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Research Paper

Variables associated with olfactory disorders in adults: A U.S. population-based analysis

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Abstract *Objective:* Olfactory dysfunction is known to have significant social, psychological, and safety implications. Despite increasingly recognized prevalence, potential risk factors for olfactory loss have been arbitrarily documented and knowledge is limited in scale. The aim of this study is to identify potential demographic and exposure variables correlating with olfactory dysfunction.
Methods: Cross-sectional analysis of the 2011–2012 and 2013–2014 editions of the National Health Examination and Nutrition Survey was performed. The utilized survey reports from a nationally representative sample of about 5000 persons each year located in counties across the United States. There is an interview and physical examination component which includes demographic, socioeconomic, dietary, and health-related questions as well as medical, dental, physiologic measurements, and laboratory tests. 3594 adult respondents from 2011 to 2012 and 3708 respondents from 2013 to 2014 were identified from the above population-based database. The frequency of self-reported disorders as well as performance on odor identification testing was determined in relation to demographic factors, occupational or environmental exposures, and urinary levels of environmental and industrial compounds.
Results: In both subjective and objective analysis, smell disorders were significantly more common with increasing age. While the non-Hispanic Black and non-Hispanic Asian populations

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were less likely to report subjective olfactory loss, they, along with Hispanics, performed more poorly on odor identification than Caucasians. Those with limited education had a decreased prevalence of hyposmia. Women outperformed men on smell testing. Those reporting exposure to vapors were more likely to experience olfactory dysfunction, and urinary levels of manganese, 2-Thioxothiazolidine-4-carboxylic acid, and 2-Aminothiazoline-4-carboxylic acid were lower among respondents with subjective smell disturbance. In odor detection, elevated serum levels of lead and urinary levels of 2,4 dichlorophenol were associated with anosmia and hyposmia, respectively.

Conclusions: This study provides current, population-based data identifying demographic and exposure elements related to smell disturbances in U.S. adults. Age, race, gender, education, exposure to vapors, urinary levels of manganese, 2-Thioxothiazolidine-4-carboxylic acid, 2-Aminothiazoline-4-carboxylic acid, 2,4 dichlorophenol, and serum lead levels were all implicated in smell disturbance. Care should be taken in interpretation due to lack of consistency between subjective and objective measures of olfaction as well as limitations related to population-based data. Prospective trials are indicated to further elucidate these relationships.

Introduction

Olfactory dysfunction is an increasingly recognized affliction that carries with it significant social, psychological, and safety implications.[1,2] Despite recent data suggesting that smell disorders may affect more than 10% of the population in the United States, knowledge regarding risk factors remains relatively sparse.[3] Decreased olfactory performance has frequently been reported with increasing age.[4–7] In the Swedish population, male gender and nasal polyposis correlated significantly with olfactory dysfunction.[8] A large German study of 1240 patients in an outpatient Otolaryngology clinic additionally suggested a gender difference, demonstrating that women performed notably better on an odor identification test.[9] Recent analyses of the United States population using the National Health and Nutrition Examination Survey (NHANES) have also implicated older age, male gender, as well as lower socioeconomic status and limited educational attainment in olfactory loss.[10,11] Few studies, however, have investigated the role of environmental and occupational exposures in smell disorders. Our aim, therefore, is to present a thorough epidemiology of olfactory dysfunction relating demographic, disease, and especially exposure variables to elucidate any associations.

Methods and data analysis

The NHANES is a program of the National Center for Health Statistics (NCHS), a component of the Center for Disease Control (CDC). The NHANES interview includes demographic, socioeconomic, dietary, and health-related questions, while the examination component consists of medical, dental, and physiological measurements, as well as laboratory tests. In the 2011–2012 edition, a section on taste and smell was introduced to the questionnaire data. In the 2013–2014 edition, an odor and taste identification test was also included in the examination data. Adults of both genders aged 40 + were eligible to participate. No exclusions were made for this portion of the questionnaire. To carry out our analysis, responses to the presence of olfactory disturbance were tabulated with selected demographic and laboratory data. This study was reviewed by our hospital's Institutional Review Board and deemed to be exempt from review due to information being part of the public record.

For the 2011–2012 dataset, the desired cohort was identified based on responses to the question "*During the past 12 months, have you had a problem with your ability to smell, such as not being able to smell things or things not smelling the way they are supposed to*?" Respondents were excluded if a response was not provided. Relationships between self-reported smell disturbance in the prior 12 months were first established with the following demographic and socio-economic variables: gender (male, female), age (years), body mass index (BMI, kg/m^2), race (non-Hispanic white, Mexican American, Other Hispanic, Non-Hispanic Black, Non-Hispanic Asian, other race – including multi-racial), active military service (yes, no), annual household income ($20,000 and over, less than $20,000, refused, did not know, missing), and highest level of education (college graduate or above, some college or associates degree, high school graduate or equivalent, 9th–11th grade including 12th grade without diploma, less than 9th grade).

Exposure variables consisted of subjective and objective comparisons of multiple environmental and occupational-related exposures obtained from self-reported questionnaire data and laboratory blood and urine values. Subjective self-reported exposure variables included cigarette smoking (current, occasional or never cigarette smoking; number of years smoking cigarettes, number of cigarettes per day, number of cigarette smoking pack years, number of household cigarette smokers; occupational cigarette smoking exposure), mineral dust, organic dust, exhaust

fumes, vapors including paint, cleaning products, glues, solvents, acids, and welding/soldering fumes. Objective environmental and occupational-related exposures were ascertained from laboratory blood and urine samples. Exposures included elemental metals, phenols and parabens, environmental pesticides, volatile organic compounds (VOC) and their metabolites, phthalates and plasticizers, and polyaromatic hydrocarbons. A detailed description of laboratory procedures and collection methods can be found on the Centers for Disease Control and Prevention website www.cdc.gov/nchs/nhanes.htm.

As the primary outcome variable (smell disorder) was considered dichotomous, the analytic cohort was stratified into respondents affirming or refuting an existing smell disorder. Demographic, socio-economic variables and subjective categorical environmental and occupational-related variables were summarized using relative column proportions and corresponding standard errors. Continuous exposure variables were summarized by arithmetic mean if normally distributed, and geometric mean if notable skewedness was observed. A Logistic regression model was constructed to evaluate the effect of demographic, socio-economic, subjective and objective environmental and occupational-related exposures on the likelihood of reporting smell disorder. Odds ratios and corresponding 95% confidence intervals were reported. Confidence intervals that did not include 1 (*i.e.* null relationship) were considered statistically significant. Odds ratios for categorical explanatory variables were interpreted as the proportional likelihood of smell disorder between categories, relative to the reference group. Odds ratios for continuous explanatory variables (*i.e.* objective environmental and occupational-related exposures measured from laboratory blood and urine samples) were interpreted as the proportional likelihood of smell disorder for a single-unit increase in exposure values. Non-normally distributed continuous exposure variables were transformed logarithmically to construct the logistic regression model, if the assumption of normal distribution was violated. Given the NHANES sampling design, all statistics reported accounted for sampling units, strata and sampling weights. Statistical analysis was performed using STATA/IC 14.0 (StataCorp LP, Texas, USA, 2015).

From the 2013—2014 dataset, respondents were identified based on responses to an 8-item odor identification test (Pocket Smell Test™, Sensonics, Inc., Haddon Heights, NJ). Respondents were categorized into 3 groups based on correct responses: anosmia (0—3), hyposmia (4—5) and normosmia (6—8). Relationships between anosmic, hyposmic and normosmic participants were established with the following demographic and socio-economic variables: gender (male, female), age (years), race (non-Hispanic white, Mexican American, Other Hispanic, Non-Hispanic Black, Non-Hispanic Asian, other race — including multiracial) and education (less than or greater than high school graduate). Exposure variables consisted of objective laboratory examinations of chemical and metabolite levels obtained from blood and urine values. Exposures again included elemental metals, phenols and parabens, environmental pesticides, VOCs and their metabolites, phthalates and plasticizers, and polyaromatic hydrocarbons.

Statistical analysis was performed using STATA/IC 14.0 (StataCorp LP, Texas, USA, 2015). Given the NHANES complex sampling design, all statistics reported accounted for sampling units, strata and sampling weights. Relationships between anosmia, hyposmia and normosmia were assessed using the chi-square test. Logistic regression models were constructed to evaluate the likelihood of 1) anosmia *versus* normosmia and 2) hyposmia *versus* normosmia, given the explanatory variables described above. Normosmic respondents were considered as the reference outcome. Odds ratios and corresponding 95% confidence intervals were reported. Confidence intervals that did not include 1 (*i.e.* null relationship) were considered statistically significant. Odds ratios for categorical explanatory variables were interpreted as the proportional likelihood of smell disorder between categories, relative to the reference group. Odds ratios for continuous explanatory variables (*i.e.* chemical and metabolite levels measured from laboratory blood and urine samples) were interpreted as the proportional likelihood of smell disorder for a single-unit increase in exposure values.

Results

The 2011—2012 NHANES respondent cohort included 9756 respondents, 3594 of which were administered the Taste and Smell Questionnaire and were included in the ensuing analysis. The 2013—2014 NHANES cohort include 10,175 participants, 3708 of which were administered an odor detection test and included in the subsequent data.

Subjective assessment of olfactory dysfunction in the 2011—2012 group revealed the incidence of reported smell disturbances was not significantly different between male and female respondents (*OR* 1.249, 95% *CI* 0.917—1.700). Body Mass Index (BMI), military service, household income, and level of education also did not demonstrate a significant correlation with olfactory dysfunction. Non-Hispanic Black and Non-Hispanic Asian ethnicities were less likely to suffer from olfactory loss (*OR* 0.570 with 95% *CI* 0.384—0.847, *OR* 0.441 with 95% *CI* 0.253—0.770, respectively). There was additionally a significant decrease in smell with advancing age, for which the *O*R was 1.061 for each 5-year incremental increase in age (95% *CI* 1.003—1.123) (Table 1).

Across all related response categories, smoking was not significantly associated with subjective olfactory dysfunction. Active smokers did not demonstrate a higher prevalence of subjective smell disturbance than non-smokers. Number of cigarettes per day as well as number of pack years was also not associated with changes in smell. Additionally, second hand exposure to smoke from household or workplace sources was not a significant factor, and was not influenced by increasing the number of smokers. Smell disorders were not more prevalent in respondents exposed to mineral dust, organic dust, or exhaust fumes. However, those who reported exposure to vapors from paints, cleaning products, glues, solvents, acids, or welding/soldering fumes were more likely to have experienced olfactory disturbance in the last 12 months (*OR* 1.480, 95% *CI* 1.092—2.007). The length of exposure was not significantly different between those with and without subjective smell loss.

Table 1 Demographic factors in respondents with and without self-reported olfactory dysfunction from respondents participating in the 2011–2012 NHANES.

Category	Variable	Normal *(Refutes problem with smell in past 12 months)* % (*SE*)	Smell Disorder *(Affirms problem with smell in past 12 months)* % (*SE*)	Odds Ratio (95% *CI*)
Gender				
	Female			Reference
	Male	53.5 (1.2)	47.2 (4.1)	1.249 (0.917–1.700)
Age				
	40–44 years	15.5 (1.6)	7.7 (2.2)	**1.061 (1.003–1.123)***
	45–49 years	14.3 (0.7)	19.4 (3.5)	
	50–54 years	15.7 (1.2)	12.5 (2.7)	
	55–59 years	14.9 (0.9)	12.7 (3.1)	
	60–64 years	12.4 (0.9)	16.6 (3.7)	
	65–69 years	8.3 (0.8)	10.8 (2.9)	
	70–74 years	7.7 (0.6)	4.3 (1.3)	
	75 + years	11.2 (0.6)	15.9 (2.6)	
Race				
	Non-Hispanic White	70.8 (3.8)	77.2 (4.9)	Reference
	Mexican American	5.5 (1.3)	4.3 (1.6)	0.715 (0.378–1.354)
	Other Hispanic	5.5 (1.4)	5.2 (2.2)	0.857 (0.477–1.542)
	Non-Hispanic Black	11.2 (2.5)	7.0 (1.9)	**0.570 (0.384–0.847)**
	Non-Hispanic Asian	4.9 (0.9)	2.4 (0.7)	**0.441 (0.253–0.770)**
	Other Race – Including Multi-Racial	2.1 (0.4)	4.0 (1.7)	1.748 (0.740–4.130)
Education Level				
	College graduate or above	31.1 (2.8)	27.6 (4.2)	Reference
	Some college or associates degree	29.2 (1.6)	31.4 (3.8)	1.207 (0.753–1.936)
	High school graduate or equivalent	21.1 (1.6)	24.5 (4.5)	1.303 (0.818–2.075)
	9th –11th grade (Includes 12th grade with no diploma)	11.4 (1.5)	11.6 (2.5)	1.141 (0.759–1.716)
	Less than 9th grade	7.2 (0.7)	4.9 (1.4)	0.771 (0.444–1.339)

Significant values in bold (%) – relative column frequency adjusted with sampling weights provided by NHANES; SE: standard error; 95% *CI*: 95% confidence interval; *: odds ratio of smell disorder per 5-year increase in age.

There was no difference in levels of urinary arsenic, or serum cadmium, lead, mercury, or selenium between those who did and did not report smell disturbance. However, the serum level of manganese was significantly lower in those with subjective olfactory dysfunction (*OR* 0.949, 95% *CI* 0.921–0.977). Urinary levels of phenols and parabens did not correlate significantly with changes in olfaction. Pesticide levels in urine were additionally not different between the two groups of respondents. Similarly, none of the phthalates, plasticizers, or polyaromatic hydrocarbons was present in higher quantities in those with smell disturbance.

Levels of two of the volatile organic compounds (VOC), 2-Thioxothiazolidine-4-carboxylic acid (2T4CA) and 2-Aminothiazoline-4-carboxylic acid (2A4CA), were lower among respondents who reported olfactory dysfunction (*OR* 0.663, 95% *CI* 0.484–0.907 and *OR* 0.710, 95% *CI* 0.547–0.922, respectively). The remainder of the VOCs did not demonstrate any significant correlation with olfactory loss (Table 2).

In the odor detection test administered to the 2013–2014 group, increasing age was again significantly associated with olfactory loss beginning in the 6th decade of life. Those greater than 80 years of age demonstrated an especially high prevalence of anosmia (*OR* 26.111, 95%*CI* 11.783–57.861) and hyposmia (*OR* 9.288, 95%*CI* 7.265–11.873) compared with younger cohorts. Men were more likely than women to be anosmic (*OR* 2.442, 95%*CI* 1.583–3.767). Contrary to subjective reports, the non-Hispanic Black (*OR* 1.574, 95% *CI* 1.125–2.2), non-Hispanic Asian (*OR* 1.955, 95%*CI* 1.2–3.187), and other Hispanic (*OR* 1.539, 95%*CI* 1.054–2.248) populations carried a greater likelihood of hyposmia as compared with Caucasians. Those who did not complete high school were less likely to experience hyposmia (*OR* 0.381, 95%*CI* 0.274–0.529) (Table 3).

Among the metals, an elevated serum lead level was the only compound associated with anosmia (*OR* 1.33, 95%*CI* 1.135–1.559). Elevated urinary levels of 2,4 dichlorophenol were also detected in respondents with hyposmia (*OR* 1.022, 95%*CI* 1.007–1.037). No other chemical exposures analyzed showed a higher prevalence of olfactory dysfunction (Table 4).

Table 2 Exposures in respondents with and without self-reported olfactory dysfunction from respondents participating in the 2011–2012 NHANES.

Variable	Normal *(Refutes problem with smell in past 12 months)* % (*SE*)	Smell Disorder *(Affirms problem with smell in past 12 months)* % (*SE*)	Odds Ratio (95%*CI*)
Ever had work exposure to vapors from paints, cleaning products, glues, solvents, acids or welding/soldering fumes?	30.1 (1.7)	38.9 (3.5)	**1.480 (1.092–2.007)**
Blood Manganese (ug/L)	9.06 (0.07)	8.73 (0.12)	**0.949 (0.921–0.977)**
Urinary 2-Thioxothiazolidine-4-carboxylic acid (ng/mL)	10.73 (0.59)	6.89 (0.85)	**0.663 (0.484–0.907)**
Urinary 2-Aminothiazoline-4-carboxylic acid (ng/mL) ^{GM}	104.05 (5.85)	72.92 (8.10)	**0.710 (0.547–0.922)**

Significant values in bold (%) – relative column frequency adjusted with sampling weights provided by NHANES; SE: standard error; 95% *CI*: 95% confidence interval.

Table 3 Comparison of demographic variables with anosmia scores (0–3), hyposmia scores (4–5) and normosmia scores (6–8) from respondents participating in the 2013–2014 NHANES.

Category	Variable	Anosmia Scores (0–3) *versus* Normosmia Scores (6–8) Odds Ratio (95% *CI*)	Hyposmia Scores (4–5) *versus* Normosmia Scores (6–8) Odds Ratio (95% *CI*)
Age	40–49 years	Reference	
	50–59 years	0.990 (0.441–2.221)	1.402 (0.923–2.129)
	60–69 years	**2.811 (1.07–7.284)**	**2.069 (1.302–3.287)**
	70–79 years	**7.165 (2.987–17.187)**	**3.371 (2.221–5.118)**
	80 + years	**26.111 (11.783–57.861)**	**9.288 (7.265–11.873)**
Gender	Female	reference	
	Male	**2.442 (1.583–3.767)**	1.319 (0.937–1.857)
Race	Non-Hispanic White	Reference	
	Mexican American	0.534 (0.243–1.170)	1.483 (0.835–2.633)
	Other Hispanic	0.828 (0.298–2.299)	**1.539 (1.054–2.248)**
	Non-Hispanic Black	1.593 (0.807–3.145)	**1.574 (1.125–2.2)**
	Non-Hispanic Asian	1.420 (0.682–2.955)	**1.955 (1.2–3.187)**
	Other	0.141 (0.015–1.297)	0.939 (0.344–2.559)
Less than high school graduate	No	Reference	
	Yes	0.672 (0.395–1.144)	**0.381 (0.274–0.529)**

Significant values in bold (%) – relative column frequency adjusted with sampling weights provided by NHANES; 95%*CI*: 95% confidence interval.

Discussion

This study endeavors to highlight the epidemiology of olfactory disorders and identify potential correlative variables via analysis of both self-reported and objective measures of smell loss. Participants in both the 2011–2012 questionnaire and the 2013–2014 odor detection test demonstrated a significantly higher prevalence of subjective olfactory dysfunction with advancing age. This finding is consistent with previous U.S. survey data collected by the NIH in 1994, which demonstrated a significant increase in the prevalence of smell disorders over each decade beyond

Table 4 Comparison of exposure variables with anosmia scores (0–3), hyposmia scores (4–5) and normosmia scores (6–8) from respondents participating in the 2013–2014 NHANES.

Variable	Anosmia Scores (0–3) *versus* Normosmia Scores (6–8) Odds Ratio (95% *CI*)	Hyposmia Scores (4–5) *versus* Normosmia Scores (6–8) Odds Ratio (95% *CI*)
Blood lead (ug/dL)	**1.330 (1.135–1.559)**	1.032 (0.873–1.22)
Urinary 2,4-Dichlorophenol (ug/L)	1.027 (0.997–1.057)	**1.022 (1.007–1.037)**

Significant values in bold (%) – relative column frequency adjusted with sampling weights provided by NHANES; 95%*CI*: 95% confidence interval.

the age of 55.[6] Several additional studies have also corroborated the decline in chemosensory function in the aging population, likely due to cumulative damage from environmental insults as well as structural and functional changes related to neurodegenerative disorders and the general aging process.[4,12,13] A decrease in self-reported smell disturbance was also noted in the non-Hispanic black and non-Hispanic Asian populations; however, these populations, in addition to the Hispanic group, all performed worse on objective smell testing as compared with their Caucasian cohorts. Previous U.S. population based analysis reported no difference in the prevalence of olfactory dysfunction among White, Black, and Hispanic populations.[6] Contrarily, Doty et al[14] in 1985 and Jones et al[15] in 1995 both reported that Caucasian cohorts outperformed African American cohorts in the University of Pennsylvania Smell Identification Test (UPSIT). Some authors have suggested that health and socioeconomic disparities as well as an increased likelihood of toxin exposure in the home and workplace may be implicated.[16] Overall, however, racial disparities in olfaction are inconsistent in the available literature and the justification for these found in the current analysis lacks explanatory evidence.

Exposures that did carry a significant association with subjective olfactory dysfunction were vapors conveyed by paints, cleaning products, glues, solvents, acids, and welding/soldering fumes. In an attempt to decipher individual compounds portending this risk, further analysis was performed with all exposure variables quantified in the NHANES 2011—2012 database, including elemental metals, pesticides, phenols, parabens, VOCs, phthalates, plasticizers, and hydrocarbons. Interestingly, none of these were found to be elevated in respondents reporting smell disturbance. In fact, serum levels of manganese and urinary levels of 2T4CA and 2A4CA were significantly higher in those with subjectively normal smell, suggesting a correlation with increased sensitivity of the olfactory system.

Though sparse, the available literature regarding manganese and its effect on olfactory function is divided. It is well known that manganese is readily absorbed by the olfactory epithelium and is transported via the olfactory bulb into the olfactory cortex and other regions of the brain.[17,18] Extensive study of inhabitants of Valcamonica, Italy, a region impacted by manganese from ferroalloy plant emissions, indicates that exposure leads to decreased odor identification.[19] Intranasal application of manganese in rats also showed a reduction of odor-related behaviors in a dose-dependent fashion.[20] However, consistent with our analysis, Antunes et al,[21] as a component of the San Francisco/Oakland Bay Bridge Welder Study, found that welders with higher levels of blood manganese exhibited better olfactory function than those with lower levels based on UPSIT scores. This paradoxical effect had also been described in a study of 34 manganese exposed ferroalloy plant workers, in which high urinary manganese levels were associated with low odor detection thresholds to phenyl-ethyl-methyl-ethyl-carbinol.[22] The reason for this observed effect is unknown, but prior investigators have proposed an early excitatory component of manganese intoxication.[21—23] It has also been found that elevated serum levels of manganese in mice, achieved by regular intra-peritoneal injection over 6 weeks, decreased concentrations of glycine in the olfactory bulb, a neurotransmitter involved in synaptic inhibition.[21,24,25] This result suggests the mechanism for improved smell detection to be related to a down-regulation of the inhibitory amino acids typically activated by glycine in the olfactory bulb. Whether this is a lasting effect, or perhaps a transitory stage before decompensation of the olfactory system begins, is currently unknown.

Chemical exposures from the environment or the workplace have frequently been linked with decreased olfactory function.[26,27] In our data, however, higher urinary levels of 2A4CA and 2T4CA, metabolites of cyanide and carbon disulfide, respectively, were seen to be associated with improved olfaction. Cyanide can be found in cigarette smoke, pesticides, the combustion of plastics and synthetic materials, metallurgy, and the manufacturing of paper, textiles, or plastics. Carbon disulphide is used in large quantities in rayon production and for fumigation. In the rat model, the enzyme rhodanese is present in high concentrations in the nasal mucosa, especially the olfactory bulb, and is responsible for metabolizing inhaled cyanide.[28] This enzyme has also been identified in human nasal mucosa, and, given its role in cyanide detoxification, potentially confers a protective effect on the olfactory mucosa.[29] Thus, increased urinary levels of the cyanide metabolite 2A4CA may imply heightened rhodanese activity or concentration, leading to reduced toxicity and preserved olfactory function. Similarly, carbon disulfide is metabolized by cytochrome P450 dependent monooxygenases, which have also been reported to occur in substantial amounts in the nasal mucosa.[30] We may, therefore, interpret higher urinary levels of 2T4CA to correlate with carbon disulfide degradation and, consequently, protection from olfactory toxicity. This possible protective effect of heightened rhodanese activity leading to increased metabolites of toxic compounds is a theory worthy of further investigation.

Analysis of the odor identification exam in the 2013—2014 group revealed additional demographic and exposure characteristics associated with smell disturbance. In objective testing, those with limited education had a lower prevalence of hyposmia. This finding contrasts with a population-based survey in Spain, which found low educational attainment to be a risk factor for anosmia,[31] as well as the Beaver Dam Offspring study, in which education level did not correlate with smell loss.[32] Men did not perform as well as women on the odor identification test. This finding is supported in several population based and longitudinal studies,[7,8,33] and is thought to be due to a protective effect of female hormones on olfactory stem cells, which may slow the deterioration of olfactory neurons in the aging process.[34,35] Additionally, men consistently show more rapid cognitive decline, which may imply faster neuronal degeneration, and, hence, degredation of the olfactory pathway.[36]

Elevated urinary levels of 2,4 dichlorophenol also portended an increased likelihood for hyposmia in our study. A derivative of phenol, it is an intermediate product in the production of herbicides and pesticides, though its specific physiologic effect on the olfactory system has not been studied. However, in a study of nasal symptoms in farmers, a population primarily exposed to 2,4 dichlorophenol, Ahman et al[37] reported a significant increase in subjective

smell disturbance as well a lower olfactory threshold. Additionally, pathologic markers and visual assessment of nasal inflammation has been shown to be elevated in farmers. Another study of 66 chemical industrial workers administered a self-reported olfactory dysfunction revealed that workers with higher exposure to phenolic resins, measured by urinary phenols, were more likely to complain of anosmia.[38]

Higher rates of anosmia were also found in participants with increased serum lead levels. This is corroborated by the analysis in the Normative Aging Study, wherein cumulative lead exposure was found to be a significant risk factor for smell disturbance in a population of elderly men.[39] Similarly, a study of Italian workers with lead exposure confirmed impaired odor detection thresholds compared with control participants.[40] The mechanism for lead's influence on olfaction is not well understood, but, based on animal models, is thought to be related to neurotransmission in olfactory related areas. Intra-peritoneal injection of lead in adult mice disrupted expression in the nitric oxide signalling pathway in the olfactory bulb.[41] And in rats, prenatal lead exposure was shown to impair olfactory discrimination[42] and acetylcholine metabolism in the olfactory bulb.[43]

There are a number of limitations to be considered in the interpretation of this data. Our analysis includes both subjective and objective assessments of olfactory dysfunction. It is well recognized that subjective smell dysfunction does not always correspond with objective smell testing.[44–46] Importantly, this does not mean that either is more valuable or informative than the other, simply that they are additive pieces of information. Though the large and representative sample ideally eliminates risk of variability of population, it should be noted that because these analyses are from different response cycles, the populations of respondents may not be entirely correlative.

Cross-sectional analysis cannot establish cause and effect relationships between the identified variables and olfactory disturbance. Questionnaire data does not allow for temporal associations with exposure variables. Respondents with subjective smell dysfunction had experienced symptoms within the last year. Exposures, however, could have occurred at any point during a respondent's lifetime. Blood and urinary levels of compounds merely represent a single time point and are not necessarily reflective of a chronic state or cumulative exposure, nor is it possible to determine if these results were obtained before, during, or after the appearance of olfactory symptoms. This investigation is also subject to confounding bias as the available questionnaire and health data did not allow for an adequately controlled study based on potentially related co-morbidities. Though population-based survey data is limited in its ability to make causal inferences and confirm definitive etiologies, it can offer leads to follow for controlled study.

Conclusions

Despite having important implications in personal safety, social interactions, and quality of life, olfaction remains a poorly understood sense. This study provides population-based data identifying demographic and exposure elements related to smell disturbances in U.S. adults. Several variables — age, race, gender, educational status, exposure to environmental and occupational vapors, and levels of manganese, 2T4CA, 2A4CA, lead, and 2,4 dichlorophenol — were found to be significantly associated with either the protection or alteration of olfaction. Caution should be taken in making conclusions about causality for reasons discussed relating to the limitations of cross-sectional analysis. However, these are factors worthy of additional investigation with longitudinal study.

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