2002–4). The prevalence of olfactory impairment was 27.0%. After multivariate adjustment, the likelihood of impaired olfaction increased twofold with each decade after 60 years and was higher in men than in women. Worse olfactory impairment was associated with a higher body mass index (BMI). Persons with PD who showed cognitive impairment had an increased likelihood of mild and moderate olfactory impairment [46]. The ability of these older adult to function and be independent was significantly impaired if they had smell dysfunction [47].

Betula (Sweden)

This study derived from the third wave of the Betula study and examined demographic and cognitive correlates of odor identification; 1906 healthy adults (age 45 to 90 years, 54.46% female) were assessed in a number of tasks which measured a variety of cognitive domains. These were: cognitive speed, semantic memory, and executive functioning. The study examined odor identification by using a modified version of the SOIT which differed from the original version so as to avoid ceiling effects. This study showed a linear deterioration in odor identification in adults across the life course. Overall, women identified more odors correctly than men did. Intrestingly, men and women in the the oldest age cohort (85–90 years) performed similarly[48].

Risk factors that have been associated with olfactory disorders

Age

Essentially all studies show that the prevalence of decreased olfactory function increases very significantly with age [26, 32, 34, 36]. Which portion of the age range that is included in the study affects this phenomenon. For example, smell recognition and identification declined after the sixth decade in the OLFACAT study [36]. In NSHAP, Pinto et al. found that the odds of poor odor identification increased 82% per decade of age in subjects aged 57 to 85 years [34]. A number of factors may explain these findings [49].

Gender

Like age, gender is a commonly identified risk factor for olfactory loss. Men are more likely to suffer from smell loss. As an example, in the Beaver Dam study, the odds of men having olfactory loss compared to women was 2.44, (95%CI 1.61–3.68)[29]. Indeed, men experience more smell loss earlier in life, perhaps due to increased likelihood of experiencing hazardous exposures [26, 27, 29, 34, 36, 50]. Other alternative explanations include the following: Hormonal differences may play a brain-protective role earlier in life, even after menopause. Estrogen and progesterone may have beneficial effects on stem cells in the peripheral or the central olfactory areas, which might retard subsequent losses after their levels decline [51, 52]. Nerve function more generally may decline more rapidly in men; for example, cognitive function declines faster in men than women [53].

However, not all studies have shown a relationship between gender and smell problems. For example, a significant difference was found between two genders in nearly every age subgroup, when the participants were categorized by decade of age [31] in the KNHANES. Nevertheless, consensus data suggests that the male gender is a major predictor of olfactory impairment.

Interestingly, a recent study found that women appear to have significantly more issues than men in terms of social and domestic disorders relating to olfactory loss [21]. This study aimed to characterize the consequences of olfactory disorders in the United Kingdom and supports the idea of gender differences in consequences of olfactory impairment. As a supporting example, about 60% of diagnoses for smell disorders were in women within two medical insurance claims populations [54]. This difference might be explained by the nature of managed-care settings where women are more likely to seek treatment, but also support a disparity in the burden of disease across genders.

Race

Small-scale studies have shown that African-Americans had lower UPSIT scores and age- and gender-adjusted percentile rank scores compared with Caucasians. Notably, these differences were significant only in the younger subjects [55]. Bolstering a potential difference in olfactory ability among populations, the 1986 National Geographic Smell Survey found that olfaction is not consistent or uniform among geographic regions. In contrast to other work, both male and female African respondents showed significantly

better detection than did American respondents [56]. Other than in these studies, there is little known about racial differences in olfaction.

Recently, the NSHAP showed that African Americans had substantially worse olfactory function compared with whites, twice the magnitude of gender differences, and comparable to aging 9 years [57] in adjusted analyses. Subsequent work looking at changes in olfaction over time has shown that African Americans in NSHAP are more likely to experience an initial olfactory decline [34]. Potential explanations for these findings include: differential environmental exposures and life experiences may interact with biological differences in the olfactory [57]. Neurodegenerative diseases are more prevalent and morbid among African Americans, which supports this study's findings [58].

Socioeconomic status

Financial Status—Although previous reports on the association between socioeconomic status and olfaction are limited [59], the Beaver Dam study showed that higher household income was associated with decreased odds of olfactory impairment (OR = 0.48, 95% CI 0.31–0.73>=$50 vs. <$50 K). This finding is consistent with extensive data showing that higher socioeconomic status is associated with better health. Those with higher income may have better access to health care or utilize health care at a higher rate [29]. An increased prevalence of olfactory impairment was also found in KNHANES, where it was significantly associated with lower income [31]. Perhaps surprisingly, the NSHAP found that no socioeconomic or health factors—several of which exhibit a cross-sectional association with olfactory function—were significantly associated with changes in olfactory function with time [34]. This may indicate differences in the effect of socioeconomic status on olfaction when one considers cross sectional versus longitudinal data (see below).

Education level—Both KNHANES and OLFACAT found that olfactory dysfunction was significantly associated with education level [32, 36]. For example, in OLFACAT, a low educational level was a risk factor for problems with smell detection, smell recognition/memory (middle school OR 1.2, 95% CI, 0.56–2.6; high school OR 0.84 95% CI, 0.72–0.97; university OR 0.93 95% CI, 0.83–1.04) and smell identification (middle school OR 0.49, 95% CI, 0.21–1.16; high school OR 1.01 95% CI, 0.88–1.15; university OR 1.21 95% CI, 1.09–1.34)[36].

Depression

A few studies showed that depression is associated with olfactory dysfunction [30, 32]. In the KNHANES, for example, the participants with olfactory dysfunction were at higher risk for a depressed mood (OR1.505, 95% CI, 1.106–2.048) and suicidal thoughts (OR 1.306, 95% CI, 1.027–1.662). Participants with olfactory dysfunction had a higher risk of mental disease than did participants without olfactory dysfunction, and this relationship persisted even after further adjustment for depressive mood [32]. In MAP, we found that more loneliness was associated with worse odor identification (OR per 1 SD, 0.78, 95% CI 0.69–0.88). Similarly, symptoms of depression were associated with worse olfaction among men (OR 0.58, 95% CI 0.37, 0.91). Although better global cognitive function was strongly associated with better odor identification (OR [per 1 SD] 2.15, 95% CI 1.86, 2.50). After controlling for multiple

factors, the associations with depression and loneliness were unchanged (Sivam A et. al, The University of Chicago, unpublished data). Interestingly, although not the focus of the NSHAP study, mental health did not affect the rate of change in olfactory function over 5 years [34].

Head trauma

Olfactory disorders related to head trauma can be present in as many as 15–30% of cases [6, 60]. Moreover, survey participants who reported head trauma had a higher risk of anosmia in the OLFACAT study [36]. There are several reasons for this association. Traumatic brain injury with injury to the region of the olfactory bulb or central olfactory areas could be a result of direct brain trauma. Peripherally in the nose, stretching or shearing of the olfactory nerves as they traverse the skull base may occur in the course of a sudden head contusion [61]. Finally, a decreased volume of the olfactory bulb may be caused by decreased sensory input [62]. We note that surgery to the nose or brain may induce similar “traumatic” changes to olfactory function.

Disease

Although many small-scale studies focused on specialized patients, there are some common diseases that were analyzed in the main studies. In the Beaver Dam study, a history of stroke and a history of epilepsy, and an ankle-brachial index (ABI) < 0.9, were associated with an increased prevalence of olfactory impairment. There was no association between olfactory dysfunction and general quality of life, symptoms of depression, or diet [13, 29]. Depressed mood (OR 1.50, 95% CI, 1.11–2.05) and suicidal thoughts (OR 1.31, 95% CI, 1.027–1.662] were associated with olfactory loss in the KNHANES (2010–2011) study [32]. The most common diseases associated with olfactory loss are prior upper respiratory tract infections [13], inflammatory sinonasal disease such as rhinitis [31, 32], chronic sinusitis [31], or nasal polyps [27, 29], which produce major congestion in the nose or frank obstruction [13]. These can impair airflow in the nasal airway, impeding odorant movement to the olfactory epithelium, and may also impair olfactory sensitivity directly via inflammatory effects on olfactory neurons. The effect may be short-term or permanent [63]. A recent study demonstrates that, even in the absence of mucosal disease on CT scan, a significant subset of patients with allergic rhinitis will exhibit hyposmia, mostly to a mild or moderate degree [64].

Endocrine Physiology

Although carefully controlled data are not available, endocrine physiology may influence olfaction in humans. For example, such changes including pregnancy [36], diabetes [13], and thyroid dysfunction [31] are associated with changes in olfactory function. Most of these data are clouded by self-report of olfactory problems, and, when they are age- and sex-adjusted there is conflicting results with diabetes and olfactory impairment [13]. As an example, diabetes mellitus appears to be associated with prevalence of anosmia (OR 2.6, 95% CI, 1.3–5.5 OR) in the Skövde study, although no relationship with the prevalence of olfactory dysfunction overall was found [27].

Environment

Toxins—Exposure to air pollution or chemical toxins that are aerosolized in the workplace can permanently damage the sense of smell [65]. Local exposures to toxins such as ammonia, gasoline, hairdressing chemicals, smoke, alcohol, and others can cause permanent smell disorders [66]. Due to the rare nature of some occupational toxic exposures, this information is generally gleaned from case series.

Smoking—Studies on the impact of the use of tobacco products on the sense of smell are not conclusive. Some studies have shown adverse effects on smell detection, identification, and intensity for some odors [13, 67]. For example, the Beaver Dam Offspring Study showed that smoking was associated with olfactory impairment only among women. In contrast, others have found no effect on smell detection and discrimination for other odorants [1, 27, 34].

The association between smoking and olfactory function might be the result of the effect of the chemicals present in cigarette smoke on the nasal epithelium [68], where some data suggest they are pro-inflammatory. However, smoking may also affect olfaction through its effects on the vascular system [67] as well, or via effects on the brain.

Air pollution—There is significant evidence that increased exposure to ambient air pollutants is associated with olfactory dysfunction. The most extensive work examining air pollution and olfaction was conducted in a comparison of residents of Mexico City, a city with notably high levels of air pollution, to residents of the nearby city of Tlaxcala, which reportedly has lower pollution levels. Control subjects (low pollution) performed significantly better in olfactory function tests compared to subjects from the high-pollution city [69]. Sorokowska et al. compared subjects from industrialized Germany to those from the Bolivian rainforest and found that the Tsimane' people of the rainforest had significantly better olfactory function than did Germans [70], which they suggested was related to differential pollution exposure (although many other confounding factors were not assessed).

Air pollution contacts the olfactory epithelium through inspiration, translocates from there to the olfactory bulb, and can migrate to the olfactory cortex. Air pollutants can be deposited at each location, causing direct damage and disruption of normal-tissue morphology, or inducing local inflammation and cellular stress responses. Formal studies on the epidemiology of air pollution have not yet been published, although the NSHAP has found an association of decreased olfactory function with increased $PM_{2.5}$ exposure in older adults (Pinto JM et. al, The University of Chicago, unpublished work).

Neurodegenerative disease and cognition

Olfactory loss has been closely linked to several neurodegenerative diseases, including AD [44], Lewy body disease [38, 45], and PD [39, 46], epilepsy, stroke [13], phobia [30], and cognitive impairment [46, 71], perhaps leading to central olfactory disorders. In support of these findings, olfactory impairment was associated with a worse performance on cognitive function tests. Each unit decrease in the SDOIT score was associated with a 1-second increase in the Trail Making Test (TMT-A) ($\beta = 1.3$, 95% CI 1.0–1.6, $p < .0001$) and

Grooved Pegboard (GPB) (β = 1.2, 95%CI 0.7–1.8, p < .0001) completion times and a 3 second increase in TMT-B (β = 3.3, 95%CI 2.3–4.3, p <0.0001) completion time in the multivariate models that included the whole cohort in the Beaver Dam Offspring Study[72]. Odor identification deficits occur in both AD and in mild cognitive impairment (MCI), and they predict clinical conversion from MCI to AD [73]. This is a complex topic; a full discussion is outside the scope of this review.

Mortality

Prediction of mortality has focused on disease and frailty. In the Blue Mountains Eye Study, 21.8% of participants with olfactory impairment died over the 5 years, compared with less than 10% of participants without olfactory loss. Moderate olfactory loss (SDOIT score ≤3) was associated with a 68% increased risk of all-cause mortality [71]. In the MAP, the association of olfactory dysfunction with mortality was examined without dementia or PD by use of a standard 12-item test of odor identification. The mortality risk was about 36% higher with a low score (6, 10th percentile) compared with a high score (11, 90th percentile), indicating that difficulty identifying familiar odors in old age is associated with increased risk of death [74]. In the NSHAP, olfactory function is strongly predicts death in 5 years. Mortality for anosmic older adults was four times that of normosmic individuals, whereas hyposmic individuals had in between mortality (p<0.001), this relationship was present across the age range. Anosmic older adults had more than three times the odds of death compared to normosmic individuals (OR 3.37, 95%CI 2.04–5.57), higher than any independent of known leading causes of death, and did not result from common mechanisms, indicating an independent effect [1].

Recently, Devanand et al. replicated this finding, even after controlling for dementia and medical comorbidity. The association between lower UPSIT score and increased mortality persisted after controlling for age, gender, education, ethnicity, language, modified Charlson medical comorbidity index, dementia, depression, alcohol abuse, head injury, smoking, body mass index, and vision and hearing impairment (HR = 1.05, 95%CI 1.03–1.07, p < 0.001) [73].

Dysfunction in cross-section vs. decline over time

To our knowledge, there are few longitudinal studies of olfactory function. In the Beaver Dam Offspring Study, Schubert et al. examined this question with data collected 5 years apart by use of the SDOIT. They found that, overall, 3.2% of participants had a decline in the SDOIT score at 5 years. In age- and sex-adjusted models, the mean intima media thickness (OR 1.17, 95%CI 1.01–1.34, per 0.1 mm) and the number of sites (range 0–6) with carotid artery plaque (OR 1.35, 95%CI 1.11–1.65, per site) at baseline were associated with an increased risk for decline. The plaque score (OR 1.24, 95%CI 1.01–1.53) was a significant independent predictor of olfactory decline in a multivariate model [67]. Pinto et. al collected 5-year follow-up data from NSHAP [34]. They also found that odor identification declined most rapidly among older individuals (p < .001) and in men (p = .005). By age 85, the probability of losing the ability to identify a specific odor over the next 5 years was high (between 0.29 and 0.45). Interestingly, African Americans declined more rapidly than did whites. Wehling et al. evaluated a longitudinal study on cognitive aging. They found a

similar age-related decline in olfactory performance, although odor identification showed a trend toward faster decline as people age. Women showed less decline compared with men, especially regarding determining if something was edibile [75]. In addition, for determination of the consequences—both health related and social—of olfactory loss, additional longer-term follow-up is needed, especially in diverse populations.

Summary

The study of incidence, prevalence, and risk factors for olfactory disorders in populations is important both for individuals and for the public at large. As with other sensory domains, age is a principal risk factor for smell impairment, although the precise risk factors that affect age-related loss of smell are not well characteized. Sex-specificity and race/ethnicity-specificity are also important factors. Educational level and social status affect olfaction, likely via general effects on health, but there is no consistent conclusion. Environmental factors seem to affect olfaction and are plausible causal players, as the nose is exposed directly. A growing body of evidence suggests that ambient-air pollution affects olfactory function.

Prior upper respiratory tract infections, nasal/sinus disease, and head trauma were the primary and the most common etiologies of olfactory loss in clinic-based studies, and epidemiologic studies support this. Studies focused upon specific subpopulations have shown that loss has also been closely linked to cognitive decline, particularly in neurodegenerative diseases, a relationship that needs further mechanistic work, but one with a large public health impact.

Conclusions

Olfactory disorders greatly compromise daily life. The current body of epidemiologic data suggests a significantly high prevalence of olfactory impairment in a wide variety of populations. Here, we have highlighted existing epidemiologic studies and discussed the risk factors for olfactory disorders. The adverse consequences of olfactory disorders and their high prevalence call for future research that will provide a better understanding of the pathogenesis and treatment of these disorders. However, epidemiologic studies primarily focused on chemosensory disorders are needed for the development and testing of approaches to preventing or delaying declines in sensory function with aging. Through major efforts in these areas, we can work toward significant progress in preventing, mitigating, or reversing the deleterious public health consequences of olfactory loss.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Results of studies of the epidemiology of olfactory disorders

Population	n	Age (range)	Gender (% Female)	Smell Test	Major findings	Strengths	Weaknesses	Reference
Skövde Sweden	1387	20–80 +	51.77 %	self-report, SOIT	-poorer-than normal odor detection sensitivity was 15.3% (self-report) -the prevalence of olfactory dysfunction was 19.1%; 13.3% had hyposmia and 5.8% suffered from anosmia	population-based data across all ages; representative of the general adult Swedish population	self-report	26; 27
Skövde Sweden	1713	13–80 +	52.13 %	self-report	=3.9% of the general population aged 13 years and older report having had parosmia (4.0% of the adults and 3.4% of the teenagers).	added a teenage population; assessed qualitative disorders	teenage data may be less reliable?	28
The Beaver Dam Study WI, USA	2491	53–97	58%	SDOIT	-prevalence of impaired olfaction was 24.5%	extensive information available on potential risk factors	limited generalizability to minority groups?	13
The Beaver Dam Offspring Study WI, USA	1993	21–84	54.4%	SDOIT	-prevalence of olfactory impairment was low at 3.8% in this primarily middle-aged cohort -this increased with age (from 0.6% in those <35 years to 13.9% among those ≥65 years)	one of the few longitudinal studies extensive information available on potential risk factors	may not be representative?	29
National Health Interview Survey (NHIS) USA	80,000	≥18	*	home interview	-1.4% of US adults complained of	large sample	likely underestimates actual prevalence due to self-report?	30

Population	n	Age (range)	Gender (% Female)	Smell Test	Major findings	Strengths	Weaknesses	Reference
					an olfactory problem -almost 40% of those who reported a chemosensory problem were ≥65 years			
KNHANES South Korea (2009)	7306	20–95	56.7%	questionnaire	-prevalence of subjective olfactory disorders was 4.5%	large sample provided a clinical association between olfactory dysfunction and mental health	self-report, not strictly controlled	31
KNHANES South Korea (2010–201 1)	11972	≥19	50.74 %	questionnaire	-prevalence of olfactory dysfunction was 5.0%	large sample provided a clinical association between olfactory dysfunction and mental health	unable to distinguish degrees of smell disturbance; cross-sectional	32
NSHAP, USA	3005	57–85	56.7%	Odor ID test	-prevalence of severe olfactory dysfunction was 2.7%	nationally representative sample	only a small percentage of the variance is explained	33
NSHAP, USA	1436	57–85	51.7%	Odor ID test	-odor identification is one of the strongest predictors of 5-year mortality	well controlled	no cause of death, no information on younger ages, acquired causes	1
OLFACAT Catalonia, Spain	9348	5–91	65.7%	Odor ID test	-prevalence of dysfunction was 19.4% - a significant age-related decline in odor detection	large sample	potential bias in this non-random sample; lack of ethnic diversity, socio-cultural class	36
Memory and Aging Project (MAP) IL, USA	481	mean age 80.6 ± 7.0	72.6%	CC-SIT	-prevalence of olfactory impairment was 55.3% -impaired odor identification in old age is associated with impaired global cognition	high rate of participation in follow-up outstanding cognitive assessment	select cohort of convenience; fewer women included	42
Memory and Aging Project (MAP) IL, USA	1162	mean age 79.7 ± 7.7	74.5%	CC-SIT	-difficulty identifying familiar odors in old age is associated with	well characterized cohort	select cohort; fewer women included	45

Population	n	Age (range)	Gender (% Female)	Smell Test	Major findings	Strengths	Weaknesses	Reference
					increased risk of death			
Blue Mountains Eye Study Australia	1636	≥60	58.1%	SDOIT	-prevalence of olfactory impairment was 27.0%.	high participation rate high follow-up rate	cross-sectional, potential bias?	46
Bet.ula Sweden	1906	45–90	54.46 %	SOIT	-a gradual/ linear deterioration in cued odor identification across the adult life span	good demographic and cognitive variables, sample size	cross-sectional	48
Honolulu-Asia Aging Study (HAAS) HI, USA	2267	71–95	0%	CCSIT	-olfactory deficits associated with the presence of incidental Lewybodies and PD	longitudinal design, large sample size with excellent follow-up, well-validated test instruments	men only; older age focused	39

* not provided

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Table 2

Key results/covariates from current knowledge about epidemiology of olfactory disorders

Population	Demographic Risk Factors			Other Risk Factors	Results Showing No Effects	References
	age	gender	race			
Skövde Sweden	age	men *	-	-	-	26
Skövde Sweden +	age	men	-	nasal polyps	diabetes mellitus, smoking: current smoking number of pack-years	27
Skövde Sweden #	age	/	-	nasal polyps diabetes mellitus	smoking	
Skovde Sweden ^	age	/	-			28
The Beaver Dam Study WI, USA	age	men	-	current smoking nasal congestion or URI history of stroke history of epilepsy	prior smoking	13
The Beaver Dam Offspring Study WI, USA	age	men	-	nasal conditions ABI < 0.9 household income history of smoking (in women)	history of: head injury epilepsy allergies carotid IMT cooking fuel quality of life dietary choice depressive symptoms	29
National Health Interview Survey (NHIS) USA	age	/	/	trouble with hearing other limitations (all) depression phobia	trouble with vision	30
KNHANES South Korea (2009)	age	/	-	low income habitual exposure to air pollutants history of hepatitis B rhinitis chronic sinusitis	blood and urine test results	31
KNHANES South Korea (2010–2011)	age	/	-	alcohol consumption waist circumference job education level rhinitis depressed mood suicidal ideation	smoking routine exercise BMI psychological counseling,	32
NSHAP USA	age	men	-	lower level of education BMI	depressive symptoms	33
NSHAP USA	age	men	African America ns		socioeconomic status health conditions cognition mental health alcohol use smoking	34
OLFACAT Catalonia, Spain $	age	men	-	smell detection: low educational level, poor self-perception	smell recognition: smoking exposure to noxious substances	36
				smell recognition: low educational level poor self-perception loss of smell history		
				smell identification: poor self-perception low educational level		

Population	Demographic Risk Factors			Other Risk Factors	Results Showing No Effects	References
				loss of smell history		
OLFACAT Catalonia, Spain[&]	age	men	-	smell detection: loss of smell history poor self-perception	smell recognition: smoking exposure to noxious substances	
				smell recognition: low educational level poor self-perception pregnancy		
				smell identification: poor self-perception history of head trauma loss of smell history		
Memory and Aging Project (MAP) IL, USA	age	/	-	perceptual speed episodic memory	education semantic memory, working memory, visuospatial ability	42
Blue Mountains Eye Study Sydney, Australia	age	men	-	mild olfactory impairment: current nasal congestion smoking BMI >30 cognitive impairment PD	mild olfactory impairment: GFR, stroke, epilepsy hypercholesterole mia stage II hypertension diabetes	46
				moderate olfactory impairment: current nasal congestion, cognitive impairment Parkinson's disease GFR <30, stroke epilepsy hypercholesterole mia stage II hypertension	moderate olfactory impairment: smoking, BMI diabetes	
Betula Sweden	age	men	-	education cognitive speed vocabulary	-	48
Honolulu-Asia Aging Study (HAAS) HI, USA	age	men	-	PD smoking less frequent bowel movements excessive daytime sleepiness lower CASI score	-	39

[*] for poorer than normal smell

[+] prevalence of olfactory dysfunction

[#] prevalence of anosmia

[^] prevalence of parosmia

[/] no significant association

[$] for hyposmia

[&] for anosmia

PD Parkinson's Disease

GFR Glomerular Filtration Rate

Curr Otorhinolaryngol Rep. Author manuscript; available in PMC 2019 January 03.

CASI Cognitive Abilities Screening Instrument

BMI Body Mass Index

ABI Ankle-Brachial Index