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Research Article

Prevalence and Correlates of Olfactory Dysfunction in Old Age: A Population-Based Study

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Abstract

Background: Olfactory dysfunction (OD) in old age is associated with poor health outcomes. Interrelationships among different correlates of OD can offer insights into the underlying mechanisms, but to date remain understudied.

Methods: Odor identification performance and self-reported olfactory functioning were studied in 2,234 people aged 60–90 years, who were free of neurodegenerative disease and enrolled in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) study, Stockholm, Sweden. OD was defined as the inability to identify more than 10 out of 16 odors (free or cued identification) in a standardized odor identification task. OD prevalence was estimated, and associations with demographic, genetic, vascular, clinical, and behavioral factors, as well as their interactions were examined using multiple logistic regression analyses.

Results: Overall prevalence of OD was 24.8% (CI: 23.1; 26.6). Self-reports were characterized by low sensitivity (35%), but high specificity (87%). Advancing age (OR = 15.50, CI = 9.40; 26.10 between the first and last age group), and history of coronary heart disease (OR = 1.35, 95% CI = 1.04; 1.75) were the principal factors associated with an increased probability of OD, whereas female gender (OR = 0.53, 95% CI = 0.43; 0.66) and more years of education (OR = 0.97, CI 0.94; 0.99) were linked to a lower probability. Exploratory interaction analyses indicated that prevalence of OD was particularly elevated among Apolipropotein E (*APOE*) ε4 allele carriers who were also obese, and that being physically active counteracted the negative impact of cerebrovascular disease on OD.

Conclusion: Demographic and genetic factors, but also prior and current health insults, are linked to OD in old age. Modulatory effects of behavioral factors highlight their value as possible prevention targets.

Keywords: Olfaction—Anosmia—Hyposmia—Perceptual decline—Odor Identification

Olfactory dysfunction (OD), a reduced or complete absence of the ability to smell, remains underdiagnosed in the general population (1,2) despite frequently described associations with poor health outcomes (3,4). This applies particularly to older adults, who are at increased risk for generalized OD (5) extending across subdomains including detection sensitivity (6,7) and quality discrimination (8), as well as tasks integrating higher-order cognitive aspects such as odor identification (9,10) or episodic odor recognition (11). Depending on study methodology (e.g., specific olfactory tests or cutoff values used) and sample characteristics, OD has been estimated to affect

40%–70% of the general aging population (1,12), as opposed to around 5%–15% in younger age groups (13,14). However, the interplay between innate vulnerabilities and risk factors accumulating over the life span remains understudied, meaning that knowledge of the etiology of these dysfunctions, and thus strategies to promote timely preventions, are scarce.

Declining olfactory function is closely linked to the state of the central nervous system as a whole. Even when neurodegenerative disease, an established factor in olfactory decline (15), is controlled for, associations with a large number of factors from the demographic

(16,17), genetic (18,19), clinical (4,20,21), and behavioral domains (13) remain. An OD prevalence study on a population free from neurodegenerative disease by Murphy et al. (1). showed univariate associations between OD and demographic (age and male gender), health-related (history of cancer, nasal dysfunctions, cardiovascular and cerebrovascular disease), and behavioral factors (smoking or having worked in a manufacturing occupation). Yet, only a subset of these associations survived in a multivariate model, indicating collinearities and interactions between individual variables. OD is also known to be linked to poor general health, suggesting that risk factors may accumulate to exacerbate age-related olfactory losses (22); yet, the mechanisms by which factors interact to promote OD in individuals free from neurodegenerative disease remain unclear.

Increased knowledge about such interrelationships between individual factors is crucial for further identification of treatment targets. As such, the present study examines the prevalence of OD in an older population and seeks to detect the major correlates and their interactions.

Materials and Methods

Participants

Data were derived from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), Stockholm, Sweden. The study used random sampling stratified by age (60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and ≥99 years). At baseline (2001–2004), 3,363 (response rate 73.3%) individuals were enrolled in the study and took part in assessment of medical, psychological, and social factors. Two thousand eight hundred and forty-eight participants underwent cognitive assessment performed by a psychologist (23), which included a standardized olfactory testing protocol. No olfactory data were collected from participants who refused or were unable to perform the olfactory tests for reasons including self-reported anosmia, olfactory over-sensitivity, asthma, allergies, or tiredness (*n* = 279). Additional criteria were applied to exclude cases with known or suspected neurodegenerative disease, as well as participants who had developed neurodegenerative disease at a follow-up measurement taking place at 3 and 6 years after data collection for participants 78 and older, and at 6 years after data collection for participants younger than 78 years of age at baseline. Taken together, this procedure resulted in a final sample of 2,234 participants (see Figure 1).

Comparisons of self-reported olfactory function with excluded participants (*n* = 1121, 8 missing both interview and standardized test) indicated that nonparticipants were on average 11.5 years older (95% CI = 10.9; 12.3), had on average about 1 year less of formal schooling (95% CI = −1.04; −0.78) and were less likely to be male (OR = 0.56, 95% CI = 0.48; 0.65). Included subjects were less likely to report reduced olfactory abilities (OR = 0.43, 95% CI = 0.36; 0.51), an effect which persisted when differences in the above demographic variables were accounted for.

Assessment of Olfactory Function
Standardized olfactory testing
A standardized 16-item odor identification task was conducted using felt tip-pens containing odorants (apple, banana, clove, coffee, cinnamon, fish, garlic, lemon, leather, liquorice, peppermint, pineapple, rose, turpentine, mushroom, and gasoline) (24). Testing procedures have been described in detail elsewhere (25). In brief, odor identification was assessed through odorant presentation at 5 seconds exposure duration per odor. Participants were instructed to freely identify the odor; if they did not respond, or responded incorrectly, they were presented with four response alternatives (cued identification). In the present context, a correct response was counted under either response
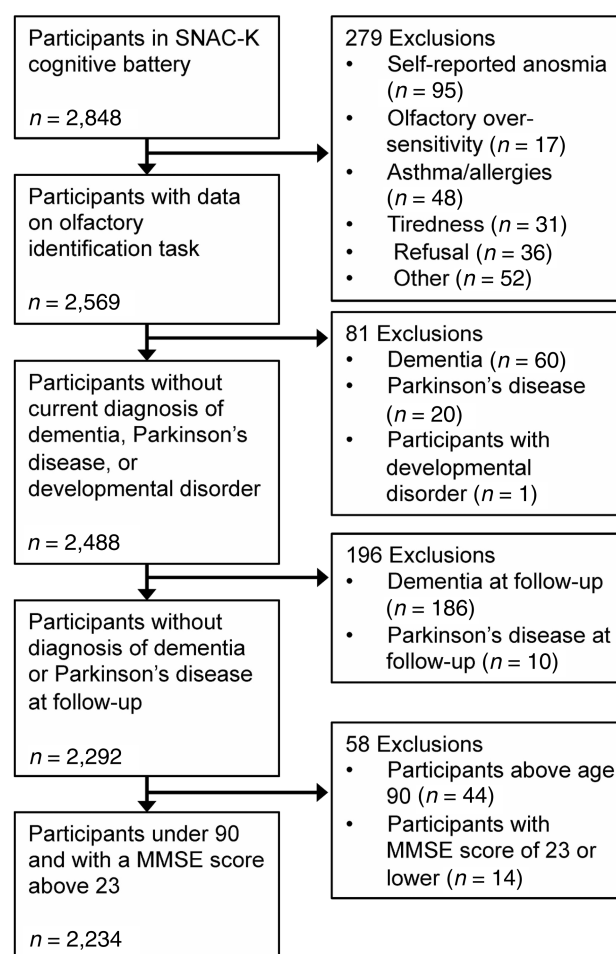

Figure 1. Exclusion flowchart.

format. Inability to perceive an odor was counted as an incorrect response. Based on established clinical cutoff scores (26), participants with 10 or less correct identifications were classified as suffering from reduced olfactory acuity (hyposmia), whereas six or less correct identifications were classified as having a functionally absent sense of smell (anosmia). These clinical cutoff scores are based on the four alternative forced choice version of the test, so their diagnostic validity already factors in a 25% chance for correct guessing.

Self-assessment
Subjective assessments of olfactory and gustatory abilities were obtained through standardized interviews. On a scale ranging from 1 to 4, 1 indicated normal perception and 4 complete perceptual loss. A score of 5 reflected above average perceptual abilities or hypersensitivity. Responses were dichotomized into "no functional loss" (score 1 or 5) versus "any observed functional loss" (scores 2–4). Participants also reported for how many years they had experienced reduced olfactory function (categorized into less than 10 years, more than 10 years, or entire life).

Potential Correlates of Olfactory Dysfunction
Demographic factors
Demographic factors (age, gender, and education) were collected following standard protocols. Age was measured as a categorical variable with each age group representing a factor level, and educational background was measured as years of formal schooling.

Genetic factors

Genotype information for Apolipropotein E (*APOE*, rs429358) and Brain-Derived Neurotrophic Factor (*BDNF*, rs6265) was obtained from peripheral blood samples using MALDI-TOF analysis on the Sequenom MassARRAY platform at the Mutation Analysis Facility, Karolinska Institutet. For *APOE*, participants were grouped as carriers or noncarriers of the ε4 allele, and for *BDNF*, participants were dichotomized into homozygous Val/Val carriers versus carriers of any met allele.

Vascular factors

Information on vascular factors was collected through clinical examinations by physicians, as well as medication lists, laboratory data, and the computerized Stockholm inpatient register (27). We included: cerebrovascular disease (ICD-10 I60-I69); heart failure (ICD-10 I50); atrial fibrillation (ICD-10 I48); and coronary heart disease (ICD-10 I25). Risk factors for vascular disease such as diabetes (defined as current use of oral glucose-lowering agents, insulin injection, fasting blood glucose level ≥ 7.0 mmol/L or non-fasting glucose level ≥ 11.0 mmol/L), hypertension (above 140/90 mmHg or current use of antihypertensive medication), and high cholesterol (total serum cholesterol level ≥ 6.22 mmol/L) were included to identify possible influences of vascular alterations on olfactory function.

Other clinical factors

Potential neurological/psychiatric correlates of OD included a current diagnosis of depression (ICD-10 F33) (28), history of head trauma (ICD-10 S06), migraine (ICD-10 G43), epilepsy (ICD-10 G40), and schizophrenia (ICD-10 F20). We also tested the impact of past diagnosis of any form of cancer, and hypothyroidism (ICD-10 E03).

Behavioral factors

Hazardous alcohol consumption based on AUDIT scores (no/possible/likely hazardous alcohol consumption (29)), and current smoking (none/less than/more than one pack per day) were assessed through standardized interviews. Odds for longest held occupation were tested as manufacturing ("blue collar") work versus low intermediate desk work ("white collar"), and highly-trained professionals/executives. Body mass index (BMI, weight [kg] divided by square of the height [m]) was used to classify obesity (BMI > 30) and underweight (BMI < 18). Loss of appetite was established through self-report (present or absent). Inadequate physical activity was classified as less or equal to 2–3 times per month of light and/or moderate/intense exercise (30).

Statistical Analyses

In a first step, OD was broken down into partial and complete loss of olfactory function and its prevalence established by age cohort and gender. Then, sensitivity (proportion of true OD detections) and specificity (proportion of true OD rejections) of self-reported odor functioning relative to objective OD were assessed. Univariate logistic regression models tested each individual factor for association with OD (Sniffin' Sticks Score of 10 or lower).

To control for interdependencies and to quantify the unique variance attributable to each factor, variables for which the univariate odds ratio was significant at a *p*-value below .05 entered a hierarchical block-wise logistic regression in domain-based blocks. Using a distal-to-proximal approach, an initial multivariate logistic regression model was conducted including only the group of demographic factors, and model fit (Nagelkerke's Pseudo-R^2) based on those factors alone was noted. Subsequently, further logistic regression models were set up which sequentially added additional blocks of factors based on when during the life course they were introduced (i.e., genetic influences were added first, followed by the vascular and other clinical diagnoses over the life course and finally considering current behavioral measures). Chi-square tests assessed whether model fit was significantly improved due to the inclusion of each block.

An exploratory analysis tested for improvements in model fit that could be achieved by consideration of interactions between individually contributing factors. To this effect, individually significant variables from the univariate logistic regression analyses were first separately tested for interactions with all other included variables. Interactions based on cell sizes smaller than five were excluded from further analysis. Any variables which formed part of a significant interaction term at *p* < .05 were then included into an updated hierarchical regression model, which, in addition to the block-wise procedure described above, tested for the contributions of these interaction terms.

Multivariate analyses only included complete cases (*n* = 1,936) in an effort to maintain comparable statistical power between analyses. All statistical analyses were conducted in the R statistical computing environment (www.R-project.org).

Finally, we conducted a sensitivity analysis to assess whether our findings were affected by the fact that participants who self-reported an inability to smell were not included in the task. All analyses were repeated including these participants as anosmic, that is, treating them as if they had completed the identification task and performed below the cut off for anosmia.

Results

Prevalence of OD and Relationship With Self-Report Measures

The overall prevalence of OD was 24.8% (CI: 23.1;26.6); Table 1 reports the age- and gender-specific prevalence figures for both hyposmia and anosmia, as well as the odds ratio for OD for each age group relative to the reference age group of participants aged 60. Prevalence of OD increased with age across both genders up to a 15-fold increased odds for OD at age 90; prevalence of OD dysfunction increased across age groups and affected partial and complete loss of olfactory function equally.

Self-reported olfactory impairment (*n* = 377, 17% of the overall sample) was linked to an olfactory identification score below the OD cutoff (OR = 3.07, 95% 2.43; 3.87). A small number of unimpaired individuals reported problems (specificity, 87%); however, many participants with impairment also failed to report deficits (sensitivity, 31%). Among those who correctly self-reported olfactory impairment (*n* = 167), 42% reported an onset within the last 10 years, 25% reported an onset earlier in life, and 5% reported to have always suffered from OD; 28% were unable to estimate the duration of their impairment. Inclusion of participants with a self-reported loss of sense of taste (8% of the sample) into an overall score of self-reported chemosensory dysfunction increased sensitivity for OD slightly to 34%, although decreasing specificity to 85%.

Determination of Univariate Associations

Prevalence data and odds ratios for all variables showing significant effects in the univariate logistic regression analysis are depicted in

Table 2. Given the strong age effect, changes in odds ratios that arise when correcting for the age effect are additionally reported. See Supplementary Materials for a results table including all tested variables, and for a correlogram of individual associations between the included factors.

Determination of Multivariate Associations

Results from the block-wise hierarchical regressions are summarized in Figure 2. Demographic factors significantly contributed to the model fit for prediction of OD, as indicated by a Nagelkerke's R^2 of 0.20. The final model confirmed the increase in the probability of OD by age, which was small for the younger old cohorts but accelerated drastically for the older age groups up to a 15-fold increase in prevalence. A 4% decrease in odds was observed with each additional year of education. Adding genetic factors as explanatory variables further improved predictiveness to an Nagelkerke's R^2 of 0.21, with a higher probability of OD among *BDNF* Val/Val carriers and

APOE ε4 carriers. Vascular factors and other clinical factors failed to add unique explained variance, with none of the individual factors showing an increased odds ratio in the joint model. Addition of the behavioral block improved prediction to Nagelkerke's R^2 of 0.23; yet, only one factor, poor appetite, was individually linked to an increased risk for OD.

Exploring the impact of possible interactions between variables, our analyses identified 12 significant effects at the bivariate level. Three of these interactions remained significant after accounting for improvements in model fit attributable to main effects of other variables, and taken together, these improved overall model fit to a Nagelkerke's Pseudo-R^2 of 0.25. The risk associated with carrying an *APOE* ε4 allele was significantly higher in participants with concurrent obesity (Figure 3A). Physical inactivity was associated with a higher risk for OD only in participants with history of cerebrovascular disease, but did not alter the probability for OD in individuals without cerebrovascular disease. (Figure 3B). Finally, an interaction

Table 1. Prevalence in Percent (P%; Number of Participants in Brackets) of All Participants With Olfactory Dysfunction (OD), Stratified by Age and Gender and Divided into Partial (Hyposmia) and Total (Anosmia) Functional Loss in the Sample (*n* = 2,234)

| Age | Women | | | | | | Men | | | | | | OR (CI) relative to age 60 by age group |
	% OD (*n*/total)		hyposmic		anosmic		% OD (*n*/total)		hyposmic		anosmic		
60	8.6	(31/361)	8.3	(30)	0.3	(1)	14.6	(42/288)	12.5	(36)	2.1	(6)	
66	10.3	(28/272)	8.1	(22)	2.2	(6)	19.8	(40/202)	14.9	(30)	5.0	(10)	1.32 (0.99–1.88)
72	17.9	(40/224)	17.0	(38)	0.9	(2)	28.8	(45/156)	23.1	(36)	5.8	(9)	2.27 (1.61–3.21)
78	29.2	(62/212)	23.6	(50)	5.7	(12)	48.5	(48/99)	32.3	(32)	16.2	(16)	4.32 (3.09–6.01)
81	43.8	(39/89)	27.0	(24)	16.7	(15)	45.8	(22/48)	31.3	(15)	14.6	(7)	6.33 (4.18–9.62)
84	36.8	(28/76)	26.3	(20)	10.5	(8)	58.1	(25/43)	48.8	(21)	9.3	(4)	6.34 (4.10–9.81)
87	53.7	(29/54)	40.7	(22)	12.9	(7)	75	(18/24)	41.6	(10)	33.3	(8)	11.96 (7.19–20.19)
90	66.2	(43/65)	49.2	(32)	16.9	(11)	66.7	(14/21)	42.9	(9)	23.8	(5)	15.50 (9.40–26.10)

Table 2. Prevalence of Olfactory Dysfunction (OD, P%; Number of Participants in Brackets Unless Otherwise Noted), as a Function of Potential Predictor Variables

| Characteristic | OD, P% (*n*) | | | | OR | OR (age-adj.) |
	No (*n* = 1,680)		Yes (*n* = 554)			
Gender						
male	37.3	(627)	45.8	(254)		
female	62.7	(1053)	54.2	(300)	0.70 (0.58–0.85)	0.53 (0.42–0.65)
Education (mean)	M = 12.8		M = 11.3		0.91 (0.89–0.94)	0.97 (0.94–0.99)
APOE (ε4 Carrier)	27.6	(442)	33.2	(169)	1.30 (1.05–1.61)	1.55 (1.23–1.96)
BDNF (Val/Val Carrier)	65.3	(986)	71.5	(348)	1.33 (1.06–1.66)	1.41 (1.11–1.80)
Heart failure	5.9	(99)	15.3	(85)	2.89 (2.13–3.94)	1.30 (0.92–1.83)
Coronary heart disease	12.9	(216)	24.2	(134)	2.16 (1.70–2.75)	1.36 (1.04–1.77)
Atrial fibrillation	11.5	(193)	19.3	(107)	1.84 (1.42–2.38)	1.10 (0.82–1.46)
Cerebrovascular disease	5.8	(98)	10.1	(56)	1.82 (1.28–2.55)	1.19 (0.81–1.72)
High cholesterol	13.8	(226)	9.8	(53)	0.68 (0.49–0.92)	0.71 (0.51–0.99)
Hypertension	46.9	(787)	59.1	(327)	1.64 (1.35–1.99)	1.06 (0.86–1.32)
Migraine	4.0	(67)	1.4	(8)	0.35 (0.16–0.70)	0.50 (0.22–1.03)
Depression	3.0	(50)	5.6	(31)	1.93 (1.21–3.04)	1.68 (1.01–2.75)
Inadequate physical activity	22.0	(369)	29.8	(165)	1.51 (1.21–1.87)	1.09 (0.86–1.38)
Manufacturing occupation	17.2	(289)	24.7	(136)	1.58 (1.25–1.98)	1.16 (0.90–1.49)
BMI						
underweight	1.1	(18)	3.6	(19)	3.40 (1.76–6.59)	2.01 (1.00–4.07)
Nutritional status	10.7	(144)	15.2	(67)	1.50 (1.09–2.04)	1.29 (0.92–1.80)
Poor appetite	0.2	(3)	1.4	(8)	8.19 (2.36–37.5)	9.19 (2.43–44.52)

Note: Only significant effects are reported here; See Supplementary Material for a full report of all variables tested. The 95% confidence interval for age-adjusted odds ratios is in brackets.
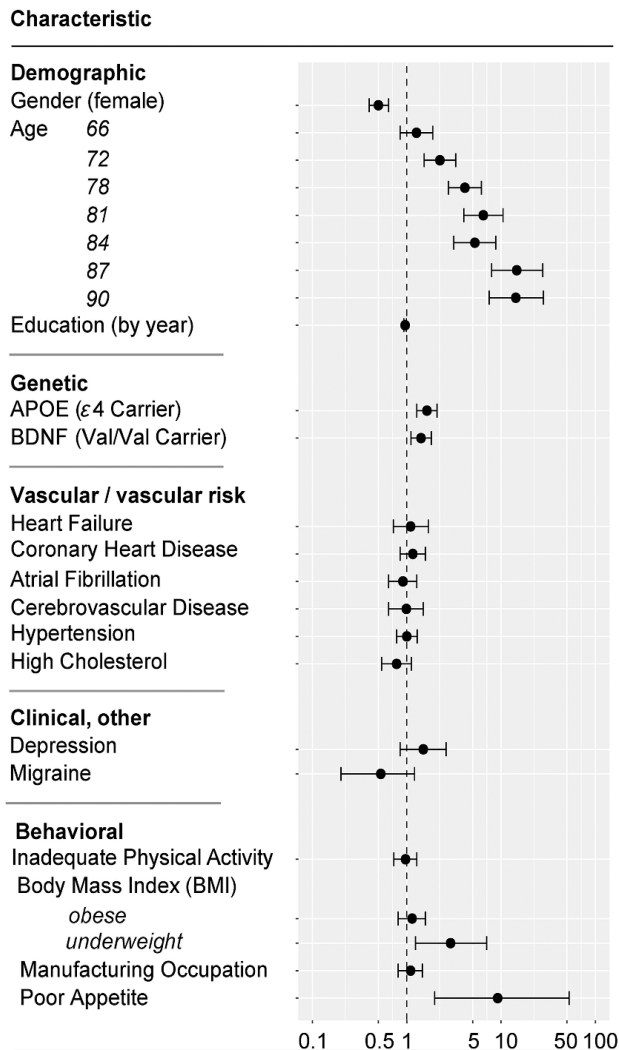
Characteristic

Demographic
Gender (female)
Age   66
       72
       78
       81
       84
       87
       90
Education (by year)

Genetic
APOE (ε4 Carrier)
BDNF (Val/Val Carrier)

Vascular / vascular risk
Heart Failure
Coronary Heart Disease
Atrial Fibrillation
Cerebrovascular Disease
Hypertension
High Cholesterol

Clinical, other
Depression
Migraine

Behavioral
Inadequate Physical Activity
Body Mass Index (BMI)
  obese
  underweight
Manufacturing Occupation
Poor Appetite

0.1   0.5 1   5   10   50 100

Figure 2. Results of multivariate logistic regression analysis. Log-transformed odds ratios are reported for individual factors in the final model adjusted for the contribution of all other variables to the model, and their 95% confidence intervals are depicted through the forest plots.

Figure 3. Interactions in odds for olfactory dysfunction. A: Body Mass Index × *APOE* status. B: Physical Activity × Cerebrovascular History. C: Atrial Fibrillation × Coronary Heart Disease.

between atrial fibrillation and coronary heart disease was observed, such that the risk for OD was increased only when coronary heart disease was present by itself, not when it was observed in combination with atrial fibrillation (Figure 3C).

Results of the sensitivity analysis showed that these findings were largely robust to the inclusion of participants who did not complete testing due to a self-reported inability to smell. Most notably, analyses (*n* = 95, of which 33 were excluded from sensitivity analysis due to meeting additional exclusion criteria) yielded an expected increased prevalence of 26.8% (CI = 25.06; 28.7) as well a significant univariate negative effect for head trauma, which, however, failed to survive multivariate analysis. Full result tables for the sensitivity analysis are depicted in the Supplementary Material.

Discussion

The present study examined the prevalence of OD, and its associations with demographic, genetic, clinical, and behavioral factors, in an urban elderly population-based sample free from neurodegenerative disease.
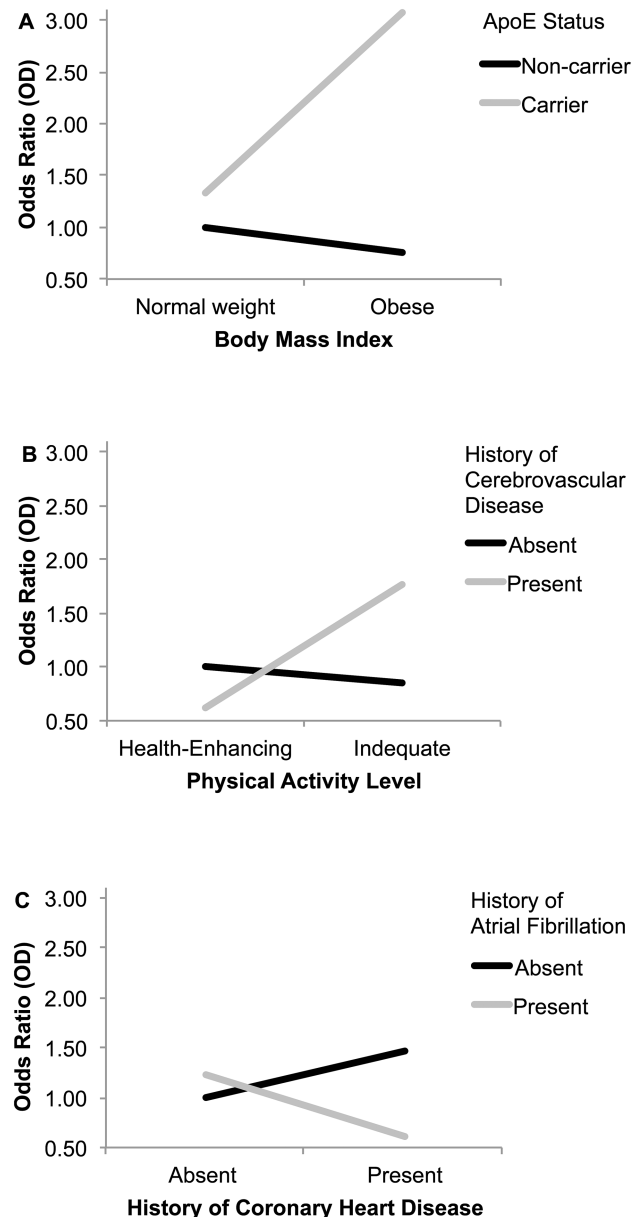
The observed OD prevalence of 24.8%, as well as age and gender effects, are consistent with past research on dementia-free elderly populations (1,13,31). Although these results clearly indicate the relevance of olfactory loss even during healthy aging, comparisons with studies without such exclusion criteria, and with self-reports of non-participants within our sample indicate that the values reported here likely underestimate prevalence rates relative to the general aging population (32).

Self-reported and objective olfactory functioning were strongly correlated, but further analyses indicated that this relationship was mainly explained by high specificity, not sensitivity, of the self-report: few participants with an intact sense of smell reported disturbances, whereas self-reports only detected a third of participants with objective impairment, indicating poor OD awareness (1,2). Consideration of self-reported taste impairment only marginally

improved sensitivity, indicating that this lack of awareness cannot be explained by confusion between the two chemical senses. Rather, the low sensitivity conceivably reflects a general lack of attention to chemosensory stimulation in a visuo-centric world, with input from more dominant and less impaired sensory modalities overshadowing self-perception of olfactory abilities (33,34). In addition, evaluations may be based on the perceived abilities relative to same-age peers, and as such underestimate olfactory impairment.

As in previous studies, demographic factors explained a large portion of variance in OD, with male gender and low education being linked to OD. Consideration of genetic factors confirmed the relationship between the *APOE* ε4 allele and OD previously reported in other population-based studies (18,35). Carriers of the *BDNF* met allele showed better olfactory performance than Val/Val homozygotes. This finding is consistent with past work on olfaction in old age (36), but at odds with the bulk of research on cognition in aging, where the met allele is typically linked to negative outcomes (37). This discrepancy may reflect task-dependent advantages and disadvantages associated with the met allele, which has been suggested to mediate a favored dominance of inhibitory over excitatory input (38). Given that olfactory identification relies heavily on the differentiation of bulbar inhibitory microcircuits (39,40), higher inhibition in met-allele carriers might thus in the case of olfaction aid the amplification of a weak input signal.

Prior work on the contribution of cardiovascular risk factors to OD etiology has yielded mixed results (1,41). Our data indicate that consideration of interactions may explain some of this disparity in the literature. Risks linked to cardiovascular factors do not linearly add up to increase the odds for OD beyond diagnosis based on a single factor; stable associations of coronary heart disease and OD only emerged when such interactive effects were statistically accounted for. Failure to address interactions between individually associated factors may thus result in a systematic underestimation of vascular effects on olfactory function.

Inspection of behavioral indicators showed that appetite loss and underweight were linked to a higher probability for OD. Likely reflecting consequences rather than causes of OD (3), this robust relationship highlights the clinical relevance of OD as a possible explanatory factor underlying changes in eating behavior during old age (42).

Importantly, our data show that behavioral factors can modulate established associations with OD. Specifically, we observed a 3-fold increased risk for OD for obese ε4 carriers relative to lean noncarriers. No increased risk was present in lean ε4 carriers, or obese noncarriers. These findings extend previous reports on associations between BMI and *APOE* ε4 in the context of olfactory performance (43), and contribute to an emerging body of work reporting associations between BMI and ε4 in their consequences on brain function in old age. Both physical activity and gene-gene interactions have been implicated as modulating factors linking ε4 to dementia. With effects on olfactory function likely representing mechanisms acting on the nervous system as a whole, smell impairment may lend itself as a model to directly test theories of potential causal mechanisms of the relationship between *APOE* ε4 and obesity such as direct effects of leptin levels on lipid homeostasis, or indirect effects of cardiovascular health.

Finally, advantageous effects of physical activity were found in participants with a history of cerebrovascular disease. Among these individuals, engagement in physical activity activity was associated with an OD prevalence comparable to or even better than for unaffected individuals, whereas odds were drastically increased (OR = 1.77) for those who did not engage in physical activity. Contributions of physical activity to improved functionality after cerebral infarction or stroke are discussed in the context of stroke-induced enhancement of neural stem cell proliferation after cerebrovascular infarction (44). Indeed, key target regions of such neural recovery are directly implicated in olfactory performance (45,46). Given recent evidence that stem cell migration to the olfactory bulb is absent in the adult human brain (47), future research should focus on the potential role of fitness-dependent stem cell proliferation in hippocampus in recovery of olfactory function after a cerebrovascular insult. This could be accomplished by analyzing the relationship between indirect markers of structural changes (e.g., angiogenesis, volumetric differences) and concurrent development of olfactory markers over the course of the rehabilitation process.

The large sample size and the population-based nature of the data allow robust inferences to the general population and, as such, constitute strengths of the present research. Inherent imitations, however, arise from the cross-sectional nature of our data; the direction of influence between associated variables cannot be determined and as a result no causal inferences on risk factors for OD can be made. In addition, it cannot be ruled out that selective survival of participants with a comparatively better sense of smell may have skewed the observed results to underestimate the true increase in OD with age. Although a sensitivity analysis treating nonparticipation in the olfaction testing due to smell problems indicated no significant changes in our results, we cannot fully rule out that nonparticipation in the study altogether influenced the dependencies observed. Finally, it should be noted that due to the restricted age range of 60–90 years, the findings of our study cannot be extended beyond this age span.

In conclusion, our results provide further evidence for increased prevalence of OD in old age even in the absence of neurodegenerative disease. The observed interactions, although exploratory, caution against OD risk assessments based on univariate or additive analytical procedures, given that these may obscure important nonlinear relationships among individually associated factors. Knowledge of the links between weight loss, physical activity, and clinical risk factors for OD may in the long-term help to establish intervention targets in clinical practice. Further investigation of the mechanisms underlying these observed interactions will be crucial to improve understanding of the close link between OD and broader cortical functions, and should be addressed in future work, for example through work on appropriate model systems, and longitudinal population-based studies.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interests

The authors report no conflicts of interest.

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