Furthering the understanding of olfaction, prevalence of loss of smell, and risk factors: a population-based survey (OLFACAT study).

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Furthering the understanding of olfaction, prevalence of loss of smell, and risk factors: a population-based survey (OLFACAT study)

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RELEVANT SURVEY HEADINGS: sense of smell, general population, olfactory disorders, normosmia, hyposmia, anosmia, risk factors.

SHORT TITLE: Olfactory disorders and risk factors in the general population.

ABSTRACT

Objectives: To investigate the sense of smell in the general population, prevalence of olfactory dysfunction, and related risk factors for the loss of smell.

Design: Cross-sectional population-based survey, by distributing four microencapsulated odorants (rose, banana, musk, gas) and two self-administered questionnaires (odour description; epidemiology/health status).

Setting: The survey was distributed to the general population through a bilingual (Catalan, Spanish) newspaper in Catalonia (Spain), on December 23rd 2003.

Participants: Newspaper readers of all ages and both gender; 9,348 surveys were finally analyzed from the 10,783 returned.

Main outcome measures: Characteristics of surveyed population, olfaction by age and gender, smell-self perception, and risk factors for smell impairment.

Results: The survey profile was a 43-year-old woman with medium-high educational level, living in a city. Sense of smell was considered normal in 80.6% for detection, 56.0% for recognition/memory, and 50.7% for forced-choice identification. Loss of smell prevalence was 19.4% for detection (0.3% anosmia, 19.1% hyposmia), 43.5% for recognition (0.2% anosmia, 43.3% hyposmia), and 48.8% for identification (0.8% anosmia, 48% hyposmia). Sense of smell was worse ($p<0.0001$) in men than in women through all ages. There was a significant age-related smell detection decline for both genders however smell recognition and identification increased up to fourth decade and then declined after sixth decade of life. Risk factors for anosmia were: male gender, loss of smell history, and poor olfactory self-perception for detection; low educational level, poor olfactory self-perception, and pregnancy for recognition; and older age, poor olfactory self-perception, and history of head trauma for identification. Smoking and exposure to noxious substances were protective factors for smell recognition.

Conclusions: Sense of smell in female is better than in male with a learning process during life span and deterioration in older ages. History of smell loss, head trauma, and pregnancy are absolute risk factors for olfactory disorders.

ABSTRACT WORD COUNT: 300 words

ARTICLE SUMMARY

Article focus:

• Population-based smell survey in 2003.

• Partial and total smell impairment by age and gender.

• Risk factors for olfactory disorders.

Key messages:

• Olfaction is better in female than in male.

• Smell improves with a learning process and deteriorates in older ages.

• Subjective smell loss, head trauma, and pregnancy are absolute risk factors for olfactory disorders.

Strengths and limitations of this study:

• Strength: The largest European population-based study providing data on partial/total loss of smell and their absolute risk factors.

• Limitations: self-administered survey (no control on how it was performed); the study was done in a middle-high socio-cultural population (newspaper readers).

INTRODUCTION

The sense of smell provides information on the surrounding environment, warns us about chemical dangers and putrid food, and may even help people to mate. Smell disorders may affect the ability to enjoy food and aromas while interfering with the ability to notice potentially harmful chemicals and gases.[1] Unlike well-documented epidemiological studies on hearing and vision, most smell-perception studies are not well standardised, some are contradictory, and few are broad enough to offer clear conclusions.

In 1987, the National Geographic Smell Survey (NGSS) studied a large US sample population (1.2 million) whereby 1% of participants could not smell three or more of six odorants using a "scratch and sniff" test.[2] Age was an important factor in smell deterioration and smell was rated better in women than in men. In 1994, the National Health Interview Survey (NHIS)[3] reported data from 42,000 United States households with 1.4% prevalence of self-reported olfactory dysfunction, exponentially increasing with age. This study, however, did not include any testing of smell function.

The prevalence and associated risk factors of olfactory impairment in the European population has been mildly investigated. In the Swedish version of the NGSS,[4] done in 532 individuals older than 45 years, increasing age was associated with impaired ability to detect/identify odorants with no effect of gender on smell perception. Education has also proved to account for a significant portion of the age-related variance in identification.[5] Another European population-based study showed a significant relationship between impaired olfaction and aging, male gender, and nasal polyps, but not with diabetes or smoking, reporting an olfactory dysfunction prevalence of 19.1%.[6]

Approximately two thirds of smell dysfunction cases are likely due to prior upper respiratory infections, head trauma, or sinonasal diseases.[7] Toxic chemical exposure, epilepsy, pollution, drugs, nutritional disturbances, and neurodegenerative diseases may also cause olfactory disorders.[8] Smoking may cause a reversible reduction on the ability to smell [9] while chronic rhinosinusitis/nasal polyps may result in a partial or total loss of smell.[10]

The aims of this study were to investigate the current status of olfaction in the general population while determining the prevalence of olfactory dysfunction and its related risk factors.

METHODS

Study Design

The OLFACAT (Olfaction in Catalonia) survey was carried out in the general population of Catalonia in Spain. Two questionnaires, olfaction and demography-health status, and a set of four microencapsulated odorants were distributed in the 250,000 daily issues of the newspaper *El Periódico de Catalunya* on December 23rd, 2003. The survey was presented in both Catalan and Spanish languages to facilitate the choice of the preferred language. The manuscript has followed the STROBE checklist guidelines.

The study was approved by the Institutional Ethic and Clinical Research Committee of Hospital Clínic de Barcelona (reference 1295).

Measurements

Survey Odorants**.** Four common odorants were included in the survey: rose (Bulgarian rose at 2% in phenyl-ethyl alcohol) as a floral odour; banana (amyl-isobutirate at 50% in dietyl-phtalate) as a food odour; musk (1:1 mixture of galaxolide and diethyl-phtalate exaltolide) as a perfume odour; and gas (mixture of 30% mercaptan and 70% tetrahydrothiophene) as an industrial odour. Each compound was prepared following established formulas and the solution magnetically homogenized. Smell products were elaborated by Antonio Puig SA (rose, banana, musk) and ENAGAS (gas). Stability test protocols were performed by accelerating the olfactory aging of products at 40ºC for 2 months, following their smell evolution after 1 to 8 weeks. The micro-encapsulation process was done by ARCADE as follows: essential oil component was contained and delivered from highly durable synthetic microcapsules manufactured using a proprietary polycondensated polymerization method. The microcapsules were blended with a water-based polymer adhesive to form printable slurry. Odorants were adhered to a smell-less paper and finally printed form-folded in such a way to prevent direct contact between odour samples.

Smell questionnaire. Participants were asked to scratch and sniff each odour and then answer three questions: First) odour detection: did you smell any scent? (yes, no); Second) odour recognition/memory: have you ever smelt this scent? (yes, no); and third) forced-choice odour identification: which name defines the scent you have smelt?, whereby only one of the four given options was correct. Normal sense of smell (normosmia) was defined when a participant was able to detect, recognize, or correctly identify all four odours; partial loss of smell (hyposmia) when a participant was not able to detect, recognize (memory), or correctly identify one, two, or three odours; and total loss of smell (anosmia) when a participant was unable to detect, recognize, or correctly identify any of the four odours.

Epidemiological and health-status questionnaire. From the twelve-question questionnaire, four questions were on demography: first) gender (male, female); second) age (years); third) current educational level (primary school, secondary school, high school, University or College); and fourth) residence area (city, postcode). Two questions described smell self-perception: fiftth) how do you consider your current sense of smell? (very good, good, poor, very poor); and sixth) have you ever lost the sense of smell? (never, up to one week, over one week). Two questions were on exposure to toxic or noxious substances: seventh) have you ever been exposed to dust, gases, fumes, vapours, or/and volatile toxics at home and/or at work? (yes, no); and eighth) do you smoke? (no, ex-smoker, smoker). Two questions were on health-status: ninth) have you ever had a severe face and/or head trauma? (yes, no); and tenth) have you ever been diagnosed with chronic rhinosinusitis? (yes, no). Finally, two questions were on women's health: 11th) are you currently pregnant? (yes, no); and 12th) are you currently menstruating? (yes, no).

Data Management and Statistical Analysis

The returned surveys were read using an optical system (BV Scan system, Voxpublica), data transferred to an electronic database, and then statistically analysed using Stata version 8 (Stata Statistical Software: Release 8.0 College Station, TX: *Stata Corporation* 2003).[11] The cleaning process was based on programmed queries to identify records containing inconsistent or uncertain data. Variables concerned in mentioned queries were recorded as missing values in the identified records.

Only those surveys fully and consistently answered were considered for statistical analysis. Differences between gender in epidemiological and health-status characteristics were evaluated by Chi-square test. Crude and multivariate logistic regression models were estimated to identify associations with smell detection, recognition/memory, and forced-choice identification, as well as for normosmia, hyposmia, and anosmia. Multivariate analyses were performed by a forward-stepwise procedure, using $p<0.05$ from the Wald test, as enter criteria. Results from estimated models were expressed as Odd Ratio (OR) and 95% Confidence Interval (CI). All tests were performed using a two-tailed significance level of 0.05.

RESULTS

Characteristics of the surveyed population

Following the cleaning process, 5.6% of answers from the 10,783 received surveys were identified as inconsistent. After the exclusion of those mentioned questionnaires, as well the incomplete ones regarding (7.7%) the epidemiological and health-status questionnaire, the sample size for analysis was 9,348 questionnaires (Figure 1).

Age and gender. The mean age of the surveyed population was 43.3 years, ranging from 5 to 91 years. The analysis was performed in seven age groups to ensure a reasonable sample size for each age and gender group. Almost two thirds of participants were women (65.7%), of which 2.1% were pregnant and 12.7% were menstruating (Table 1).

Education and residence area. Most participants (83.8%) had a high educational level (high school or University/College) and were living (93.9%) in an urban area, with no differences between gender.

Exposure to tobacco and noxious substances. More than one fifth (21.4%) of participants were smokers, 28·3% were ex-smokers, while almost a third (29.9%) reported to be regularly exposed to toxic or noxious substances, either at home or at work. Men reported a higher exposure to both tobacco smoke (24.8%, $p<0.0001$) and noxious substances (33.9%, $p<0.0001$) than women (19.7% and 27.7%, respectively).

Health status. 4.4% of participants had received a diagnosis of chronic rhinosinusitis, with similar prevalence in women and men, while 5.0% reported a history of face/head trauma, this prevalence being higher in men than in women (6.2% versus 4.3%, $p<0.0001$).

Sense of smell. All four odours (normal sense of smell or normosmia) were detected by 80.6%, recognised by 56.0%, and identified by 50.7% of the surveyed population. A reduced number of odours (partial loss of smell or hyposmia) were detected by 19.1%, recognised by

43.3%, and identified by 48.0%. No odours (total loss of smell or anosmia) were detected by 0.3%, recognised by 0.2%, and identified by 0.8%. Individual odours were more highly detected (rose 99.4%, banana 98.9%, gas 96.9%, musk 84.4%) than recognised (rose 94.8%, banana 96.2%, gas 94.9%, musk 66.2%) or correctly identified (rose 91.8%, banana 89.8%, gas 92.1%, musk 65.4%). Moreover, individual odours were always better detected, recognised, and identified by women than by men, except for rose and banana recognition.

Smell by gender and age

Within the population experiencing normosmia, there was a significant and progressive age-related decline of smell detection while smell recognition and identification increased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and declined thereafter. Significant but opposite findings were found for hyposmia and anosmia. Normosmia was higher in women than in men ($p<0.0001$) either in smell detection (82.8% versus 76.5%), recognition (58.0% versus 51.9%), or identification (54.1% versus 44.3%) (Figure 1). Hyposmia was higher in men than in women ($p<0.0001$) either in smell detection (22.8% versus 17.1%), recognition (47.1% versus 41.4%), and identification (54.0% versus 44.9%) (Figure 2). Finally, anosmia was higher in men than in women in both smell detection (0.9% versus 0.1%; $p<0.0001$) and identification (1.2% versus 0.6%; p=0·0057), but not in smell recognition (0.2% versus 0.2%, p=0.9569) (Figure 3). In the oldest group (over 70 years), the prevalence for anosmia of detection (4.4%) and identification (6.6%) was especially higher in men than in women (0% and 1·4%, respectively).

Smell self-perception

Subjective description of smell. Regardless of gender and age, 93.1% of participants subjectively rated their sense of smell as good or very good, while 6.9% of them reported their smell as poor or very poor, the smell score being better in women than in men (p<0.0001).

Loss of smell history. A past history of loss of smell was reported by almost one third (30.4%) of participants, predominantly for less than one week (25.1%). The smell loss for over one week was more frequent in men (6.4% vs 4.8%, p=0.0042).

Risk factors for smell impairment

Smell detection. Women detected odours more frequently than men (82.8% versus 76.5%, p<0.0001). The risk for anosmia of detection was higher in men, in subjects reporting a loss of smell history for over one week, anosmia being also correlated to a worse smell self-perception (Table 2). The risk for hyposmia of detection was higher in men and highly correlated to older age (>40 years old), a lower educational level, and a worse smell self-perception (Table 2).

Smell recognition / memory**.** Women showed a better capability to recognise odours than men (58.0% versus 51.9%; p<0.0001). The risk for anosmia of recognition was higher in pregnant women, correlating to a lower educational level and a worse smell self-perception (Table 3). The risk for hyposmia of recognition was higher in men and in subjects reporting a loss of smell history for over one week and being highly correlated to older age (>70 years old), a lower educational level, and a worse smell self-perception. Smoking (both ex-smokers and smokers) and frequent contact with noxious substances were found to have a protective effect on odour recognition (Table 3).

Forced-choice smell identification. Women performed better than men on odour identification (54.1% versus 44.3%, p<0.0001). The risk for anosmia of identification was higher in subjects reporting a history of head trauma, and highly correlated to older age (>60 years old) and a worse smell self-perception (Table 4). The risk for hyposmia of identification was higher in men and in subjects reporting a loss of smell history for over one week, being highly correlated to older age (>60 years old), a lower educational level, and a smell worse self-perception (Table 4).

DISCUSSION

The most important findings of the OLFACAT survey were: First) the overall prevalence of olfactory dysfunction for detection was 19.4%, with a total loss of smell (anosmia) of 0.3%. Despite this high prevalence of smell impairment, only 6.9% of the subjects considered having a poor or very poor sense of smell. Second) there was a significant age-related decline in smell detection for both genders. However, cognitive smell (recognition and identification) was increased and/or maintained up to the sixth decade of life, declining thereafter. Third) besides women having a better smell self-perception than men, they also scored better than men in smell detection, recognition, and identification, all throughout their lifetime. Fourth) pregnancy although not menstruation was strongly associated with a partial loss (hyposmia) of smell recognition. Fifth) male gender, poor smell self-perception, low educational level, and ageing, however not chronic rhinosinusitis, were risk factors related to smell impairment in either detection, recognition, or identification. Subjects with history of persistent olfactory loss or head trauma were also at higher risk of smell impairment. Sixth) finally and surprisingly, persistent exposure to noxious substances and smoking showed to be protective factors for cognitive smell impairment in either recognition or identification.

Since approximately 39.5 million Spaniards and 425 million EU citizens are aged 15 years or older, according to Catalan, Spanish, and European Statistic Institutes, our survey provides an estimate of 1.2 million adult Catalans, 7.7 million Spaniards, and over 82 million EU citizens suffering from olfactory dysfunction, among them 20,000 Catalans, 120,000 Spaniards, and 1.5 million EU citizens having a total loss of the sense of smell (anosmia).

Brämerson et al.[6] reported an overall prevalence of olfactory impairment of 19.1% in a Swedish population which was very similar to our 19.4%. This prevalence is considerably higher than self-reported loss of smell in the NGSS (1.4%) and in our own survey where 6.9%

of participants were considered to have a poor or very poor sense of smell, suggesting a low sensitivity for the subjective assessment of smell loss. The fact that many people may be unaware of their smell dysfunction, especially the elderly and/or those living alone, implies an increased risk for both nutritional problems [12] and safety in the face of a potential domestic fire or gas leak.[13]

In accordance with the OLFACAT survey data, previous studies have indicated that sense of smell detection is impaired with ageing, even in healthy individuals [14] and from the second to the eighth decade of life.[15] Our data also aligns with the NGSS and other studies in that the age decline in odour perception is universal across subjects regardless of gender odorants, outcome measures, or cultural diversity.[2,6] Smell changes observed across the survey's age span are similar to a previous study reporting a progressive decline in odour.[16] Concerning cognitive smell (memory and identification), we observed an increase in performance in the first decades of life, reaching a plateau during the third through to fifth decades of life and declining thereafter. Larsson et al.[4] reported that age was associated with an increased ability to identify banana odour (amylacetate) while our survey, in agreement with the NGSS findings, not only found an increased ability to recognise and identify banana, but also rose and gas, up to the fifth decade of life but decreasing thereafter. Due to the fact that repeated exposure to odorants and olfactory training may increase olfactory identification skills without modifying odour detection,[16] these age-increased abilities for smell identification however not for detection could be explained by the acquiring of cognitive smell skills through learning experience.

Among the potential mechanisms proposed for age-related olfactory loss are the replacement of olfactory mucosa with respiratory epithelium caused by disease or pollutant exposure,[17] cribiform plate calcification,[18] olfactory bulb atrophy,[19] decreased number of glomeruli/mitral cells in the olfactory tract,[20] and/or volume loss in temporal lobe areas.[21]

In accordance with other studies,[2,6,8] our survey found that women performed better in olfactory tasks compared with men of the same age group as well as self-reporting a better perception of smell sense. This gender difference was maintained across the life span, and increased considerably after the seventh decade of life. However, other studies have not found gender differences in olfactory sensitivity and identification, although women were slightly better.[4]

Interestingly, our survey found than pregnancy but not menstruation was associated with a lack of odour recognition/memory. Changes in odour perception during pregnancy have been investigated in small studies and with controversial findings,[22] with olfactory dysfunction being more linked to changes in nasal sensitivity than in real smell perception.[23] Clearly, our survey showed that women had a worse smell recognition during pregnancy (n=128, OD=8.09).

In addition to male gender and ageing, we found that a history of transient olfactory loss for more than one week was associated to impairment in odour detection, recognition, and identification. Post-viral olfactory dysfunction has been found among the common causes of olfactory disorders of which spontaneous recovery might occur within two years.[19,24]

Moreover, survey participants with a history of head trauma had a higher risk for anosmia in the forced-choice identification task. One of the major causes of smell dysfunction, affecting all ages, is traumatic brain injury, secondary to a partial or total damage of olfactory bulbs and tracts, which can involve frontal and temporal brain poles, being anosmia usually correlated to trauma severity.[25]

Although severe chronic rhinosinusitis with nasal polyps usually has a negative impact on smell function,[10] our data did not find chronic rhinosinusitis as being a risk factor for the loss of smell. This controversial finding, also described in other surveys,[23] could be due either to the potential mild severity of participants or a disease self misdiagnosis.

Studies on the impact of smoking on the sense of smell are not conclusive. Some studies have shown adverse effects on smell detection, identification, and intensity for some odours [8,9] whereas others have found no effect on smell detection and discrimination for other odorants.[23,26] In our survey, data showed that smoking might be a protective factor for cognitive smell. An explanation for this contradictory finding could be the activation of subtype-selective nicotinic receptors in the olfactory bulb. For instance, in neurodegenerative disorders such as Parkinson Disease olfactory loss is being considered as a significant early symptom that correlates with the progression of disease.[27] In addition to the current evidence for the protective effect of smoking in PD,[28] recent studies suggest that therapy with nicotine receptor agonists mediate enhancement of olfactory working memory in rats [29] and could delay the progress of neurodegeneration in PD. [30]

Another interesting finding showed that odour performance was positively related to a level of education superior to primary school. It is known that odour identification and semantic memory proficiency tap the same domain,[31] and that educational background is one of the most important predictors of cognitive decline with age, with cognitive deficits occurring earlier and more extensively in people with a low educational level.[32] From an olfactory perspective, education and training may help to develop a wider repertoire of cognitive strategies to assist performance in verbal memory tasks, such as odour identification.[33]

As with all epidemiological studies, the OLFACAT survey may have some weaknesses. One) the survey population cannot be considered a random sample since there was no control over who and how the survey was performed or whether participants were preferentially motivated to answer the survey. Two) the survey's data may not be fully representative of the general population since the readership survey (2003) shows that the newspaper's readers belong to a higher socio-cultural class (85.1% middle class) and have a higher educational level (31.1% with finished secondary school) than the general Catalan population (65.0% and 25.6%, respectively, 2002 census). Three) although other studies have not found smell differences among different ethnic groups, the lack of ethnic diversity in our sample (mainly Caucasians) could limit the generalisation to other ethnic groups. Four) cognitive disturbances in elderly individuals are characterised by impaired smell function but also potentially accounting for unwillingness to participate in the survey. Five) subjects with smell impairment could have been more/less interested in participating in the survey leading to an over/underestimation of the dysfunction prevalence. Six) observations were based on cross-sectional data, making it impossible to disentangle true ageing effects from cohort membership. Seven) the survey could have a positive female response bias since almost two thirds of participants who returned the surveys were women (65.7%).

In agreement with earlier findings in other cultures, the present survey on the general population indicates an age-related deterioration in odour detection, recognition, and identification, with a higher prevalence and a more manifest age decline in men than in women. Pregnancy, head trauma, and a transient olfactory loss history are absolute risk factors for olfactory dysfunction while having a higher educational level and smoking may be protective factors for smell. In order to understand the role of smell on human behaviour and determine the potential influence of cognitive, sensorial, and environmental factors, there is however an obvious need for well-designed longitudinal population-based studies, with validated smell tests while considering individual characteristics of the studied populations.

CONTRIBUTORSHIP STATEMENT

JM is the guarantor of the study, and has contributed with the conception and design of the study, literature search, acquisition of data, analysis and interpretation of data, and writing the manuscript. IA and FM have contributed with the study literature search, interpretation of data, drafting the manuscript, and approved the final version. LQ has contributed with the study design, acquisition of data, statistical analysis and interpretation of data, drafting the manuscript, and approved the final version. JH has contributed with the conception and design of the study, acquisition and interpretation of data, revising critically the manuscript, and approved the final version. CP, AV, and MB have contributed with the study design, interpretation of data, revising critically the manuscript, and approved the final version. CM has contributed with the conception and design of the study, acquisition of data, analysis and interpretation of data, revising critically the manuscript, and approved the final version. All authors had full access to all of the data of the study including statistical reports and tables.

COMPETING INTERESTS STATEMENT

None.

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

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DATA SHARING

Data from this study are not in the public domain.

FIGURE LEGENDS

Figure 1. Flow-chart of participants in the OLFACAT (Olfaction in Catalonia) survey.

Figure 2. Evolution of normal sense of smell (normosmia) during lifetime. Smell detection showed a progressive decrease during the life span, while smell recognition/memory and identification increased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and declined thereafter. For either detection, recognition/memory, or identification the sense of smell was significantly higher (p<0.0001) in women (blue line) than in men (red line).

Figure 3. Evolution of the partial loss of smell (hyposmia) during lifetime. For detection, hyposmia showed a progressive increase during the life span, while for recognition/memory and identification hyposmia decreased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and increased thereafter. For either detection, recognition/memory, or identification the partial loss of smell was significantly lower (p<0.0001) in women (blue line) than in men (red line).

Figure 4. Evolution of the total loss of smell (anosmia) during lifetime. Anosmia showed a progressive mild increase during the life span but being more significant after the sixth decade of life. For either detection, recognition/memory, or identification the total loss of smell was significantly lower (p<0.0001) in women (blue line) than in men (red line), with a maximal difference after the seventh decade of life.

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Table 1. OLFACAT epidemiological characteristics and gender comparison: age, women's health, education level, smoking and toxic exposure, subjective description of smell, zone of residence, history of head trauma, chronic rhinosinusitis, and loss of smell history.

Population characteristics [1]		**Male** 3,211 (34.3)	**Female** 6,137 (65.7)	**Total** 9,348 (100)	**p-value**
Age (years) [1]	< 20	127 (3.9)	315 (5.1)	442 (4.7)	< 0.0001 [2]
	20 - 29	241 (7.5)	878 (14.3)	1,119 (12.0)	
	30 - 39	668 (20.8)	1,487 (24.2)	2,155 (23.1)	
	40 - 49	861 (26.8)	1,673 (27.3)	2,534 (27.1)	
	50 - 59	766 (23.9)	1,181 (19.3)	1,947 (20.8)	
	60 - 69	355 (11.1)	454 (7.4)	809 (8.6)	
	> 70	193 (6.0)	149 (2.4)	342 (3.7)	
Menstruation [1]			781 (12.7)		
Pregnancy [1]			128 (2.1)		
Educational level [1]	elementary school	7 (0.2)	26 (0.4)	33 (0.3)	< 0.0001 [2]
	secondary school	508 (15.8)	978 (15.9)	1,486 (15.9)	
	high school	1,505 (46.9)	2,568 (41.9)	4,073 (43.6)	
	university/college	1,191 (37.1)	2,565 (41.8)	3,756 (40.2)	
Smoking [1]	non-smokers	1,185 (36.9)	3,513 (57.2)	4,698 (50.3)	< 0.0001 [2]
	ex-smokers	1,231 (38.3)	1,418 (23.1)	2,649 (28.3)	
	smoker	795 (24.8)	1,206 (19.7)	2,001 (21.4)	
Subjective description of sense of smell [1]	very good	407 (12.7)	1,576 (25.7)	1,983 (21.2)	< 0.0001 [2]
	good	2,472 (77.0)	4,243 (69.1)	6,715 (71.9)	
	poor	315 (9.8)	305 (5.0)	620 (6.6)	
	very poor	17 (0.5)	13 (0.2)	30 (0.3)	
Residency zone [1]	rural	57 (1.8)	109 (1.8)	166 (1.8)	0.9535 [2]
	semi-rural	142 (4.4)	263 (4.3)	405 (4.3)	
	urban	3,012 (93.8)	5,765 (93.9)	8,777 (93.9)	
History of head trauma [1]		200 (6.2)	264 (4.3)	464 (5.0)	< 0.0001 [2]
Exposure to noxious substances [1]		1,090 (33.9)	1,703 (27.7)	2,793 (29.9)	< 0.0001 [2]
Chronic rhinosinusitis [1]		137 (4.3)	277 (4.5)	414 (4.4)	0.5814 [2]
Loss of smell history [1]	never	2,217 (69.0)	4,289 (69.9)	6,506 (69.6)	0.0042 [2]
	≤ 1 week	789 (24.6)	1,555 (25.3)	2,344 (25.1)	
	> 1 week	205 (6.4)	293 (4.8)	498 (5.3)	

1: number of subjects (percentage)
2: Chi-square test

Table 2. Relative risk for the partial (hyposmia) or total (anosmia) loss of smell detection using a multivariate logistic analysis of demographic and health problems. Data presented as OR (Odd Ratio), 95% CI (Confidence Interval).

Smell detection	Variable		OR	95% CI	p-value
Anosmia (n= 9,251)	Subjective description of sense of smell	very good	1		< 0.0001
		good	0.21	0.03; 1.55	
		poor	2.14	0.32; 14.32)	
		very poor	207.18	31.70; 1353.78	
	Gender	male	1		0.0096
		female	0.23	0.08; 0.70	
	Loss of smell history	never	1		0.0263
		≤ 1 week	0.70	0.08; 6.24	
		> 1 week	5.76	1.45; 22.95	
Hyposmia (n= 8,601)	Subjective description of sense of smell	very good	1		< 0.0001
		good	1.24	1.07; 1.43	
		poor	2.44	1.96; 3.04	
		very poor	1.99	0.90; 4.42	
	Gender	male	1		< 0.0001
		female	0.77	0.69; 0.87	
	Age (years)	< 20	1		< 0.0001
		20 - 29	1.12	0.80; 1.58	
		30 - 39	1.32	0.96; 1.80	
		40 - 49	1.50	1.10; 2.04	
		50 - 59	1.77	1.30; 2.41	
		60 - 69	1.89	1.35; 2.65	
		> 70	1.61	1.07; 2.42	
	Educational level	elementary school	1		0.0473
		secondary school	0.75	0.32; 1.80	
		high school	0.76	0.32; 1.80	
		university/college	0.89	0.37; 2.12	

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Table 3. Relative risk for the partial (hyposmia) or total (anosmia) loss of smell recognition/memory using a multivariate logistic analysis of demographic characteristics and health problems. Data presented as OR (Odd Ratio), 95% CI (Confidence Interval).

Smell recognition	Variable		OR	95% CI	p-value
Anosmia (n= 9,079)	Subjective description of sense of smell	very good	1		< 0.0001
		good	1.16	0.33; 4.14	
		poor	1.20	0.12; 11.76	
		very poor	128.62	18.48; 895.23	
	Educational level	elementary school	1		< 0.0001
		secondary school	0.04	0.01; 0.21	
		high school	0.04	0.01; 0.17	
		university/college	0.00	0.00; 0.04	
	Pregnancy	no	1		0.0472
		yes	8.09	1.03; 63.81	
Hyposmia (n= 6,778)	Age (years)	< 20	1		< 0.0001
		20 - 29	0.81	0.63; 1.03	
		30 - 39	0.65	0.51; 0.82	
		40 - 49	0.59	0.47; 0.74	
		50 - 59	0.62	0.49; 0.79	
		60 - 69	0.76	0.58; 1.00	
		> 70	1.23	0.87; 1.73	
	Subjective description of sense of smell	very good	1		< 0.0001
		good	1.45	1.28; 1.64	
		poor	2.34	1.84; 2.96	
		very poor	2.25	0.61; 8.39	
	Smoking	non-smokers	1		< 0.0001
		ex-smokers	0.80	0.71; 0.90	
		smoker	0.67	0.59; 0.77	
	Gender	male	1		0.0001
		female	0.80	0.72; 0.90	
	Loss of smell history	never	1		0.0044
		≤ 1 week	0.83	0.74; 0.93	
		> 1 week	1.05	0.82; 1.34	
	Exposure to noxious substances	no	1		0.0015
		yes	0.84	0.75; 0.93	
	Educational level	elementary school	1		0.0230
		secondary school	1.22	0.56; 2.63	
		high school	1.02	0.48; 2.20	
		university/college	0.95	0.44; 2.05	

Table 4. Relative risk for the partial (hyposmia) or total (anosmia) loss of smell identification using a multivariate logistic analysis of demographic characteristics and health problems. Data presented as OR (Odd Ratio), 95% CI (Confidence Interval).

Smell identification	Variable		OR	95% CI	p-value
Anosmia (n= 9,195)	Subjective description of sense of smell	very good	1		< 0.0001
		good	1.33	0.62; 2.86	
		poor	4.56	1.86; 11.18	
		very poor	199.87	68.70; 581.49	
	Age (years)	< 20	1		0.0001
		20 - 29	0.85	0.22; 3.28	
		30 - 39	0.61	0.17; 2.21	
		40 - 49	0.44	0.12; 1.63	
		50 - 59	0.63	0.17; 2.31	
		60 - 69	1.99	0.56; 7.02	
		> 70	3.01	0.80; 11.31	
	History of head trauma	no	1		0.0002
		yes	3.67	1.87; 7.23	
Hyposmia (n= 8,107)	Subjective description of sense of smell	very good	1		< 0.0001
		good	1.42	1.26; 1.58	
		poor	2.91	2.34; 3.61	
		very poor	0.73	0.34; 1.60	
	Age (years)	< 20	1		< 0.0001
		20 - 29	0.81	0.63; 1.02	
		30 - 39	0.76	0.61; 0.95	
		40 - 49	0.79	0.64; 0.98	
		50 - 59	0.95	0.76; 1.18	
		60 - 69	1.14	0.88; 1.46	
		> 70	1.62	1.18; 2.22	
	Gender	male	1		< 0.0001
		female	0.77	0.70; 0.85	
	Loss of smell history	never	1		0.0007
		≤ 1 week	0.82	0.74; 0.92	
		> 1 week	1.08	0.86; 1.35	
	Educational level	elementary school	1		0.0003
		secondary school	0.49	0.21; 1.16	
		high school	0.50	0.21; 1.16	
		university/college	0.60	0.26; 1.41	

Figure 1

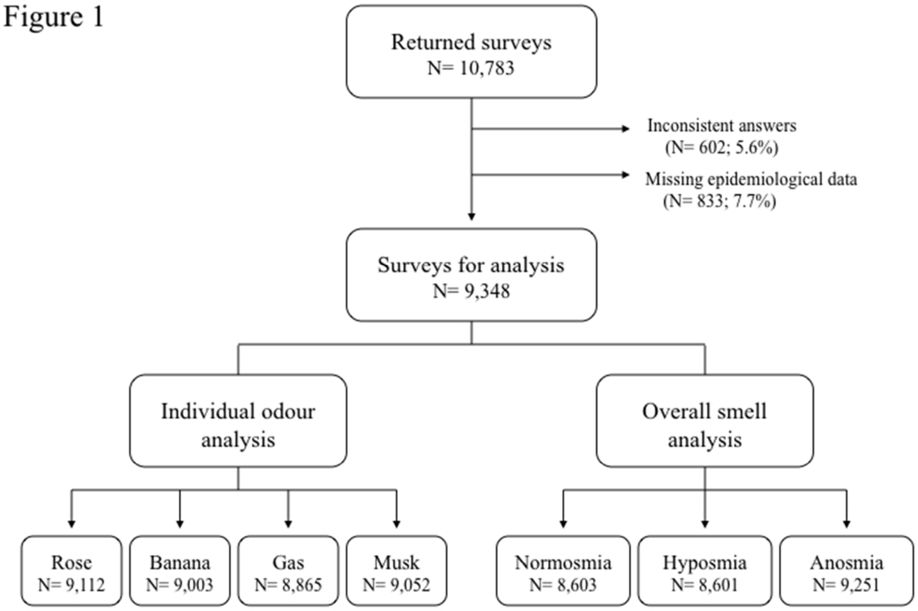

Figure 1. Flow-chart of participants in the OLFACAT (Olfaction in Catalonia) survey.
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Figure 2

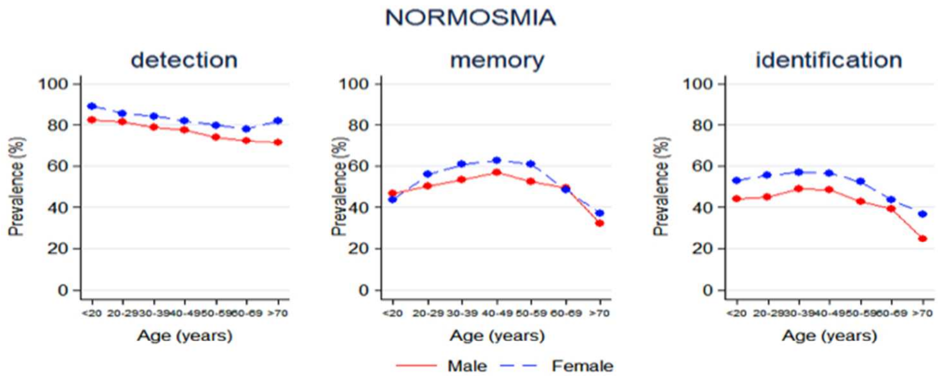

Figure 2. Evolution of normal sense of smell (normosmia) during lifetime. Smell detection showed a progressive decrease during the life span, while smell recognition/memory and identification increased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and declined thereafter. For either detection, recognition/memory, or identification the sense of smell was significantly higher (p<0.0001) in women (blue line) than in men (red line).
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Figure 3

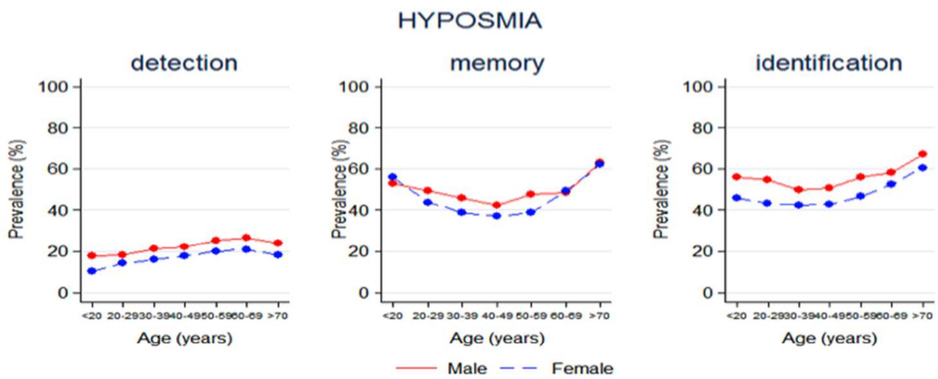

Figure 3. Evolution of the partial loss of smell (hyposmia) during lifetime. For detection, hyposmia showed a progressive increase during the life span, while for recognition/memory and identification hyposmia decreased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and increased thereafter. For either detection, recognition/memory, or identification the partial loss of smell was significantly lower (p<0.0001) in women (blue line) than in men (red line).
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Figure 4

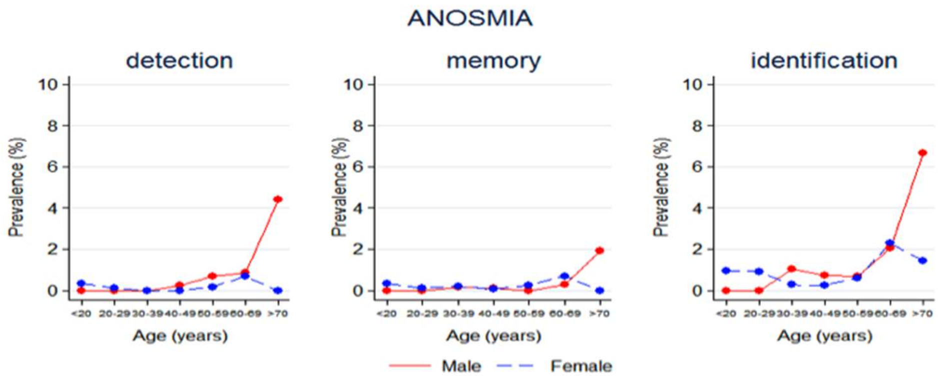

Figure 4. Evolution of the total loss of smell (anosmia) during lifetime. Anosmia showed a progressive mild increase during the life span but being more significant after the sixth decade of life. For either detection, recognition/memory, or identification the total loss of smell was significantly lower ($p<0.0001$) in women (blue line) than in men (red line), with a maximal difference after the seventh decade of life.
275x190mm (72 x 72 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

YOU MUST NOTE THE PAGE NUMBER WHERE EACH ITEM IS REPORTED INSIDE THE BRACKETS [ ]. IF NOT APPLICABLE WRITE N/A

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Page 1]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[Page 3]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[Pages 5 and 6]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[Page 6]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Page 7]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Page 7]**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[Pages 7 to 9]** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **[N/A]** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **[N/A]**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **[Pages 7 to 9]** *Case-control study*—For matched studies, give matching criteria and the number of controls per case **[N/A]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Pages 7 to 9]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Pages 7 to 9]**
Bias	9	Describe any efforts to address potential sources of bias **[Pages 17 and 18]**
Study size	10	Explain how the study size was arrived at **[Page 9, Figure 1]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Page 9]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Page 9]**
		(*b*) Describe any methods used to examine subgroups and interactions **[Page 9]**
		(*c*) Explain how missing data were addressed **[Page 9, Figure 1]**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **[N/A]** *Case-control study*—If applicable, explain how matching of cases and controls was addressed **[N/A]** *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy **[N/A]**
		(*e*) Describe any sensitivity analyses **[N/A]**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Pages 10 to 13, Figure 1, Table 1]**
		(b) Give reasons for non-participation at each stage **[Figure 1]**
		(c) Consider use of a flow diagram **[Figure 1]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Pages 10 and 11, Table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[Pages 10 to 13, Figure 1]**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **[Page 10]**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **[N/A]**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure **[N/A]**
		Cross-sectional study—Report numbers of outcome events or summary measures **[N/A]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Pages 10 to 13, Figure 2 to 4, Tables 2 to 4]**
		(*b*) Report category boundaries when continuous variables were categorized **[Pages 10 to 13, Tables 2 to 4]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[Page 14]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[N/A]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Page 14]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Pages 17 and 18]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Page 18]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Pages 14 to 18]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[Pages 20 and 21]**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Once you have completed this checklist, please save a copy and upload it as part of your submission. When requested to do so as part of the upload process, please select the file type: *Checklist*. You will NOT be able to proceed with submission unless the checklist has

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Furthering the understanding of olfaction, prevalence of loss of smell, and risk factors: a population-based survey (OLFACAT study).

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Furthering the understanding of olfaction, prevalence of loss of smell, and risk factors: a population-based survey (OLFACAT)

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RELEVANT SURVEY HEADINGS: sense of smell, general population, olfactory disorders, normosmia, hyposmia, anosmia, risk factors.

ABSTRACT

Objectives: To investigate the sense of smell in the general population, prevalence of olfactory dysfunction and its related risk factors.

Design: Cross-sectional population-based survey, by distributing four microencapsulated odorants (rose, banana, musk, gas) and two self-administered questionnaires (odour description; epidemiology/health status).

Setting: The survey was distributed to the general population through a bilingual (Catalan, Spanish) newspaper in Catalonia (Spain), on December 2003.

Participants: Newspaper readers of all ages and gender; 9,348 surveys were analyzed from the 10,783 returned.

Main outcome measures: Characteristics of surveyed population, olfaction by age and gender, smell-self perception, and risk factors for smell impairment.

Results: The survey profile was a 43-year-old woman with medium-high educational level, living in a city. Sense of smell was considered normal in 80.6% for detection, 56.0% for recognition/memory, and 50.7% for forced-choice identification. Prevalence of smell dysfunction was 19.4% for detection (0.3% anosmia, 19.1% hyposmia), 43.5% for recognition (0.2% anosmia, 43.3% hyposmia), and 48.8% for identification (0.8% anosmia, 48% hyposmia). Sense of smell was worse ($p<0.0001$) in men than in women through all ages. There was a significant age-related smell detection decline for both genders however smell recognition and identification increased up to the fourth decade and then declined after the sixth decade of life. Risk factors for anosmia were: male gender, loss of smell history, and poor olfactory self-perception for detection; low educational level, poor olfactory self-perception, and pregnancy for recognition; and older age, poor olfactory self-perception, and

history of head trauma and loss of smell for identification. Smoking and exposure to noxious substances were mild protective factors for smell recognition.

Conclusions: Sense of smell in women is better than in men suggesting a learning process during life with deterioration in older ages. Poor self-perception, history of smell loss, head trauma, and pregnancy are potential risk factors for olfactory disorders.

ABSTRACT WORD COUNT: 300 words

ARTICLE SUMMARY

Article focus

• Population-based smell survey in 2003.

• Partial and total smell impairment by age and gender.

• Risk factors for olfactory disorders.

Key messages

• Olfaction is better in female than in male.

• Smell improves with a learning process and deteriorates in older ages.

• Poor olfactory self-perception, history of smell loss for over one week, head trauma, and pregnancy are ~~absolute~~ potential risk factors for olfactory disorders.

Strengths and limitations of this study

• Strength: The largest European population-based study providing data on partial/total loss of smell and their absolute risk factors.

• Limitations: self-administered survey (no control on how it was performed); the study was done in a middle-high socio-cultural population (newspaper readers).

INTRODUCTION

The sense of smell provides information on the surrounding environment, warns us about chemical dangers and putrid food, and may even help people to mate. Smell disorders may affect the ability to enjoy food and aromas while interfering with the ability to notice potentially harmful chemicals and gases.[1] Unlike well-documented epidemiological studies on hearing and vision, most smell-perception studies are not well standardised, some are contradictory, and few are broad enough to offer clear conclusions.

In 1987, the National Geographic Smell Survey (NGSS) studied a large US sample population (1.2 million) whereby 1% of participants could not smell three or more of six odorants using a "scratch and sniff" test.[2] Age was an important factor in smell deterioration and smell was rated better in women than in men. In 1994, the National Health Interview Survey (NHIS)[3] reported data from 42,000 United States households with 1.4% prevalence of self-reported olfactory dysfunction, exponentially increasing with age. This study, however, did not include any testing of smell function.

The prevalence and associated risk factors of olfactory impairment in the European population has been investigated to a limited extent. In the Swedish version of the NGSS,[4] done in 532 individuals older than 45 years, increasing age was associated with impaired ability to detect/identify odorants, with no effect of gender on smell perception. Education has also been shown to account for a significant portion of the age-related variance in identification.[5] Another European population-based study identified a significant relationship between impaired olfaction and aging, male gender, and nasal polyps, but not with diabetes or smoking, reporting an olfactory dysfunction prevalence of 19.1%.[6]

Approximately two thirds of smell dysfunction cases are likely due to prior upper respiratory infections, head trauma, or sinonasal diseases.[7] Toxic chemical exposure, epilepsy, pollution, drugs, nutritional disturbances, and neurodegenerative diseases may also cause olfactory disorders.[8,9] Smoking may cause a reversible reduction in the ability to smell[10,11] while chronic rhinosinusitis/nasal polyps may result in a partial or total loss of smell.[12]

The aims of this study were to investigate the current status of olfaction in the general population while determining the prevalence of olfactory dysfunction and its related risk factors.

METHODS

Study Design

The OLFACAT (Olfaction in Catalonia) survey was carried out in the general population of Catalonia in Spain. Two questionnaires, olfaction and demography-health status, and a set of four microencapsulated odorants were distributed in the 250,000 daily issues of the newspaper *El Periódico de Catalunya* on December 23rd, 2003. The survey was presented in both Catalan and Spanish languages to facilitate the choice of the preferred language. The present manuscript has followed the STROBE checklist guidelines.

The study was approved by the Institutional Ethics and Clinical Research Committee of Hospital Clínic de Barcelona (reference 1295).

Measurements

Survey Odorants**.** Four common odorants were included in the survey: rose (2% of Bulgarian rose in 98% of phenyl-ethyl alcohol) as a floral odour; banana (amyl-isobutirate at 50% in dietyl-phtalate) as a food odour; musk (1:1 mixture of galaxolide and diethyl-phtalate exaltolide) as a perfume odour; and gas (mixture of 30% mercaptan and 70% tetrahydrothiophene) as an industrial odour. Each compound was prepared following established formulas and the solution magnetically homogenized. Rose, banana, and musk odorants were elaborated by Antonio Puig SA (Barcelona, Catalonia, Spain) and gas odorant by ENAGAS (Saragossa, Spain). Stability test protocols were performed by accelerating the olfactory aging of products at 40ºC for 2 months, following their smell evolution after 1 to 8 weeks. The micro-encapsulation process was done by ARCADE Europe (Paris France) as follows: essential oil component was contained and delivered from highly durable synthetic microcapsules manufactured using a proprietary polycondensated polymerization method.

The microcapsules were blended with a water-based polymer adhesive to form printable slurry. Odorants were adhered to a smell-less paper and dispatched using a folded-form design so as to prevent direct contact between odour samples.

Smell questionnaire. Participants were asked to scratch and sniff each odour and then answer three questions: First) odour detection: did you smell any scent? (yes, no); Second) odour recognition/memory: have you ever smelt this scent? (yes, no); and third) forced-choice odour identification: which name defines the scent you have smelt?, whereby only one of the four given options was correct. The term "normosmia" was used when a participant was able to detect, recognize (memory), or correctly identify all four tested odours; the term "hyposmia" was used when a participant was not able to detect, recognize (memory), or correctly identify one, two, or three tested odours; and the term "anosmia" was used when a participant was unable to detect, recognize (memory), or correctly identify any of the four tested odours.

Epidemiological and health-status questionnaire. From the twelve-question questionnaire, four questions were on demography: first) gender (male, female); second) age (years); third) current educational level (primary school, secondary school, high school, University or College); and fourth) residential area (city, postcode). Two questions described smell self-perception: fiftth) how do you consider your current sense of smell? (very good, good, poor, very poor); and sixth) have you ever lost the sense of smell? (never, up to one week, over one week). Two questions were on exposure to toxic or noxious substances: seventh) have you ever been exposed to dust, gases, fumes, vapours, or/and volatile toxics at home and/or at work? (yes, no); and eighth) do you smoke? (no, ex-smoker, smoker). Two questions were on health-status: ninth) have you ever had a severe face and/or head trauma? (yes, no); and tenth) have you ever been diagnosed with chronic rhinosinusitis? (yes, no). Finally, two questions

were on women's health: eleventh) are you currently pregnant? (yes, no); and twelfth) are you currently menstruating? (yes, no).

Data Management and Statistical Analysis

The returned surveys were read using an optical system (BV Scan system, Voxpublica), the data were transferred to an electronic database, and then statistically analysed using Stata version 8 (Stata Statistical Software: Release 8.0 College Station, TX: *Stata Corporation* 2003).[13] The data cleaning process was based on programmed queries to identify records containing inconsistent or uncertain data. The corrupt or inaccurate values identified by these queries were subsequently recorded as missing values in the data set.

Only those surveys fully and consistently answered were considered for statistical analysis. Differences between gender in epidemiological and health-status characteristics were evaluated by Chi-square test. ~~Crude and multivariate logistic regression models were estimated to identify associations with smell detection, recognition/memory, and forced-choice identification, as well as for normosmia, hyposmia, and anosmia. Multivariate analyses were performed by a forward-stepwise procedure, using p<0.05 from the Wald test, as enter criteria.~~ Adjusted (multivariate) logistic regression models for anosmia and hyposmia were estimated (Tables 2, 3 and 4). To estimate the multivariate models for anosmia, the covariates that do not have any events (anosmia cases) in any of its categories were not included. Results from estimated models were expressed as adjusted Odd Ratio (OR) and 95% Confidence Interval (CI). The reference category used to calculate the OR for each level of variables measured on an ordinal scale was the immediately previous category, starting with the second. Results from estimated models were expressed as Odd Ratio (OR) and 95% Confidence Interval (CI). All tests were performed using a two-tailed significance level of 0.05.

RESULTS

Characteristics of the surveyed population

Following the data cleaning process, 5.6% of answers from the 10,783 received surveys were identified as inconsistent. After the exclusion of both these inconsistent questionnaire returns and the incomplete epidemiological and health-status questionnaires (7.7%), the sample size for analysis was 9,348 questionnaires (Figure 1).

Age and gender. The mean age of the surveyed population was 43.3 years, ranging from 5 to 91 years. The analysis was performed in seven age groups to ensure a reasonable sample size for each age and gender group. Almost two thirds of participants were women (65.7%), of which 2.1% were pregnant and 12.7% were menstruating (Table 1).

Education and residential zone. Most participants (83.8%) had a high educational level (high school or University/College) and were living (93.9%) in an urban area, with no differences between gender.

Exposure to tobacco and noxious substances. More than one fifth (21.4%) of participants were smokers, 28·3% were ex-smokers, while almost a third (29.9%) reported to be regularly exposed to toxic or noxious substances, either at home or at work. Men reported a higher exposure to both tobacco smoke (24.8%, p<0.0001) and noxious substances (33.9%, p<0.0001) than women (19.7% and 27.7%, respectively).

Health status. 4.4% of participants had received a diagnosis of chronic rhinosinusitis, with similar prevalence in women and men, while 5.0% reported a history of face/head trauma, this prevalence being higher in men than in women (6.2% versus 4.3%, p<0.0001).

Sense of smell. All four odours (~~normal sense of smell or~~ normosmia) were detected by 80.6%, recognised by 56.0%, and identified by 50.7% of the surveyed population. One to three odours (~~partial loss of smell or~~ hyposmia) were detected by 19.1%, recognised by

43.3%, and identified by 48.0%. None of the four odours (~~total loss of smell or~~ anosmia) were detected by 0.3%, recognised by 0.2%, and identified by 0.8%. Individual odours were more highly detected (rose 99.4%, banana 98.9%, gas 96.9%, musk 84.4%) than recognised (rose 94.8%, banana 96.2%, gas 94.9%, musk 66.2%) or correctly identified (rose 91.8%, banana 89.8%, gas 92.1%, musk 65.4%). Moreover, individual odours were always better detected, recognised, and identified by women than by men, except for rose and banana recognition.

Smell by gender and age

Within the population experiencing normosmia, there was a significant and progressive age-related decline of smell detection while smell recognition and identification increased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and declined thereafter. Significant but opposite findings were found for hyposmia and anosmia. Normosmia was higher in women than in men ($p<0.0001$) either in smell detection (82.8% versus 76.5%), recognition/memory (58.0% versus 51.9%), or identification (54.1% versus 44.3%) (Figure 1). Hyposmia was higher in men than in women ($p<0.0001$) either in smell detection (22.8% versus 17.1%), recognition/memory (47.1% versus 41.4%), and identification (54.0% versus 44.9%) (Figure 2). Finally, anosmia was higher in men than in women in both smell detection (0.9% versus 0.1%; $p<0.0001$) and identification (1.2% versus 0.6%; p=0·0057), but not in smell recognition/memory (0.2% versus 0.2%, p=0.9569) (Figure 3). In the oldest group (over 70 years), the prevalence for anosmia of detection (4.4%) and identification (6.6%) was especially higher in men than in women (0% and 1·4%, respectively).

Smell self-perception

Subjective description of smell. Regardless of gender and age, 93.1% of participants subjectively rated their sense of smell as good or very good, while 6.9% of them reported their smell as poor or very poor, the smell score being better in women than in men ($p<0.0001$).

Loss of smell history. A past history of loss of smell was reported by almost one third (30.4%) of participants, predominantly for less than one week (25.1%). The smell loss for over one week was more frequent in men (6.4% vs 4.8%, $p=0.0042$).

Risk factors for smell impairment

Smell detection. Women detected odours more frequently than men (82.8% versus 76.5%, $p<0.0001$). The risk for anosmia of detection was lower in women (OR=0.22) and higher in subjects reporting a loss of smell history for over one week (OR=9.26); and anosmia was also associated with a worse smell self-perception (Table 2). The risk for hyposmia of detection was lower in women (OR=0.78) and associated with older age (>50 years old), a lower educational level, and a worse smell self-perception (Table 2).

Smell recognition / memory**.** Women showed a better capability to recognise odours than men (58.0% versus 51.9%; $p<0.0001$). The risk for anosmia of recognition was higher in pregnant women (OR=6.94) and associated with a lower educational level and a worse smell self-perception (Table 3). The risk for hyposmia of recognition was lower in women (OR=0.79) and higher in subjects reporting a loss of smell history for over one week (OR=1.23); and it was associated with older age (>70 years old), a lower educational level, and a worse smell self-perception. Smoking (both ex-smokers and smokers) (OR=0.80 and 0.68, respectively) and frequent contact with noxious substances (OR=0.83) were found to have a mild but significant protective effect on odour recognition/memory (Table 3).

Forced-choice smell identification. Women performed better than men on odour identification (54.1% versus 44.3%, p<0.0001). The risk for anosmia of identification was higher in subjects reporting a history of head trauma (OR=3.38) and a loss of smell for over one week (OR=2.79), and it was associated with older age (>60 years old) and a worse smell self-perception (Table 4). The risk for hyposmia of identification was lower in women (OR=0.76) and higher in subjects reporting a loss of smell history for over one week (OR=1.28), and it was associated with older age (>60 years old), a lower educational level, and a smell worse self-perception (Table 4).

DISCUSSION

The most important findings of the OLFACAT survey were: First) the overall prevalence of olfactory dysfunction in the case of detection was 19.4%, with a total loss of smell (anosmia) of 0.3%. Despite this high prevalence of smell impairment, only 6.9% of the subjects considered having a poor or very poor sense of smell. Second) there was a significant age-related decline in smell detection for both genders. However, cognitive smell (recognition and identification) was increased and/or was maintained up to the sixth decade of life, declining thereafter. Third) besides women having a better self-perception of smell capabilities than men, women also scored better than men in smell detection, recognition, and identification, and did so throughout their lifetime. Fourth) pregnancy, but not menstruation was ~~strongly~~ associated with a partial loss (hyposmia) of smell recognition. Fifth) male gender, poor smell self-perception, low educational level, and ageing, but not chronic rhinosinusitis, were risk factors related to smell impairment whether in terms of detection, recognition, or identification. Subjects with a history of persistent olfactory loss or head trauma were also at higher risk of smell impairment. Sixth) finally and surprisingly, persistent exposure to noxious substances and smoking showed to be protective factors for cognitive smell impairment in either recognition or identification.

Approximately 39.5 million Spaniards and 425 million EU citizens are aged 15 years or older, according to Catalan, Spanish, and European Statistic Institutes. Our survey therefore estimates that 1.2 million adult Catalans, 7.7 million Spaniards, and over 82 million EU citizens suffering from olfactory dysfunction, of which 20,000 Catalans, 120,000 Spaniards, and 1.5 million EU citizens have a total loss of sense of smell. ~~(anosmia).~~

Brämerson et al.[6] reported an overall prevalence of olfactory impairment of 19.1% in a Swedish population which was very similar to our 19.4%. This prevalence is considerably

higher than self-reported loss of smell in the NGSS[2] (1.4%) and in our own survey where 6.9% of participants were considered to have a poor or very poor sense of smell, suggesting a low sensitivity for the subjective assessment of smell loss. The fact that many people may be unaware of their smell dysfunction, especially the elderly and/or those living alone, implies an increased risk for both nutritional problems[14] and safety in the face of a potential domestic fire or gas leak.[15]

In accordance with the OLFACAT survey data, previous studies have indicated that sense of smell detection is impaired with ageing, even in healthy individuals[16] and from the second to the eighth decade of life.[17] Our data also aligns with the NGSS and other studies in that the age decline in odour perception is universal across subjects regardless of gender odorants, outcome measures, or cultural diversity.[2,6] Smell changes observed across the survey's age span are similar to a previous study reporting a progressive decline in odour.[18] Concerning cognitive smell (memory and identification), we observed an increase in performance in the first decades of life, reaching a plateau during the third through to fifth decades of life and declining thereafter. Larsson et al.[4] reported that age was associated with an increased ability to identify banana odour (amylacetate). Our survey, in agreement with the NGSS findings, found not only an increased ability to recognise and identify banana, but rose and gas also, with increase indicated up to the fifth decade of life but decreasing thereafter. Due to the fact that repeated exposure to odorants and olfactory training may increase olfactory identification skills without modifying odour detection,[18] these age-increased abilities for smell identification but not for detection, could be explained by the acquisition of cognitive smell skills through learnt experience.

Among the potential mechanisms proposed for age-related olfactory loss are the replacement of olfactory mucosa with respiratory epithelium caused by disease or pollutant exposure,[19]

cribiform plate calcification,[20] olfactory bulb atrophy,[21] decreased number of glomeruli/mitral cells in the olfactory tract,[22] and/or volume loss in temporal lobe areas.[23]

In accordance with other studies,[2,6,8] our survey found that women performed better in olfactory tasks compared with men of the same age group as well as self-reporting a better perception of smell sense. This gender difference was maintained across the life span, and increased considerably after the seventh decade of life. However, other studies have not found gender differences in olfactory sensitivity and identification, although women were slightly better.[4] We have to note that the rates of correctly identified odours (54.1% by women, 44.3% by men) are lower than those found in the BAST-24 validation,[24] in which the present survey is based, and a potential explanation could be that the OLFACAT study was done in the general population, with both healthy and diseased participants, when in the BAST-24 validation all participant were healthy.

Interestingly, our survey found than pregnancy but not menstruation was associated with a lack of odour recognition/memory. Changes in odour perception during pregnancy have been investigated in small studies and with controversial findings,[25] with olfactory dysfunction being more linked to changes in nasal sensitivity than in real smell perception.[26] Clearly but not significantly, our survey showed that women had an increased risk for anosmia of smell recognition/memory during pregnancy (n=125, OR=6.94).

In addition to male gender and ageing, we found that a history of transient olfactory loss for more than one week was associated to impairment in odour detection, recognition, and identification. Post-viral olfactory dysfunction has been found among the common causes of olfactory disorders of which spontaneous recovery might occur within two years.[21,27]

Moreover, survey participants with a history of head trauma had a higher risk of anosmia in the forced-choice identification task. One of the major causes of smell dysfunction, affecting all ages, is traumatic brain injury, secondary to a partial or total damage of olfactory bulbs and

tracts. This can involve frontal and temporal brain poles, as anosmia usually correlated with trauma severity.[28]

Although severe chronic rhinosinusitis with nasal polyps usually has a negative impact on smell function,[12] our data did not identify chronic rhinosinusitis as being a risk factor for the loss of smell. This controversial finding, also described in other surveys,[26] may be due either to possible mild levels of severity or self-misdiagnosis of the disease among survey participants.

Studies on the impact of smoking on the sense of smell are not conclusive, specially when different smell qualities are considered. Some studies have shown adverse effects on smell detection, identification, and intensity for some odours[8,10,11] whereas others have found no effect on smell detection and discrimination for other odorants.[9,26,29] In our survey, data showed that smoking might be a mild but significant protective factor for cognitive smell. An explanation for this contradictory finding could be the activation of subtype-selective nicotinic receptors in the olfactory bulb. For instance, in neurodegenerative disorders such as Parkinson Disease olfactory loss is being considered as a significant early symptom that correlates with the progression of disease.[30] In addition to the current evidence for the protective effect of smoking in PD,[31] recent studies suggest that therapy with nicotine receptor agonists mediate enhancement of olfactory working memory in rats[32] and could delay the progress of neurodegeneration in PD.[33] However, further epidemiologic and mechanistic studies need to be done taking in account the different smell qualities (detection, memory, identification) to bring definitive light to the impact of smoking in the sense of smell.

Another interesting finding showed that odour performance was positively related to a level of education superior to primary school. It is known that odour identification and semantic memory proficiency tap the same domain,[34] and that educational background is one of the most important predictors of cognitive decline with age, with cognitive deficits occurring

earlier and more extensively in people with a low educational level.[35] From an olfactory perspective, education and training may help to develop a wider repertoire of cognitive strategies to assist performance in verbal memory tasks, such as odour identification.[36]

As with all epidemiological studies, the OLFACAT survey may have some weaknesses. One) the survey population cannot be considered a random sample since there was no control over who and how the survey was performed or whether participants were preferentially motivated to answer the survey. Two) the survey's data may not be fully representative of the general population since the readership survey (2003) shows that the newspaper's readers belong to a higher socio-cultural class (85.1% middle class) and have a higher educational level (31.1% with finished secondary school) than the general Catalan population (65.0% and 25.6%, respectively, 2002 census). Three) although other studies have not found smell differences among different ethnic groups, the lack of ethnic diversity in our sample (mainly Caucasians) could limit the generalisation to other ethnic groups. Four) cognitive disturbances in elderly individuals are characterised by impaired smell function but also potentially accounting for unwillingness to participate in the survey. Five) subjects with smell impairment could have been more/less interested in participating in the survey leading to an over/underestimation of the prevalence of dysfunction. Six) observations were based on cross-sectional data, making it impossible to disentangle true ageing effects from cohort membership. Seven) the survey could have a positive female response bias since almost two thirds of participants who returned the surveys were women (65.7%).

In agreement with earlier findings in other cultures, the present survey on the general population indicates an age-related deterioration in odour detection, recognition, and identification, with a higher prevalence and a more manifest age decline in men than in women. Pregnancy, head trauma, and a transient olfactory loss history are absolute risk

factors for olfactory dysfunction while having a higher educational level and smoking may be protective factors for smell. In order to understand the role of smell in human behaviour and determine the potential influence of cognitive, sensorial, and environmental factors, there is however an obvious need for well-designed longitudinal population-based studies, which deploy validated smell tests and consider the characteristics of the populations studied.

CONTRIBUTORSHIP STATEMENT

JM is the guarantor of the study, and has contributed with the conception and design of the study, literature search, acquisition of data, analysis and interpretation of data, and writing the manuscript. IA and FM have contributed through literature research, interpretation of data, and by drafting the manuscript; they approved the final version. LQ has contributed with the study design, acquisition of data, statistical analysis and interpretation of data, and drafting the manuscript; and approved the final version. JH has contributed with the conception and design of the study, acquisition and interpretation of data, and a critical reading of the manuscript; and approved the final version. CP, AV, and MB have contributed with the study design, interpretation of data, a critical reading of the manuscript, and approved the final version. CM has contributed with the conception and design of the study, acquisition of data, analysis and interpretation of data, and a critical reading of the manuscript; and approved the final version. All authors had full access to all of the data of the study including statistical reports and tables.

COMPETING INTERESTS STATEMENT

None.

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

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sponsors participated in the analysis and interpretation of data, writing of the report and the decision to submit the report for publication.

DATA SHARING

Data from this study are not in the public domain.

FIGURE LEGENDS

Figure 1. Flow-chart of participants in the OLFACAT (Olfaction in Catalonia) survey.

Figure 2. Evolution of normosmia (smell of all four odours) during lifetime. Smell detection showed a progressive decrease during the life span, while smell recognition/memory and identification increased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and declined thereafter. For ~~either~~ detection, recognition/memory, or identification, normosmia was significantly higher ($p<0.0001$) in women (blue line) than in men (red line).

Figure 3. Evolution of hyposmia (smell of one to three odours) during lifetime. For detection, hyposmia showed a progressive increase during the life span, while for recognition/memory and identification hyposmia decreased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and increased thereafter. For ~~either~~ detection, recognition/memory, or identification, hyposmia was significantly lower ($p<0.0001$) in women (blue line) than in men (red line).

Figure 4. Evolution of anosmia (smell of none of the four odours) during lifetime. Anosmia showed a progressive mild increase during the life span but being more significant after the sixth decade of life. For ~~either~~ detection, recognition/memory, or identification, anosmia was significantly lower ($p<0.0001$) in women (blue line) than in men (red line), with a maximal difference after the seventh decade of life.

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Table 1. OLFACAT epidemiological characteristics and gender comparison: age, women's health, education level, smoking and toxic exposure, subjective description of smell, residential zone, history of head trauma, chronic rhinosinusitis, and loss of smell history.

Population characteristics [1]		Male	Female	Total	p-value
		3,211 (34.3)	6,137 (65.7)	9,348 (100)	
Age (years) [1]	< 20	127 (3.9)	315 (5.1)	442 (4.7)	< 0.0001 [2]
	20 - 29	241 (7.5)	878 (14.3)	1,119 (12.0)	
	30 - 39	668 (20.8)	1,487 (24.2)	2,155 (23.1)	
	40 - 49	861 (26.8)	1,673 (27.3)	2,534 (27.1)	
	50 - 59	766 (23.9)	1,181 (19.3)	1,947 (20.8)	
	60 - 69	355 (11.1)	454 (7.4)	809 (8.6)	
	> 70	193 (6.0)	149 (2.4)	342 (3.7)	
Menstruation [1]			781 (12.7)		
Pregnancy [1]			128 (2.1)		
Educational level [1]	elementary school	7 (0.2)	26 (0.4)	33 (0.3)	< 0.0001 [2]
	secondary school	508 (15.8)	978 (15.9)	1,486 (15.9)	
	high school	1,505 (46.9)	2,568 (41.9)	4,073 (43.6)	
	university/college	1,191 (37.1)	2,565 (41.8)	3,756 (40.2)	
Smoking [1]	non-smokers	1,185 (36.9)	3,513 (57.2)	4,698 (50.3)	< 0.0001 [2]
	ex-smokers	1,231 (38.3)	1,418 (23.1)	2,649 (28.3)	
	smoker	795 (24.8)	1,206 (19.7)	2,001 (21.4)	
Subjective description of sense of smell [1]	very good	407 (12.7)	1,576 (25.7)	1,983 (21.2)	< 0.0001 [2]
	good	2,472 (77.0)	4,243 (69.1)	6,715 (71.9)	
	poor	315 (9.8)	305 (5.0)	620 (6.6)	
	very poor	17 (0.5)	13 (0.2)	30 (0.3)	
Residential zone [1]	rural	57 (1.8)	109 (1.8)	166 (1.8)	0.9535 [2]
	semi-rural	142 (4.4)	263 (4.3)	405 (4.3)	
	urban	3,012 (93.8)	5,765 (93.9)	8,777 (93.9)	
History of head trauma [1]		200 (6.2)	264 (4.3)	464 (5.0)	< 0.0001 [2]
Exposure to noxious substances [1]		1,090 (33.9)	1,703 (27.7)	2,793 (29.9)	< 0.0001 [2]
Chronic rhinosinusitis [1]		137 (4.3)	277 (4.5)	414 (4.4)	0.5814 [2]
Loss of smell history [1]	never	2,217 (69.0)	4,289 (69.9)	6,506 (69.6)	0.0042 [2]
	≤ 1 week	789 (24.6)	1,555 (25.3)	2,344 (25.1)	
	> 1 week	205 (6.4)	293 (4.8)	498 (5.3)	

1: number of subjects (percentage)
2: Chi-square test

Table 2. Distribution and relative risk for hyposmia (smell of one to three odours) or anosmia (smell of none of the four odours) in the case of smell detection using a multivariate logistic analysis of demographic and health problems. Data presented as adjusted OR (Odd Ratio), 95% CI (Confidence Interval).

Covariable		Hyposmia (detection) 8,601 subjects, 1,639 with hyposmia (19%)					Anosmia (detection) 9,251 subjects, 25 with anosmia (0.3%)				
		No	Yes	Adjusted OR	(95% CI)	p-value	No	Yes	Adjusted OR	(95% CI)	p-value
Female		4,686 (67.3%)	967 (59.0%)	0.78	(0.69, 0.88)	< 0.0001	6,077 (65.9%)	7 (28.0%)	0.22	(0.07, 0.71)	0.0111
Educational level [1]	elementary school	23 (0.3%)	7 (0.4%)	-	-	0.0352	32 (0.3%)	0 (0.0%)	-	-	-
	middle school	1,061 (15.2%)	247 (15.1%)	0.76	(0.32, 1.81)		1,436 (15.6%)	8 (32.0%)	-	-	
	high school	3,053 (43.9%)	683 (41.7%)	1.02	(0.86, 1.21)		4,020 (43.6%)	11 (44.0%)	-	-	
	university	2,825 (40.6%)	702 (42.8%)	1.18	(1.05, 1.34)		3,738 (40.5%)	6 (24.0%)	-	-	
Subjective description of sense of smell [1]	very good	1,563 (22.5%)	275 (16.8%)	-	-	< 0.0001	1,968 (21.3%)	2 (8.0%)	-	-	< 0.0001
	good	4,990 (71.7%)	1,167 (71.2%)	1.24	(1.08, 1.44)		6,636 (71.9%)	2 (8.0%)	0.20	(0.03, 1.48)	
	bad	388 (5.6%)	188 (11.5%)	1.94	(1.58, 2.37)		608 (6.6%)	5 (20.0%)	9.69	(1.58, 59.30)	
	very bad	21 (0.3%)	9 (0.5%)	0.75	(0.33, 1.70)		14 (0.2%)	16 (64.0%)	109.54	(30.51, 393.35)	
Loss of smell history [1]	never	4,829 (69.4%)	1,130 (68.9%)	-	-	0.0935	6,429 (69.7%)	5 (20.0%)	-	-	0.0172
	≤ 1 week	1,796 (25.8%)	384 (23.4%)	0.88	(0.78, 1.01)		2,324 (25.2%)	1 (4.0%)	0.71	(0.08, 6.35)	
	> 1 week	337 (4.8%)	125 (7.6%)	1.25	(0.97, 1.62)		473 (5.1%)	19 (76.0%)	9.26	(0.98, 87.07)	
Exposure to noxious substances		2,023 (29.1%)	491 (30.0%)	1.02	(0.91, 1.16)	0.7025	2,749 (29.8%)	9 (36.0%)	2.00	(0.67, 5.92)	0.2117
Chronic rhinosinusitis		296 (4.3%)	75 (4.6%)	0.99	(0.76, 1.30)	0.9662	410 (4.4%)	3 (12.0%)	0.59	(0.09, 3.96)	0.5887
Menstruation		616 (8.8%)	116 (7.1%)	0.97	(0.78, 1.20)	0.7655	777 (8.4%)	0 (0.0%)	-	-	-
Age (years) [1]	< 20	374 (5.4%)	54 (3.3%)	-	-	< 0.0001	441 (4.8%)	1 (4.0%)	-	-	-
	20 - 29	914 (13.1%)	163 (9.9%)	1.12	(0.80, 1.57)		1,118 (12.1%)	1 (4.0%)	-	-	
	30 - 39	1,667 (23.9%)	356 (21.7%)	1.17	(0.95, 1.44)		2,150 (23.3%)	0 (0.0%)	-	-	
	40 - 49	1,893 (27.2%)	456 (27.8%)	1.14	(0.97, 1.33)		2,514 (27.2%)	2 (8.0%)	-	-	

	50 - 59	1,360 (19.5%)	386 (23.6%)	1.17	(1.00, 1.37)		1,909 (20.7%)	7 (28.0%)	-	-	
	60 - 69	528 (7.6%)	162 (9.9%)	1.08	(0.88, 1.34)		779 (8.4%)	6 (24.0%)	-	-	
	> 70	226 (3.2%)	62 (3.8%)	0.85	(0.61, 1.19)		315 (3.4%)	8 (32.0%)	-	-	
Residential zone [2]	rural *(reference)*	121 (1.7%)	31 (1.9%)	1	-	0.0821	165 (1.8%)	0 (0.0%)	-	-	-
	semi-rural	294 (4.2%)	85 (5.2%)	1.15	(0.72, 1.83)		403 (4.4%)	1 (4.0%)	-	-	
	City	6,547 (94.0%)	1,523 (92.9%)	0.87	(0.58, 1.30)		8,658 (93.8%)	24 (96.0%)	-	-	
Smoking [2]	non-smoker *(reference)*	3,535 (50.8%)	789 (48.1%)	1	-	0.9331	4,646 (50.4%)	10 (40.0%)	1	-	0.9608
	ex-smoker	1,939 (27.9%)	498 (30.4%)	1.00	(0.88, 1.14)		2,603 (28.2%)	11 (44.0%)	1.10	(0.34, 3.57)	
	smoker	1,488 (21.4%)	352 (21.5%)	1.03	(0.89, 1.19)		1,977 (21.4%)	4 (16.0%)	0.88	(0.19, 4.12)	
History of head trauma		343 (4.9%)	75 (4.6%)	0.85	(0.66, 1.11)	0.2298	456 (4.9%)	1 (4.0%)	0.33	(0.03, 3.98)	0.3832
Pregnancy		99 (1.2%)	19 (1.2%)	1.00	(0.60, 1.65)	0.9893	128 (1.4%)	0 (0.0%)	-	-	-

1: OR relative to the previous category
2: OR relative to the reference category

Table 3. Relative risk for hyposmia (smell of one to three odours) or anosmia (smell of none of the four odours) in the case of smell recognition/memory using a multivariate logistic analysis of demographic characteristics and health problems. Data presented as adjusted OR (Odd Ratio), 95% CI (Confidence Interval).

Covariable		Hyposmia (recognition/memory) 6,778 subjects, 2,936 with hyposmia (43%)					Anosmia (recognition/memory) 9,079 subjects, 18 with anosmia (0.2%)				
		No	Yes	Adjusted OR	(95% CI)	p-value	No	Yes	Adjusted OR	(95% CI)	p-value
Female		2,663 (69.3%)	1,885 (64.2%)	0.79	(0.71, 0.88)	< 0.0001	5,986 (66.1%)	12 (66.7%)	1.26	(0.41, 3.81)	0.6879
Educational level [1]	elementary school	14 (0.4%)	14 (0.5%)	-	-	0.0200	31 (0.3%)	2 (11.1%)	-	-	0.0005
	middle school	536 (14.0%)	505 (17.2%)	1.20	(0.56, 2.60)		1,387 (15.3%)	4 (22.2%)	0.05	(0.01, 0.29)	
	high school	1,671 (43.5%)	1,272 (43.3%)	0.84	(0.72, 0.97)		3,942 (43.5%)	11 (61.1%)	1.18	(0.34, 4.08)	
	university	1,621 (42.2%)	1,145 (39.0%)	0.93	(0.83, 1.04)		3,701 (40.8%)	1 (5.6%)	0.09	(0.01, 0.73)	
Subjective description of sense of smell [1]	very good	961 (25.0%)	532 (18.1%)	-	-	< 0.0001	1,939 (21.4%)	3 (16.7%)	-	-	0.0039
	good	2,690 (70.0%)	2,164 (73.7%)	1.45	(1.28, 1.64)		6,510 (71.8%)	12 (66.7%)	1.13	(0.31, 4.10)	
	Bad	187 (4.9%)	234 (8.0%)	1.62	(1.30, 2.01)		600 (6.6%)	1 (5.6%)	0.75	(0.08, 7.40)	
	very bad	4 (0.1%)	6 (0.2%)	0.98	(0.26, 3.66)		12 (0.1%)	2 (11.1%)	65.35	(4.60, 927.55)	
Loss of smell history [1]	never	2,620 (68.2%)	2,087 (71.1%)	-	-	0.0020	6,303 (69.6%)	11 (61.1%)	-	-	0.7159
	≤ 1 week	1,050 (27.3%)	685 (23.3%)	0.81	(0.73, 0.91)		2,299 (25.4%)	4 (22.2%)	1.22	(0.38, 3.91)	
	> 1 week	172 (4.5%)	164 (5.6%)	1.23	(0.95, 1.59)		459 (5.1%)	3 (16.7%)	1.76	(0.23, 13.60)	
Exposure to noxious substances		1,201 (31.3%)	803 (27.4%)	0.83	(0.74, 0.93)	0.0010	2,694 (29.7%)	4 (22.2%)	0.58	(0.18, 1.82)	0.3497
Chronic rhinosinusitis		168 (4.4%)	127 (4.3%)	1.02	(0.80, 1.30)	0.8574	404 (4.5%)	1 (5.6%)	0.72	(0.08, 6.40)	0.7720
Menstruation		347 (9.0%)	249 (8.5%)	1.08	(0.90, 1.29)	0.4244	774 (8.5%)	1 (5.6%)	1.14	(0.13, 9.87)	0.9070
Age (years) [1]	< 20	175 (4.6%)	214 (7.3%)	-	-	< 0.0001	437 (4.8%)	1 (5.6%)	-	-	0.7500
	20 - 29	494 (12.9%)	405 (13.8%)	0.80	(0.62, 1.03)		1,108 (12.2%)	1 (5.6%)	1.06	(0.06, 18.62)	
	30 - 39	956 (24.9%)	663 (22.6%)	0.81	(0.68, 0.96)		2,115 (23.3%)	4 (22.2%)	1.29	(0.14, 11.82)	
	40 - 49	1,088 (28.3%)	689 (23.5%)	0.91	(0.79, 1.04)		2,475 (27.3%)	2 (11.1%)	0.46	(0.08, 2.66)	
	50 - 59	775 (20.2%)	564 (19.2%)	1.06	(0.92, 1.24)		1,881 (20.8%)	3 (16.7%)	1.74	(0.28, 10.81)	
	60 - 69	268 (7.0%)	257 (8.8%)	1.22	(0.99, 1.50)		755 (8.3%)	4 (22.2%)	1.84	(0.37, 9.12)	

	> 70	86 (2.2%)	144 (4.9%)	1.64	(1.19, 2.26)		290 (3.2%)	3 (16.7%)	1.73	(0.35, 8.63)	
Residential zone [2]	rural *(reference)*	73 (1.9%)	49 (1.7%)	1	-	0.4187	164 (1.8%)	0 (0.0%)	-	-	-
	semi-rural	157 (4.1%)	139 (4.7%)	1.27	(0.82, 1.96)		390 (4.3%)	2 (11.1%)	-	-	
	City	3,612 (94.0%)	2,748 (93.6%)	1.10	(0.76, 1.59)		8,507 (93.9%)	16 (88.9%)	-	-	
Smoking [2]	non-smoker *(reference)*	1,857 (48.3%)	1,648 (56.1%)	1	-	< 0.0001	4,567 (50.4%)	12 (66.7%)	-	-	-
	ex-smoker	1,081 (28.1%)	766 (26.1%)	0.80	(0.71, 0.91)		2,537 (28.0%)	6 (33.3%)	-	-	
	smoker	904 (23.5%)	522 (17.8%)	0.68	(0.60, 0.78)		1,957 (21.6%)	0 (0.0%)	-	-	
History of head trauma		201 (5.2%)	134 (4.6%)	0.86	(0.68, 1.08)	0.1917	446 (4.9%)	0 (0.0%)	-	-	-
Pregnancy		60 (1.6%)	35 (1.2%)	0.84	(0.55, 1.29)	0.4243	125 (1.4%)	1 (5.6%)	6.94	(0.74, 65.52)	0.0907

1: OR relative to the previous category
2: OR relative to the reference category

Table 4. Relative risk for hyposmia (smell of one to three odours) or anosmia (smell of none of the four odours) in the case of smell identification using a multivariate logistic analysis of demographic characteristics and health problems. Data presented as adjusted OR (Odd Ratio), 95% CI (Confidence Interval).

Covariable		Hyposmia (identification) 8,107 subjects, 3,894 with hyposmia (48%)					Anosmia (identification) 9,195 subjects, 75 with anosmia (1%)				
		No	Yes	Adjusted OR	(95% CI)	p-value	No	Yes	Adjusted OR	(95% CI)	p-value
Female		2,911 (69.1%)	2,368 (60.8%)	0.76	(0.69, 0.84)	< 0.0001	6,008 (65.9%)	38 (50.7%)	0.96	(0.55, 1.67)	0.8850
Educational level [1]	elementary school	8 (0.2%)	18 (0.5%)	-	-	0.0007	31 (0.3%)	0 (0.0%)	-	-	-
	middle school	654 (15.5%)	608 (15.6%)	0.49	(0.21, 1.16)		1,419 (15.6%)	24 (32.0%)	-	-	
	high school	1,881 (44.6%)	1,636 (42.0%)	1.01	(0.88, 1.15)		3,970 (43.5%)	28 (37.3%)	-	-	
	university	1,670 (39.6%)	1,632 (41.9%)	1.21	(1.09, 1.34)		3,700 (40.6%)	23 (30.7%)	-	-	
Subjective description of sense of smell [1]	very good	1,034 (24.5%)	667 (17.1%)	-	-	< 0.0001	1,948 (21.4%)	8 (10.7%)	-	-	< 0.0001
	good	2,979 (70.7%)	2,841 (73.0%)	1.42	(1.27, 1.58)		6,567 (72.0%)	38 (50.7%)	1.27	(0.59, 2.76)	
	poor	183 (4.3%)	374 (9.6%)	2.06	(1.69, 2.51)		592 (6.5%)	13 (17.3%)	2.16	(1.00, 4.66)	
	very poor	17 (0.4%)	12 (0.3%)	0.26	(0.12, 0.56)		13 (0.1%)	16 (21.3%)	36.06	(13.12, 99.13)	
Loss of smell history [1]	never	2,895 (68.7%)	2,741 (70.4%)	-	-	0.0005	6,361 (69.7%)	38 (50.7%)	-	-	0.0415
	≤ 1 week	1,130 (26.8%)	901 (23.1%)	0.82	(0.74, 0.91)		2,301 (25.2%)	12 (16.0%)	0.93	(0.48, 1.81)	
	> 1 week	188 (4.5%)	252 (6.5%)	1.28	(1.02, 1.62)		458 (5.0%)	25 (33.3%)	2.79	(1.14, 6.88)	
Exposure to noxious substances		1,255 (29.8%)	1,132 (29.1%)	0.98	(0.89, 1.08)	0.6930	2,716 (29.8%)	23 (30.7%)	1.03	(0.60, 1.77)	0.9111
Chronic rhinosinusitis		187 (4.4%)	170 (4.4%)	0.96	(0.77, 1.20)	0.7290	403 (4.4%)	5 (6.7%)	0.80	(0.28, 2.29)	0.6824
Menstruation		390 (9.3%)	304 (7.8%)	1.03	(0.87, 1.22)	0.7157	772 (8.5%)	2 (2.7%)	0.49	(0.11, 2.14)	0.3421
Age (years) [1]	< 20	203 (4.8%)	194 (5.0%)	-	-	< 0.0001	438 (4.8%)	3 (4.0%)	-	-	0.0006
	20 - 29	551 (13.1%)	466 (12.0%)	0.82	(0.64, 1.04)		1,106 (12.1%)	8 (10.7%)	0.76	(0.19, 2.96)	
	30 - 39	1,032 (24.5%)	839 (21.5%)	0.94	(0.80, 1.10)		2,131 (23.4%)	11 (14.7%)	0.65	(0.25, 1.68)	
	40 - 49	1,198 (28.4%)	1,004 (25.8%)	1.05	(0.93, 1.19)		2,490 (27.3%)	10 (13.3%)	0.68	(0.28, 1.65)	
	50 - 59	822 (19.5%)	831 (21.3%)	1.20	(1.05, 1.37)		1,886 (20.7%)	12 (16.0%)	1.40	(0.58, 3.38)	

	60 - 69	302 (7.2%)	371 (9.5%)	1.19	(0.99, 1.43)		763 (8.4%)	17 (22.7%)	3.38	(1.51, 7.55)	
	> 70	105 (2.5%)	189 (4.9%)	1.43	(1.07, 1.91)		306 (3.4%)	14 (18.7%)	1.24	(0.51, 3.01)	
Residential zone [2]	rural *(reference)*	76 (1.8%)	71 (1.8%)	1	-	0.3585	162 (1.8%)	1 (1.3%)	1	-	0.9858
	semi-rural	176 (4.2%)	181 (4.6%)	1.11	(0.75, 1.65)		400 (4.4%)	3 (4.0%)	0.87	(0.08, 8.95)	
	city	3,961 (94.0%)	3,642 (93.5%)	0.95	(0.68, 1.33)		8,558 (93.8%)	71 (94.7%)	0.85	(0.12, 6.21)	
Smoking [2]	non-smoker *(reference)*	2,118 (50.3%)	1,968 (50.5%)	1	-	0.5326	4,594 (50.4%)	30 (40.0%)	1	-	0.2814
	ex-smoker	1,169 (27.7%)	1,131 (29.0%)	0.96	(0.86, 1.07)		2,567 (28.1%)	30 (40.0%)	1.61	(0.88, 2.93)	
	smoker	926 (22.0%)	795 (20.4%)	0.94	(0.83, 1.06)		1,959 (21.5%)	15 (20.0%)	1.41	(0.70, 2.82)	
History of head trauma		204 (4.8%)	193 (5.0%)	0.97	(0.79, 1.20)	0.7963	442 (4.8%)	12 (16.0%)	3.38	(1.69, 6.74)	0.0006
Pregnancy		62 (1.5%)	48 (1.2%)	1.02	(0.69, 1.51)	0.9157	126 (1.4%)	1 (1.3%)	1.72	(0.22, 13.33)	0.6017

1: OR relative to the previous category
2: OR relative to the reference category

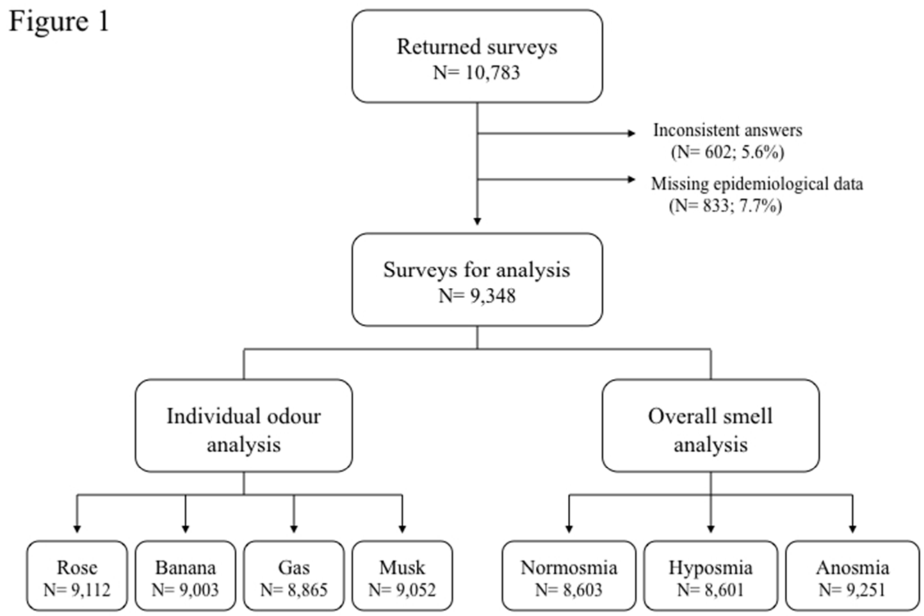

Figure 1. Flow-chart of participants in the OLFACAT (Olfaction in Catalonia) survey.
275x190mm (72 x 72 DPI)

Figure 2

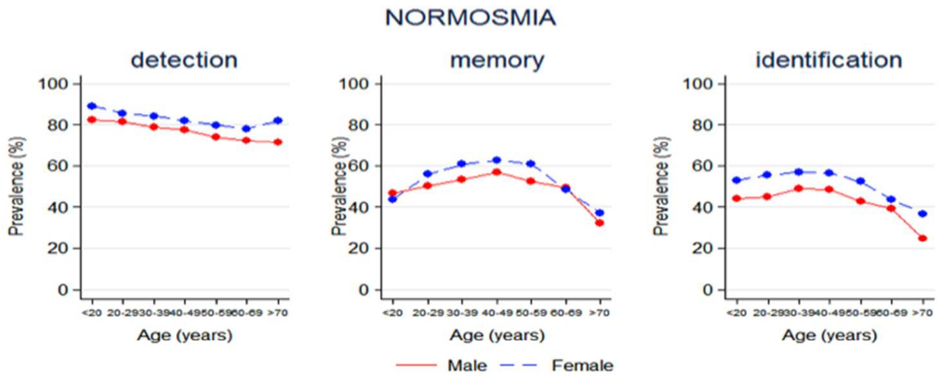

Figure 2. Evolution of normosmia (smell of all four odours) during lifetime. Smell detection showed a progressive decrease during the life span, while smell recognition/memory and identification increased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and declined thereafter. For detection, recognition/memory, or identification, normosmia was significantly higher ($p<0.0001$) in women (blue line) than in men (red line).
275x190mm (72 x 72 DPI)

Figure 3

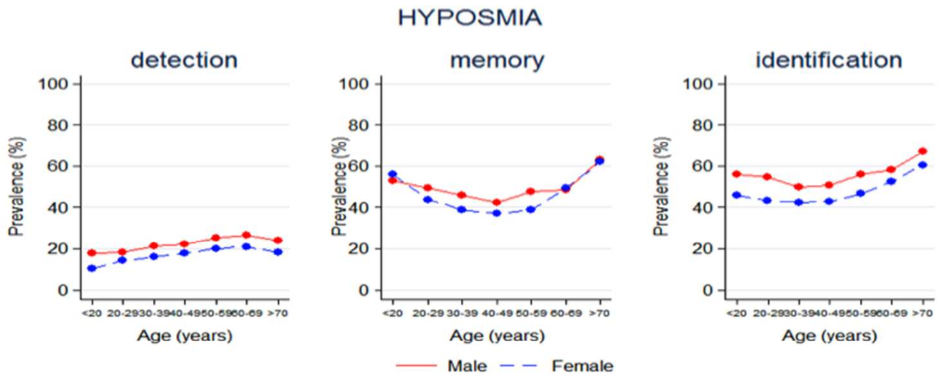

Figure 3. Evolution of hyposmia (smell of one to three odours) during lifetime. For detection, hyposmia showed a progressive increase during the life span, while for recognition/memory and identification hyposmia decreased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and increased thereafter. For detection, recognition/memory, or identification, hyposmia was significantly lower (p<0.0001) in women (blue line) than in men (red line).
275x190mm (72 x 72 DPI)

Figure 4

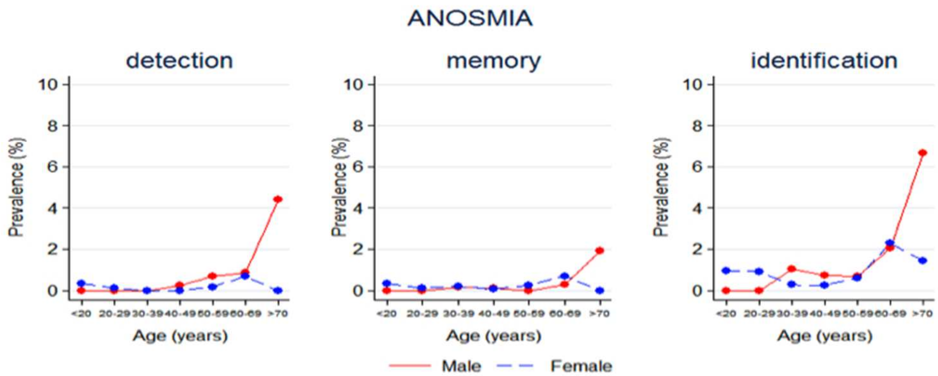

Figure 4. Evolution of anosmia (smell of none of the four odours) during lifetime. Anosmia showed a progressive mild increase during the life span but being more significant after the sixth decade of life. For detection, recognition/memory, or identification, anosmia was significantly lower (p<0.0001) in women (blue line) than in men (red line), with a maximal difference after the seventh decade of life.
275x190mm (72 x 72 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

YOU MUST NOTE THE PAGE NUMBER WHERE EACH ITEM IS REPORTED INSIDE THE BRACKETS [ ]. IF NOT APPLICABLE WRITE N/A

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Page 1]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[Page 3]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[Pages 5 and 6]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[Page 6]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Page 7]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Page 7]**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[Pages 7 to 9]** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **[N/A]** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **[N/A]**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **[Pages 7 to 9]** *Case-control study*—For matched studies, give matching criteria and the number of controls per case **[N/A]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Pages 7 to 9]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Pages 7 to 9]**
Bias	9	Describe any efforts to address potential sources of bias **[Pages 17 and 18]**
Study size	10	Explain how the study size was arrived at **[Page 9, Figure 1]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Page 9]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Page 9]**
		(*b*) Describe any methods used to examine subgroups and interactions **[Page 9]**
		(*c*) Explain how missing data were addressed **[Page 9, Figure 1]**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **[N/A]** *Case-control study*—If applicable, explain how matching of cases and controls was addressed **[N/A]** *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy **[N/A]**
		(*e*) Describe any sensitivity analyses **[N/A]**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Pages 10 to 13, Figure 1, Table 1]**
		(b) Give reasons for non-participation at each stage **[Figure 1]**
		(c) Consider use of a flow diagram **[Figure 1]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Pages 10 and 11, Table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[Pages 10 to 13, Figure 1]**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **[Page 10]**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **[N/A]**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure **[N/A]**
		Cross-sectional study—Report numbers of outcome events or summary measures **[N/A]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Pages 10 to 13, Figure 2 to 4, Tables 2 to 4]**
		(*b*) Report category boundaries when continuous variables were categorized **[Pages 10 to 13, Tables 2 to 4]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[Page 14]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[N/A]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Page 14]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Pages 17 and 18]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Page 18]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Pages 14 to 18]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[Pages 20 and 21]**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Once you have completed this checklist, please save a copy and upload it as part of your submission. When requested to do so as part of the upload process, please select the file type: *Checklist*. You will NOT be able to proceed with submission unless the checklist has

been uploaded. Please DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

Furthering the understanding of olfaction, prevalence of loss of smell, and risk factors: a population-based survey (OLFACAT study).

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Furthering the understanding of olfaction, prevalence of loss of smell, and risk factors: a population-based survey (OLFACAT)

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WORD COUNT: 3,681 words

RELEVANT SURVEY HEADINGS: sense of smell, general population, olfactory disorders, normosmia, hyposmia, anosmia, risk factors.

ABSTRACT

Objectives: To investigate olfaction in general population, prevalence of olfactory dysfunction, and related risk factors.

Design: Cross-sectional population-based survey, distributing four microencapsulated odorants (rose, banana, musk, gas) and two self-administered questionnaires (odour description; epidemiology/health status).

Setting: The survey was distributed to general population through a bilingual (Catalan, Spanish) newspaper in Catalonia (Spain), on December 2003.

Participants: Newspaper readers of all ages and gender; 9,348 surveys were analyzed from the 10,783 returned.

Main outcome measures: Characteristics of surveyed population, olfaction by age and gender, smell-self perception, and smell impairment risk factors. Terms normosmia, hyposmia, and anosmia were used when participants detected, recognized, or identified all four, one to three, or none of the odours, respectively.

Results: Survey profile was a 43-year-old woman with medium-high educational level, living in a city. Olfaction was considered normal in 80.6% (detection), 56.0% (recognition/memory), and 50.7% (identification). Prevalence of smell dysfunction was 19.4% for detection (0.3% anosmia, 19.1% hyposmia), 43.5% for recognition (0.2% anosmia, 43.3% hyposmia), and 48.8% for identification (0.8% anosmia, 48% hyposmia). Olfaction was worse ($p<0.0001$) in men than in women through all ages. There was a significant age-related smell detection decline however smell recognition and identification increased up to fourth decade and declined after the sixth decade of life. Risk factors for anosmia were: male gender, loss of smell history, and poor olfactory self-perception for detection; low educational level, poor self-perception, and pregnancy for recognition; and older age, poor self-perception, and history of head trauma and loss of smell for identification. Smoking and exposure to noxious substances were mild protective factors for smell recognition.

Conclusions: Sense of smell in women is better than in men suggesting a learning process during life with deterioration in older ages. Poor self-perception, history of smell loss, head trauma, and pregnancy are potential risk factors for olfactory disorders.

ABSTRACT WORD COUNT: 300 words

ARTICLE SUMMARY

Article focus

• Population-based smell survey in 2003.

• Partial and total smell impairment by age and gender.

• Risk factors for olfactory disorders.

Key messages

• Olfaction is better in female than in male.

• Smell improves with a learning process and deteriorates in older ages.

• Poor olfactory self-perception, history of smell loss for over one week, head trauma, and pregnancy are potential risk factors for olfactory disorders.

Strengths and limitations of this study

• Strength: The largest European population-based study providing data on partial/total loss of smell and their absolute risk factors.

• Limitations: self-administered survey (no control on how it was performed); the study was done in a middle-high socio-cultural population (newspaper readers).

INTRODUCTION

The sense of smell provides information on the surrounding environment, warns us about chemical dangers and putrid food, and may even help people to mate. Smell disorders may affect the ability to enjoy food and aromas while interfering with the ability to notice potentially harmful chemicals and gases.[1]

In 1987, the National Geographic Smell Survey (NGSS) studied a large US sample population (1.2 million) whereby 1% of participants could not smell three or more of six odorants using a "scratch and sniff" test.[2] Age was an important factor in smell deterioration and smell was rated better in women than in men. In 1994, the National Health Interview Survey (NHIS)[3] reported data from 42,000 United States households with 1.4% prevalence of self-reported olfactory dysfunction, exponentially increasing with age. This study, however, did not include any testing of smell function.

The prevalence and associated risk factors of olfactory impairment in the European population has been investigated to a limited extent. In the Swedish version of the NGSS,[4] done in 532 individuals older than 45 years, increasing age was associated with impaired ability to detect/identify odorants, with no effect of gender on smell perception. Education has also been shown to account for a significant portion of the age-related variance in identification.[5] Another European population-based study identified a significant relationship between impaired olfaction and aging, male gender, and nasal polyps, but not with diabetes or smoking, reporting an olfactory dysfunction prevalence of 19.1%.[6]

Approximately two thirds of smell dysfunction cases are likely due to prior upper respiratory infections, head trauma, or sinonasal diseases.[7] Toxic chemical exposure, epilepsy, pollution, drugs, nutritional disturbances, and neurodegenerative diseases may also cause olfactory disorders.[8,9] Smoking may cause a reversible reduction in the ability to smell[10,11] while chronic rhinosinusitis/nasal polyps may result in a partial or total loss of smell.[12]

The aims of this study were to investigate the ~~current~~ status of olfaction in the general population while determining the prevalence of olfactory dysfunction and its related risk factors.

METHODS

Study Design

The OLFACAT (Olfaction in Catalonia) survey was carried out in the general population of Catalonia in Spain. Two questionnaires, olfaction and demography-health status, and a set of four microencapsulated odorants were distributed in the 250,000 daily issues of the newspaper *El Periódico de Catalunya* on December 23rd, 2003. The survey was presented in both Catalan and Spanish languages to facilitate the choice of the preferred language. The present manuscript has followed the STROBE checklist guidelines.

The study was approved by the Institutional Ethics and Clinical Research Committee of Hospital Clínic de Barcelona (reference 1295).

Measurements

Survey Odorants**.** Four common odorants were included in the survey: rose (2% of Bulgarian rose in 98% of phenyl-ethyl alcohol) as a floral odour; banana (amyl-isobutirate at 50% in dietyl-phtalate) as a food odour; musk (1:1 mixture of galaxolide and diethyl-phtalate exaltolide) as a perfume odour; and gas (mixture of 30% mercaptan and 70% tetrahydrothiophene) as an industrial odour. Each compound was prepared following established formulas and the solution magnetically homogenized. Rose, banana, and musk odorants were elaborated by Antonio Puig SA (Barcelona, Catalonia, Spain) and gas odorant by ENAGAS (Saragossa, Spain). Stability test protocols were performed by accelerating the olfactory aging of products at 40ºC for 2 months, following their smell evolution after 1 to 8 weeks. The micro-encapsulation process was done by ARCADE Europe (Paris France) as follows: essential oil component was contained and delivered from highly durable synthetic microcapsules manufactured using a proprietary polycondensated polymerization method.

The microcapsules were blended with a water-based polymer adhesive to form printable slurry. Odorants were adhered to a smell-less paper and dispatched using a folded-form design so as to prevent direct contact between odour samples.

Smell questionnaire. Participants were asked to scratch and sniff each odour and then answer three questions: First) odour detection: did you smell any scent? (yes, no); Second) odour recognition/memory: have you ever smelt this scent? (yes, no); and third) forced-choice odour identification: which name defines the scent you have smelt?, whereby only one of the four given options was correct. The term "normosmia" was used when a participant was able to detect, recognize (memory), or correctly identify all four tested odours; the term "hyposmia" was used when a participant was not able to detect, recognize (memory), or correctly identify one, two, or three tested odours; and the term "anosmia" was used when a participant was unable to detect, recognize (memory), or correctly identify any of the four tested odours.

Epidemiological and health-status questionnaire. From the twelve-question questionnaire, four questions were on demography: first) gender (male, female); second) age (years); third) current educational level (primary school, secondary school, high school, University or College); and fourth) residential area (city, postcode). Two questions described smell self-perception: fiftth) how do you consider your current sense of smell? (very good, good, poor, very poor); and sixth) have you ever lost the sense of smell? (never, up to one week, over one week). Two questions were on exposure to toxic or noxious substances: seventh) have you ever been exposed to dust, gases, fumes, vapours, or/and volatile toxics at home and/or at work? (yes, no); and eighth) do you smoke? (no, ex-smoker, smoker). Two questions were on health-status: ninth) have you ever had a severe face and/or head trauma? (yes, no); and tenth) have you ever been diagnosed with chronic rhinosinusitis? (yes, no). Finally, two questions

were on women's health: eleventh) are you currently pregnant? (yes, no); and twelfth) are you currently menstruating? (yes, no).

Data Management and Statistical Analysis

The returned surveys were read using an optical system (BV Scan system, Voxpublica), the data were transferred to an electronic database, and then statistically analysed using Stata version 8 (Stata Statistical Software: Release 8.0 College Station, TX: *Stata Corporation* 2003).[13] The data cleaning process was based on programmed queries to identify records containing inconsistent or uncertain data. The corrupt or inaccurate values identified by these queries were subsequently recorded as missing values in the data set.

Only those surveys fully and consistently answered were considered for statistical analysis. Differences between gender in epidemiological and health-status characteristics were evaluated by Chi-square test. Adjusted (multivariate) logistic regression models for anosmia and hyposmia were estimated (Tables 2, 3 and 4). To estimate the multivariate models for anosmia, the covariates that do not have any events (anosmia cases) in any of its categories were not included. Results from estimated models were expressed as adjusted Odd Ratio (OR) and 95% Confidence Interval (CI). The reference category used to calculate the OR for each level of variables measured on an ordinal scale was the immediately previous category, starting with the second. Results from estimated models were expressed as Odd Ratio (OR) and 95% Confidence Interval (CI). All tests were performed using a two-tailed significance level of 0.05.

RESULTS

Characteristics of the surveyed population

Following the data cleaning process, 5.6% of answers from the 10,783 received surveys were identified as inconsistent. After the exclusion of both these inconsistent questionnaire returns and the incomplete epidemiological and health-status questionnaires (7.7%), the sample size for analysis was 9,348 questionnaires (Figure 1).

Age and gender. The mean age of the surveyed population was 43.3 years, ranging from 5 to 91 years. The analysis was performed in seven age groups to ensure a reasonable sample size for each age and gender group. Almost two thirds of participants were women (65.7%), of which 2.1% were pregnant and 12.7% were menstruating (Table 1).

Education and residential zone. Most participants (83.8%) had a high educational level (high school or University/College) and were living (93.9%) in an urban area, with no differences between gender.

Exposure to tobacco and noxious substances. More than one fifth (21.4%) of participants were smokers, 28·3% were ex-smokers, while almost a third (29.9%) reported to be regularly exposed to toxic or noxious substances, either at home or at work. Men reported a higher exposure to both tobacco smoke (24.8%, p<0.0001) and noxious substances (33.9%, p<0.0001) than women (19.7% and 27.7%, respectively).

Health status. 4.4% of participants had received a diagnosis of chronic rhinosinusitis, with similar prevalence in women and men, while 5.0% reported a history of face/head trauma, this prevalence being higher in men than in women (6.2% versus 4.3%, p<0.0001).

Sense of smell. All four odours (normosmia) were detected by 80.6%, recognised by 56.0%, and identified by 50.7% of the surveyed population. One to three odours (hyposmia) were detected by 19.1%, recognised by 43.3%, and identified by 48.0%. None of the four odours (anosmia) were detected by 0.3%, recognised by 0.2%, and identified by 0.8%. Individual odours were more highly detected (rose 99.4%, banana 98.9%, gas 96.9%, musk 84.4%) than recognised (rose 94.8%, banana 96.2%, gas 94.9%, musk 66.2%) or correctly identified (rose 91.8%, banana 89.8%, gas 92.1%, musk 65.4%). Moreover, individual odours were always better detected, recognised, and identified by women than by men, except for rose and banana recognition.

Smell by gender and age

Within the population experiencing normosmia, there was a significant and progressive age-related decline of smell detection while smell recognition and identification increased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and declined thereafter. Significant but opposite findings were found for hyposmia and anosmia. Normosmia was higher in women than in men ($p<0.0001$) either in smell detection (82.8% versus 76.5%), recognition/memory (58.0% versus 51.9%), or identification (54.1% versus 44.3%) (Figure 1). Hyposmia was higher in men than in women ($p<0.0001$) either in smell detection (22.8% versus 17.1%), recognition/memory (47.1% versus 41.4%), and identification (54.0% versus 44.9%) (Figure 2). Finally, anosmia was higher in men than in women in both smell detection (0.9% versus 0.1%; $p<0.0001$) and identification (1.2% versus 0.6%; p=0·0057), but not in smell recognition/memory (0.2% versus 0.2%, $p=0.9569$) (Figure 3). In the oldest group (over 70 years), the prevalence for anosmia of detection (4.4%) and identification (6.6%) was especially higher in men than in women (0% and 1·4%, respectively).

Smell self-perception

Subjective description of smell. Regardless of gender and age, 93.1% of participants subjectively rated their sense of smell as good or very good, while 6.9% of them reported their smell as poor or very poor, the smell score being better in women than in men (p<0.0001).

Loss of smell history. A past history of loss of smell was reported by almost one third (30.4%) of participants, predominantly for less than one week (25.1%). The smell loss for over one week was more frequent in men (6.4% vs 4.8%, p=0.0042).

Risk factors for smell impairment

Smell detection. Women detected odours more frequently than men (82.8% versus 76.5%, p<0.0001). The risk for anosmia of detection was lower in women (OR=0.22) and higher in subjects reporting a loss of smell history for over one week (OR=9.26); and anosmia was also associated with a worse smell self-perception (Table 2). The risk for hyposmia of detection was lower in women (OR=0.78) and associated with older age (>50 years old), a lower educational level, and a worse smell self-perception (Table 2).

Smell recognition / memory**.** Women showed a better capability to recognise odours than men (58.0% versus 51.9%; p<0.0001). The risk for anosmia of recognition was higher in pregnant women (OR=6.94) and associated with a lower educational level and a worse smell self-perception (Table 3). The risk for hyposmia of recognition was lower in women (OR=0.79) and higher in subjects reporting a loss of smell history for over one week (OR=1.23); and it was associated with older age (>70 years old), a lower educational level, and a worse smell self-perception. Smoking (both ex-smokers and smokers) (OR=0.80 and 0.68, respectively) and frequent contact with noxious substances (OR=0.83) were found to have a mild but significant protective effect on odour recognition/memory (Table 3).

Forced-choice smell identification. Women performed better than men on odour identification (54.1% versus 44.3%, p<0.0001). The risk for anosmia of identification was higher in subjects reporting a history of head trauma (OR=3.38) and a loss of smell for over one week (OR=2.79), and it was associated with older age (>60 years old) and a worse smell self-perception (Table 4). The risk for hyposmia of identification was lower in women (OR=0.76) and higher in subjects reporting a loss of smell history for over one week (OR=1.28), and it was associated with older age (>60 years old), a lower educational level, and a smell worse self-perception (Table 4).

DISCUSSION

The most important findings of the OLFACAT survey were: First) the overall prevalence of olfactory dysfunction in the case of detection was 19.4%, with a total loss of smell (anosmia) of 0.3%. Despite this high prevalence of smell impairment, only 6.9% of the subjects considered having a poor or very poor sense of smell. Second) there was a significant age-related decline in smell detection for both genders. However, cognitive smell (recognition and identification) was increased and/or was maintained up to the sixth decade of life, declining thereafter. Third) besides women having a better self-perception of smell capabilities than men, women also scored better than men in smell detection, recognition, and identification, and did so throughout their lifetime. Fourth) pregnancy, but not menstruation was associated with a partial loss (hyposmia) of smell recognition. Fifth) male gender, poor smell self-perception, low educational level, and ageing, but not chronic rhinosinusitis, were risk factors related to smell impairment whether in terms of detection, recognition, or identification. Subjects with a history of persistent olfactory loss or head trauma were also at higher risk of smell impairment. Sixth) finally and surprisingly, persistent exposure to noxious substances and smoking showed to be protective factors for cognitive smell impairment in either recognition or identification.

Approximately 39.5 million Spaniards and 425 million EU citizens are aged 15 years or older, according to Catalan, Spanish, and European Statistic Institutes. Our survey therefore estimates that 1.2 million adult Catalans, 7.7 million Spaniards, and over 82 million EU citizens suffering from olfactory dysfunction, of which 20,000 Catalans, 120,000 Spaniards, and 1.5 million EU citizens have a total loss of sense of smell.

Brämerson et al.[6] reported an overall prevalence of olfactory impairment of 19.1% in a Swedish population which was very similar to our 19.4%. This prevalence is considerably

higher than self-reported loss of smell in the NGSS[2] (1.4%) and in our own survey where 6.9% of participants were considered to have a poor or very poor sense of smell, suggesting a low sensitivity for the subjective assessment of smell loss. The fact that many people may be unaware of their smell dysfunction, especially the elderly and/or those living alone, implies an increased risk for both nutritional problems[14] and safety in the face of a potential domestic fire or gas leak.[15]

In accordance with the OLFACAT survey data, previous studies have indicated that sense of smell detection is impaired with ageing, even in healthy individuals[16] and from the second to the eighth decade of life.[17] Our data also aligns with the NGSS and other studies in that the age decline in odour perception is universal across subjects regardless of gender odorants, outcome measures, or cultural diversity.[2,6] Smell changes observed across the survey's age span are similar to a previous study reporting a progressive decline in odour.[18] Concerning cognitive smell (memory and identification), we observed an increase in performance in the first decades of life, reaching a plateau during the third through to fifth decades of life and declining thereafter. Larsson et al.[4] reported that age was associated with an increased ability to identify banana odour (amylacetate). Our survey, in agreement with the NGSS findings, found not only an increased ability to recognise and identify banana, but rose and gas also, with increase indicated up to the fifth decade of life but decreasing thereafter. Due to the fact that repeated exposure to odorants and olfactory training may increase olfactory identification skills without modifying odour detection,[18] these age-increased abilities for smell identification but not for detection, could be explained by the acquisition of cognitive smell skills through learnt experience.

Among the potential mechanisms proposed for age-related olfactory loss are the replacement of olfactory mucosa with respiratory epithelium caused by disease or pollutant exposure,[19]

cribiform plate calcification,[20] olfactory bulb atrophy,[21] decreased number of glomeruli/mitral cells in the olfactory tract,[22] and/or volume loss in temporal lobe areas.[23]

In accordance with other studies,[2,6,8] our survey found that women performed better in olfactory tasks compared with men of the same age group as well as self-reporting a better perception of smell sense. This gender difference was maintained across the life span, and increased considerably after the seventh decade of life. However, other studies have not found gender differences in olfactory sensitivity and identification, although women were slightly better.[4] We have to note that the rates of correctly identified odours (54.1% by women, 44.3% by men) are lower than those found in the BAST-24 validation,[24] in which the present survey is based, and a potential explanation could be that the OLFACAT study was done in the general population, with both healthy and diseased participants, when in the BAST-24 validation all participant were healthy.

Interestingly, our survey found than pregnancy but not menstruation was associated with a lack of odour recognition/memory. Changes in odour perception during pregnancy have been investigated in small studies and with controversial findings,[25] with olfactory dysfunction being more linked to changes in nasal sensitivity than in real smell perception.[26] Clearly but not significantly, our survey showed that women had an increased risk for anosmia of smell recognition/memory during pregnancy (n=125, OR=6.94).

In addition to male gender and ageing, we found that a history of transient olfactory loss for more than one week was associated to impairment in odour detection, recognition, and identification. Post-viral olfactory dysfunction has been found among the common causes of olfactory disorders of which spontaneous recovery might occur within two years.[21,27]

Moreover, survey participants with a history of head trauma had a higher risk of anosmia in the forced-choice identification task. One of the major causes of smell dysfunction, affecting all ages, is traumatic brain injury, secondary to a partial or total damage of olfactory bulbs and

tracts. This can involve frontal and temporal brain poles, as anosmia usually correlated with trauma severity.[28]

Although severe chronic rhinosinusitis with nasal polyps usually has a negative impact on smell function,[12] our data did not identify chronic rhinosinusitis as being a risk factor for the loss of smell. This controversial finding, also described in other surveys,[26] may be due either to possible mild levels of severity or self-misdiagnosis of the disease among survey participants.

Studies on the impact of smoking on the sense of smell are not conclusive, specially when different smell qualities are considered. Some studies have shown adverse effects on smell detection, identification, and intensity for some odours[8,10,11] whereas others have found no effect on smell detection and discrimination for other odorants.[9,26,29] In our survey, data showed that smoking might be a mild but significant protective factor for cognitive smell. An explanation for this contradictory finding could be the activation of subtype-selective nicotinic receptors in the olfactory bulb. For instance, in neurodegenerative disorders such as Parkinson Disease olfactory loss is being considered as a significant early symptom that correlates with the progression of disease.[30] In addition to the current evidence for the protective effect of smoking in PD,[31] recent studies suggest that therapy with nicotine receptor agonists mediate enhancement of olfactory working memory in rats[32] and could delay the progress of neurodegeneration in PD.[33] However, further epidemiologic and mechanistic studies need to be done taking in account the different smell qualities (detection, memory, identification) to bring definitive light to the impact of smoking in the sense of smell.

Another interesting finding showed that odour performance was positively related to a level of education superior to primary school. It is known that odour identification and semantic memory proficiency tap the same domain,[34] and that educational background is one of the most important predictors of cognitive decline with age, with cognitive deficits occurring

earlier and more extensively in people with a low educational level.[35] From an olfactory perspective, education and training may help to develop a wider repertoire of cognitive strategies to assist performance in verbal memory tasks, such as odour identification.[36]

As with all epidemiological studies, the OLFACAT survey may have some weaknesses. One) the survey population cannot be considered a random sample since there was no control over who and how the survey was performed or whether participants were preferentially motivated to answer the survey. Two) the survey's data may not be fully representative of the general population since the readership survey (2003) shows that the newspaper's readers belong to a higher socio-cultural class (85.1% middle class) and have a higher educational level (31.1% finished secondary school) than the general Catalan population (65.0% and 25.6%, respectively, 2002 census). Three) although other studies have not found smell differences among different ethnic groups, the lack of ethnic diversity in our sample (mainly Caucasians) could limit the generalisation to other ethnic groups. Four) cognitive disturbances in elderly individuals are characterised by impaired smell function but also potentially accounting for unwillingness to participate in the survey. Five) subjects with smell impairment could have been more/less interested in participating in the survey leading to an over/underestimation of the prevalence of dysfunction. Six) observations were based on cross-sectional data, making it impossible to disentangle true ageing effects from cohort membership. Seven) the survey could have a positive female response bias since almost two thirds of participants who returned the surveys were women (65.7%).

In agreement with earlier findings in other cultures, the present survey on the general population indicates an age-related deterioration in odour detection, recognition, and identification, with a higher prevalence and a more manifest age decline in men than in women. Pregnancy, head trauma, and a transient olfactory loss history are absolute risk

factors for olfactory dysfunction while having a higher educational level and smoking may be protective factors for smell. In order to understand the role of smell in human behaviour and determine the potential influence of cognitive, sensorial, and environmental factors, there is however an obvious need for well-designed longitudinal population-based studies, which deploy validated smell tests and consider the characteristics of the populations studied.

CONTRIBUTORSHIP STATEMENT

JM is the guarantor of the study, and has contributed with the conception and design of the study, literature search, acquisition of data, analysis and interpretation of data, and writing the manuscript. IA and FM have contributed through literature research, interpretation of data, and by drafting the manuscript; they approved the final version. LQ has contributed with the study design, acquisition of data, statistical analysis and interpretation of data, and drafting the manuscript; and approved the final version. JH has contributed with the conception and design of the study, acquisition and interpretation of data, and a critical reading of the manuscript; and approved the final version. CP, AV, and MB have contributed with the study design, interpretation of data, a critical reading of the manuscript, and approved the final version. CM has contributed with the conception and design of the study, acquisition of data, analysis and interpretation of data, and a critical reading of the manuscript; and approved the final version. All authors had full access to all of the data of the study including statistical reports and tables.

COMPETING INTERESTS STATEMENT

None.

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

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sponsors participated in the analysis and interpretation of data, writing of the report and the decision to submit the report for publication.

DATA SHARING

Data from this study are not in the public domain.

FIGURE LEGENDS

Figure 1. Flow-chart of participants in the OLFACAT (Olfaction in Catalonia) survey.

Figure 2. Evolution of normosmia (smell of all four odours) during lifetime. Smell detection showed a progressive decrease during the life span, while smell recognition/memory and identification increased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and declined thereafter. For detection, recognition/memory, or identification, normosmia was significantly higher ($p<0.0001$) in women (blue line) than in men (red line).

Figure 3. Evolution of hyposmia (smell of one to three odours) during lifetime. For detection, hyposmia showed a progressive increase during the life span, while for recognition/memory and identification hyposmia decreased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and increased thereafter. For detection, recognition/memory, or identification, hyposmia was significantly lower ($p<0.0001$) in women (blue line) than in men (red line).

Figure 4. Evolution of anosmia (smell of none of the four odours) during lifetime. Anosmia showed a progressive mild increase during the life span but being more significant after the sixth decade of life. For detection, recognition/memory, or identification, anosmia was significantly lower ($p<0.0001$) in women (blue line) than in men (red line), with a maximal difference after the seventh decade of life.

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Table 1. OLFACAT epidemiological characteristics and gender comparison: age, women's health, education level, smoking and toxic exposure, subjective description of smell, residential zone, history of head trauma, chronic rhinosinusitis, and loss of smell history.

Population characteristics [1]		Male 3,211 (34.3)	Female 6,137 (65.7)	Total 9,348 (100)	p-value
Age (years) [1]	< 20	127 (3.9)	315 (5.1)	442 (4.7)	< 0.0001 [2]
	20 - 29	241 (7.5)	878 (14.3)	1,119 (12.0)	
	30 - 39	668 (20.8)	1,487 (24.2)	2,155 (23.1)	
	40 - 49	861 (26.8)	1,673 (27.3)	2,534 (27.1)	
	50 - 59	766 (23.9)	1,181 (19.3)	1,947 (20.8)	
	60 - 69	355 (11.1)	454 (7.4)	809 (8.6)	
	> 70	193 (6.0)	149 (2.4)	342 (3.7)	
Menstruation [1]			781 (12.7)		
Pregnancy [1]			128 (2.1)		
Educational level [1]	elementary school	7 (0.2)	26 (0.4)	33 (0.3)	< 0.0001 [2]
	secondary school	508 (15.8)	978 (15.9)	1,486 (15.9)	
	high school	1,505 (46.9)	2,568 (41.9)	4,073 (43.6)	
	university/college	1,191 (37.1)	2,565 (41.8)	3,756 (40.2)	
Smoking [1]	non-smokers	1,185 (36.9)	3,513 (57.2)	4,698 (50.3)	< 0.0001 [2]
	ex-smokers	1,231 (38.3)	1,418 (23.1)	2,649 (28.3)	
	smoker	795 (24.8)	1,206 (19.7)	2,001 (21.4)	
Subjective description of sense of smell [1]	very good	407 (12.7)	1,576 (25.7)	1,983 (21.2)	< 0.0001 [2]
	good	2,472 (77.0)	4,243 (69.1)	6,715 (71.9)	
	poor	315 (9.8)	305 (5.0)	620 (6.6)	
	very poor	17 (0.5)	13 (0.2)	30 (0.3)	
Residential zone [1]	rural	57 (1.8)	109 (1.8)	166 (1.8)	0.9535 [2]
	semi-rural	142 (4.4)	263 (4.3)	405 (4.3)	
	urban	3,012 (93.8)	5,765 (93.9)	8,777 (93.9)	
History of head trauma [1]		200 (6.2)	264 (4.3)	464 (5.0)	< 0.0001 [2]
Exposure to noxious substances [1]		1,090 (33.9)	1,703 (27.7)	2,793 (29.9)	< 0.0001 [2]
Chronic rhinosinusitis [1]		137 (4.3)	277 (4.5)	414 (4.4)	0.5814 [2]
Loss of smell history [1]	never	2,217 (69.0)	4,289 (69.9)	6,506 (69.6)	0.0042 [2]
	≤ 1 week	789 (24.6)	1,555 (25.3)	2,344 (25.1)	
	> 1 week	205 (6.4)	293 (4.8)	498 (5.3)	

1: number of subjects (percentage)
2: Chi-square test

Table 2. Distribution and relative risk for hyposmia (smell of one to three odours) or anosmia (smell of none of the four odours) in the case of smell detection using a multivariate logistic analysis of demographic and health problems. Data presented as adjusted OR (Odd Ratio), 95% CI (Confidence Interval).

Covariable		Hyposmia (detection) 8,601 subjects, 1,639 with hyposmia (19%)					Anosmia (detection) 9,251 subjects, 25 with anosmia (0.3%)				
		No	Yes	Adjusted OR	(95% CI)	p-value	No	Yes	Adjusted OR	(95% CI)	p-value
Female		4,686 (67.3%)	967 (59.0%)	0.78	(0.69, 0.88)	< 0.0001	6,077 (65.9%)	7 (28.0%)	0.22	(0.07, 0.71)	0.0111
Educational level [1]	elementary school	23 (0.3%)	7 (0.4%)	-	-	0.0352	32 (0.3%)	0 (0.0%)	-	-	-
	middle school	1,061 (15.2%)	247 (15.1%)	0.76	(0.32, 1.81)		1,436 (15.6%)	8 (32.0%)	-	-	
	high school	3,053 (43.9%)	683 (41.7%)	1.02	(0.86, 1.21)		4,020 (43.6%)	11 (44.0%)	-	-	
	university	2,825 (40.6%)	702 (42.8%)	1.18	(1.05, 1.34)		3,738 (40.5%)	6 (24.0%)	-	-	
Subjective description of sense of smell [1]	very good	1,563 (22.5%)	275 (16.8%)	-	-	< 0.0001	1,968 (21.3%)	2 (8.0%)	-	-	< 0.0001
	good	4,990 (71.7%)	1,167 (71.2%)	1.24	(1.08, 1.44)		6,636 (71.9%)	2 (8.0%)	0.20	(0.03, 1.48)	
	bad	388 (5.6%)	188 (11.5%)	1.94	(1.58, 2.37)		608 (6.6%)	5 (20.0%)	9.69	(1.58, 59.30)	
	very bad	21 (0.3%)	9 (0.5%)	0.75	(0.33, 1.70)		14 (0.2%)	16 (64.0%)	109.54	(30.51, 393.35)	
Loss of smell history [1]	never	4,829 (69.4%)	1,130 (68.9%)	-	-	0.0935	6,429 (69.7%)	5 (20.0%)	-	-	0.0172
	≤ 1 week	1,796 (25.8%)	384 (23.4%)	0.88	(0.78, 1.01)		2,324 (25.2%)	1 (4.0%)	0.71	(0.08, 6.35)	
	> 1 week	337 (4.8%)	125 (7.6%)	1.25	(0.97, 1.62)		473 (5.1%)	19 (76.0%)	9.26	(0.98, 87.07)	
Exposure to noxious substances		2,023 (29.1%)	491 (30.0%)	1.02	(0.91, 1.16)	0.7025	2,749 (29.8%)	9 (36.0%)	2.00	(0.67, 5.92)	0.2117
Chronic rhinosinusitis		296 (4.3%)	75 (4.6%)	0.99	(0.76, 1.30)	0.9662	410 (4.4%)	3 (12.0%)	0.59	(0.09, 3.96)	0.5887
Menstruation		616 (8.8%)	116 (7.1%)	0.97	(0.78, 1.20)	0.7655	777 (8.4%)	0 (0.0%)	-	-	-
Age (years) [1]	< 20	374 (5.4%)	54 (3.3%)	-	-	< 0.0001	441 (4.8%)	1 (4.0%)	-	-	-
	20 - 29	914 (13.1%)	163 (9.9%)	1.12	(0.80, 1.57)		1,118 (12.1%)	1 (4.0%)	-	-	
	30 - 39	1,667 (23.9%)	356 (21.7%)	1.17	(0.95, 1.44)		2,150 (23.3%)	0 (0.0%)	-	-	
	40 - 49	1,893 (27.2%)	456 (27.8%)	1.14	(0.97, 1.33)		2,514 (27.2%)	2 (8.0%)	-	-	

	50 - 59	1,360 (19.5%)	386 (23.6%)	1.17	(1.00, 1.37)		1,909 (20.7%)	7 (28.0%)	-	-	
	60 - 69	528 (7.6%)	162 (9.9%)	1.08	(0.88, 1.34)		779 (8.4%)	6 (24.0%)	-	-	
	> 70	226 (3.2%)	62 (3.8%)	0.85	(0.61, 1.19)		315 (3.4%)	8 (32.0%)	-	-	
Residential zone [2]	rural *(reference)*	121 (1.7%)	31 (1.9%)	1	-	0.0821	165 (1.8%)	0 (0.0%)	-	-	-
	semi-rural	294 (4.2%)	85 (5.2%)	1.15	(0.72, 1.83)		403 (4.4%)	1 (4.0%)	-	-	
	City	6,547 (94.0%)	1,523 (92.9%)	0.87	(0.58, 1.30)		8,658 (93.8%)	24 (96.0%)	-	-	
Smoking [2]	non-smoker *(reference)*	3,535 (50.8%)	789 (48.1%)	1	-	0.9331	4,646 (50.4%)	10 (40.0%)	1	-	0.9608
	ex-smoker	1,939 (27.9%)	498 (30.4%)	1.00	(0.88, 1.14)		2,603 (28.2%)	11 (44.0%)	1.10	(0.34, 3.57)	
	smoker	1,488 (21.4%)	352 (21.5%)	1.03	(0.89, 1.19)		1,977 (21.4%)	4 (16.0%)	0.88	(0.19, 4.12)	
History of head trauma		343 (4.9%)	75 (4.6%)	0.85	(0.66, 1.11)	0.2298	456 (4.9%)	1 (4.0%)	0.33	(0.03, 3.98)	0.3832
Pregnancy		99 (1.2%)	19 (1.2%)	1.00	(0.60, 1.65)	0.9893	128 (1.4%)	0 (0.0%)	-	-	-

1: OR relative to the previous category
2: OR relative to the reference category

Table 3. Relative risk for hyposmia (smell of one to three odours) or anosmia (smell of none of the four odours) in the case of smell recognition/memory using a multivariate logistic analysis of demographic characteristics and health problems. Data presented as adjusted OR (Odd Ratio), 95% CI (Confidence Interval).

Covariable		Hyposmia (recognition/memory) 6,778 subjects, 2,936 with hyposmia (43%)					Anosmia (recognition/memory) 9,079 subjects, 18 with anosmia (0.2%)				
		No	Yes	Adjusted OR	(95% CI)	p-value	No	Yes	Adjusted OR	(95% CI)	p-value
Female		2,663 (69.3%)	1,885 (64.2%)	0.79	(0.71, 0.88)	< 0.0001	5,986 (66.1%)	12 (66.7%)	1.26	(0.41, 3.81)	0.6879
Educational level [1]	elementary school	14 (0.4%)	14 (0.5%)	-	-	0.0200	31 (0.3%)	2 (11.1%)	-	-	0.0005
	middle school	536 (14.0%)	505 (17.2%)	1.20	(0.56, 2.60)		1,387 (15.3%)	4 (22.2%)	0.05	(0.01, 0.29)	
	high school	1,671 (43.5%)	1,272 (43.3%)	0.84	(0.72, 0.97)		3,942 (43.5%)	11 (61.1%)	1.18	(0.34, 4.08)	
	university	1,621 (42.2%)	1,145 (39.0%)	0.93	(0.83, 1.04)		3,701 (40.8%)	1 (5.6%)	0.09	(0.01, 0.73)	
Subjective description of sense of smell [1]	very good	961 (25.0%)	532 (18.1%)	-	-	< 0.0001	1,939 (21.4%)	3 (16.7%)	-	-	0.0039
	good	2,690 (70.0%)	2,164 (73.7%)	1.45	(1.28, 1.64)		6,510 (71.8%)	12 (66.7%)	1.13	(0.31, 4.10)	
	Bad	187 (4.9%)	234 (8.0%)	1.62	(1.30, 2.01)		600 (6.6%)	1 (5.6%)	0.75	(0.08, 7.40)	
	very bad	4 (0.1%)	6 (0.2%)	0.98	(0.26, 3.66)		12 (0.1%)	2 (11.1%)	65.35	(4.60, 927.55)	
Loss of smell history [1]	never	2,620 (68.2%)	2,087 (71.1%)	-	-	0.0020	6,303 (69.6%)	11 (61.1%)	-	-	0.7159
	≤ 1 week	1,050 (27.3%)	685 (23.3%)	0.81	(0.73, 0.91)		2,299 (25.4%)	4 (22.2%)	1.22	(0.38, 3.91)	
	> 1 week	172 (4.5%)	164 (5.6%)	1.23	(0.95, 1.59)		459 (5.1%)	3 (16.7%)	1.76	(0.23, 13.60)	
Exposure to noxious substances		1,201 (31.3%)	803 (27.4%)	0.83	(0.74, 0.93)	0.0010	2,694 (29.7%)	4 (22.2%)	0.58	(0.18, 1.82)	0.3497
Chronic rhinosinusitis		168 (4.4%)	127 (4.3%)	1.02	(0.80, 1.30)	0.8574	404 (4.5%)	1 (5.6%)	0.72	(0.08, 6.40)	0.7720
Menstruation		347 (9.0%)	249 (8.5%)	1.08	(0.90, 1.29)	0.4244	774 (8.5%)	1 (5.6%)	1.14	(0.13, 9.87)	0.9070
Age (years) [1]	< 20	175 (4.6%)	214 (7.3%)	-	-	< 0.0001	437 (4.8%)	1 (5.6%)	-	-	0.7500
	20 - 29	494 (12.9%)	405 (13.8%)	0.80	(0.62, 1.03)		1,108 (12.2%)	1 (5.6%)	1.06	(0.06, 18.62)	
	30 - 39	956 (24.9%)	663 (22.6%)	0.81	(0.68, 0.96)		2,115 (23.3%)	4 (22.2%)	1.29	(0.14, 11.82)	
	40 - 49	1,088 (28.3%)	689 (23.5%)	0.91	(0.79, 1.04)		2,475 (27.3%)	2 (11.1%)	0.46	(0.08, 2.66)	
	50 - 59	775 (20.2%)	564 (19.2%)	1.06	(0.92, 1.24)		1,881 (20.8%)	3 (16.7%)	1.74	(0.28, 10.81)	
	60 - 69	268 (7.0%)	257 (8.8%)	1.22	(0.99, 1.50)		755 (8.3%)	4 (22.2%)	1.84	(0.37, 9.12)	

	> 70	86 (2.2%)	144 (4.9%)	1.64	(1.19, 2.26)		290 (3.2%)	3 (16.7%)	1.73	(0.35, 8.63)	
Residential zone [2]	rural *(reference)*	73 (1.9%)	49 (1.7%)	1	-	0.4187	164 (1.8%)	0 (0.0%)	-	-	-
	semi-rural	157 (4.1%)	139 (4.7%)	1.27	(0.82, 1.96)		390 (4.3%)	2 (11.1%)	-	-	
	City	3,612 (94.0%)	2,748 (93.6%)	1.10	(0.76, 1.59)		8,507 (93.9%)	16 (88.9%)	-	-	
Smoking [2]	non-smoker *(reference)*	1,857 (48.3%)	1,648 (56.1%)	1	-	< 0.0001	4,567 (50.4%)	12 (66.7%)	-	-	-
	ex-smoker	1,081 (28.1%)	766 (26.1%)	0.80	(0.71, 0.91)		2,537 (28.0%)	6 (33.3%)	-	-	
	smoker	904 (23.5%)	522 (17.8%)	0.68	(0.60, 0.78)		1,957 (21.6%)	0 (0.0%)	-	-	
History of head trauma		201 (5.2%)	134 (4.6%)	0.86	(0.68, 1.08)	0.1917	446 (4.9%)	0 (0.0%)	-	-	-
Pregnancy		60 (1.6%)	35 (1.2%)	0.84	(0.55, 1.29)	0.4243	125 (1.4%)	1 (5.6%)	6.94	(0.74, 65.52)	0.0907

1: OR relative to the previous category
2: OR relative to the reference category

Table 4. Relative risk for hyposmia (smell of one to three odours) or anosmia (smell of none of the four odours) in the case of smell identification using a multivariate logistic analysis of demographic characteristics and health problems. Data presented as adjusted OR (Odd Ratio), 95% CI (Confidence Interval).

Covariable		Hyposmia (identification) 8,107 subjects, 3,894 with hyposmia (48%)					Anosmia (identification) 9,195 subjects, 75 with anosmia (1%)				
		No	Yes	Adjusted OR	(95% CI)	p-value	No	Yes	Adjusted OR	(95% CI)	p-value
Female		2,911 (69.1%)	2,368 (60.8%)	0.76	(0.69, 0.84)	< 0.0001	6,008 (65.9%)	38 (50.7%)	0.96	(0.55, 1.67)	0.8850
Educational level [1]	elementary school	8 (0.2%)	18 (0.5%)	-	-	0.0007	31 (0.3%)	0 (0.0%)	-	-	-
	middle school	654 (15.5%)	608 (15.6%)	0.49	(0.21, 1.16)		1,419 (15.6%)	24 (32.0%)	-	-	
	high school	1,881 (44.6%)	1,636 (42.0%)	1.01	(0.88, 1.15)		3,970 (43.5%)	28 (37.3%)	-	-	
	university	1,670 (39.6%)	1,632 (41.9%)	1.21	(1.09, 1.34)		3,700 (40.6%)	23 (30.7%)	-	-	
Subjective description of sense of smell [1]	very good	1,034 (24.5%)	667 (17.1%)	-	-	< 0.0001	1,948 (21.4%)	8 (10.7%)	-	-	< 0.0001
	good	2,979 (70.7%)	2,841 (73.0%)	1.42	(1.27, 1.58)		6,567 (72.0%)	38 (50.7%)	1.27	(0.59, 2.76)	
	poor	183 (4.3%)	374 (9.6%)	2.06	(1.69, 2.51)		592 (6.5%)	13 (17.3%)	2.16	(1.00, 4.66)	
	very poor	17 (0.4%)	12 (0.3%)	0.26	(0.12, 0.56)		13 (0.1%)	16 (21.3%)	36.06	(13.12, 99.13)	
Loss of smell history [1]	never	2,895 (68.7%)	2,741 (70.4%)	-	-	0.0005	6,361 (69.7%)	38 (50.7%)	-	-	0.0415
	≤ 1 week	1,130 (26.8%)	901 (23.1%)	0.82	(0.74, 0.91)		2,301 (25.2%)	12 (16.0%)	0.93	(0.48, 1.81)	
	> 1 week	188 (4.5%)	252 (6.5%)	1.28	(1.02, 1.62)		458 (5.0%)	25 (33.3%)	2.79	(1.14, 6.88)	
Exposure to noxious substances		1,255 (29.8%)	1,132 (29.1%)	0.98	(0.89, 1.08)	0.6930	2,716 (29.8%)	23 (30.7%)	1.03	(0.60, 1.77)	0.9111
Chronic rhinosinusitis		187 (4.4%)	170 (4.4%)	0.96	(0.77, 1.20)	0.7290	403 (4.4%)	5 (6.7%)	0.80	(0.28, 2.29)	0.6824
Menstruation		390 (9.3%)	304 (7.8%)	1.03	(0.87, 1.22)	0.7157	772 (8.5%)	2 (2.7%)	0.49	(0.11, 2.14)	0.3421
Age (years) [1]	< 20	203 (4.8%)	194 (5.0%)	-	-	< 0.0001	438 (4.8%)	3 (4.0%)	-	-	0.0006
	20 - 29	551 (13.1%)	466 (12.0%)	0.82	(0.64, 1.04)		1,106 (12.1%)	8 (10.7%)	0.76	(0.19, 2.96)	
	30 - 39	1,032 (24.5%)	839 (21.5%)	0.94	(0.80, 1.10)		2,131 (23.4%)	11 (14.7%)	0.65	(0.25, 1.68)	
	40 - 49	1,198 (28.4%)	1,004 (25.8%)	1.05	(0.93, 1.19)		2,490 (27.3%)	10 (13.3%)	0.68	(0.28, 1.65)	
	50 - 59	822 (19.5%)	831 (21.3%)	1.20	(1.05, 1.37)		1,886 (20.7%)	12 (16.0%)	1.40	(0.58, 3.38)	

	60 - 69	302 (7.2%)	371 (9.5%)	1.19	(0.99, 1.43)		763 (8.4%)	17 (22.7%)	3.38	(1.51, 7.55)	
	> 70	105 (2.5%)	189 (4.9%)	1.43	(1.07, 1.91)		306 (3.4%)	14 (18.7%)	1.24	(0.51, 3.01)	
Residential zone [2]	rural *(reference)*	76 (1.8%)	71 (1.8%)	1	-	0.3585	162 (1.8%)	1 (1.3%)	1	-	0.9858
	semi-rural	176 (4.2%)	181 (4.6%)	1.11	(0.75, 1.65)		400 (4.4%)	3 (4.0%)	0.87	(0.08, 8.95)	
	city	3,961 (94.0%)	3,642 (93.5%)	0.95	(0.68, 1.33)		8,558 (93.8%)	71 (94.7%)	0.85	(0.12, 6.21)	
Smoking [2]	non-smoker *(reference)*	2,118 (50.3%)	1,968 (50.5%)	1	-	0.5326	4,594 (50.4%)	30 (40.0%)	1	-	0.2814
	ex-smoker	1,169 (27.7%)	1,131 (29.0%)	0.96	(0.86, 1.07)		2,567 (28.1%)	30 (40.0%)	1.61	(0.88, 2.93)	
	smoker	926 (22.0%)	795 (20.4%)	0.94	(0.83, 1.06)		1,959 (21.5%)	15 (20.0%)	1.41	(0.70, 2.82)	
History of head trauma		204 (4.8%)	193 (5.0%)	0.97	(0.79, 1.20)	0.7963	442 (4.8%)	12 (16.0%)	3.38	(1.69, 6.74)	0.0006
Pregnancy		62 (1.5%)	48 (1.2%)	1.02	(0.69, 1.51)	0.9157	126 (1.4%)	1 (1.3%)	1.72	(0.22, 13.33)	0.6017

1: OR relative to the previous category
2: OR relative to the reference category

Furthering the understanding of olfaction, prevalence of loss of smell, and risk factors: a population-based survey (OLFACAT)

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RELEVANT SURVEY HEADINGS: sense of smell, general population, olfactory disorders, normosmia, hyposmia, anosmia, risk factors.

ABSTRACT

Objectives: To investigate olfaction in general population, prevalence of olfactory dysfunction, and related risk factors.

Design: Cross-sectional population-based survey, distributing four microencapsulated odorants (rose, banana, musk, gas) and two self-administered questionnaires (odour description; epidemiology/health status).

Setting: The survey was distributed to general population through a bilingual (Catalan, Spanish) newspaper in Catalonia (Spain), on December 2003.

Participants: Newspaper readers of all ages and gender; 9,348 surveys were analyzed from the 10,783 returned.

Main outcome measures: Characteristics of surveyed population, olfaction by age and gender, smell-self perception, and smell impairment risk factors. Terms normosmia, hyposmia, and anosmia were used when participants detected, recognized, or identified all four, one to three, or none of the odours, respectively.

Results: Survey profile was a 43-year-old woman with medium-high educational level, living in a city. Olfaction was considered normal in 80.6% (detection), 56.0% (recognition/memory), and 50.7% (identification). Prevalence of smell dysfunction was 19.4% for detection (0.3% anosmia, 19.1% hyposmia), 43.5% for recognition (0.2% anosmia, 43.3% hyposmia), and 48.8% for identification (0.8% anosmia, 48% hyposmia). Olfaction was worse ($p<0.0001$) in men than in women through all ages. There was a significant age-related smell detection decline however smell recognition and identification increased up to fourth decade and declined after the sixth decade of life. Risk factors for anosmia were: male gender, loss of smell history, and poor olfactory self-perception for detection; low educational level, poor self-perception, and pregnancy for recognition; and older age, poor self-perception, and history of head trauma and loss of smell for identification. Smoking and exposure to noxious substances were mild protective factors for smell recognition.

Conclusions: Sense of smell in women is better than in men suggesting a learning process during life with deterioration in older ages. Poor self-perception, history of smell loss, head trauma, and pregnancy are potential risk factors for olfactory disorders.

ABSTRACT WORD COUNT: 300 words

ARTICLE SUMMARY

Article focus

- Population-based smell survey in 2003.
- Partial and total smell impairment by age and gender.
- Risk factors for olfactory disorders.

Key messages

- Olfaction is better in female than in male.
- Smell improves with a learning process and deteriorates in older ages.
- Poor olfactory self-perception, history of smell loss for over one week, head trauma, and pregnancy are potential risk factors for olfactory disorders.

Strengths and limitations of this study

- Strength: The largest European population-based study providing data on partial/total loss of smell and their absolute risk factors.
- Limitations: self-administered survey (no control on how it was performed); the study was done in a middle-high socio-cultural population (newspaper readers).

INTRODUCTION

The sense of smell provides information on the surrounding environment, warns us about chemical dangers and putrid food, and may even help people to mate. Smell disorders may affect the ability to enjoy food and aromas while interfering with the ability to notice potentially harmful chemicals and gases.[1]

In 1987, the National Geographic Smell Survey (NGSS) studied a large US sample population (1.2 million) whereby 1% of participants could not smell three or more of six odorants using a "scratch and sniff" test.[2] Age was an important factor in smell deterioration and smell was rated better in women than in men. In 1994, the National Health Interview Survey (NHIS)[3] reported data from 42,000 United States households with 1.4% prevalence of self-reported olfactory dysfunction, exponentially increasing with age. This study, however, did not include any testing of smell function.

The prevalence and associated risk factors of olfactory impairment in the European population has been investigated to a limited extent. In the Swedish version of the NGSS,[4] done in 532 individuals older than 45 years, increasing age was associated with impaired ability to detect/identify odorants, with no effect of gender on smell perception. Education has also been shown to account for a significant portion of the age-related variance in identification.[5] Another European population-based study identified a significant relationship between impaired olfaction and aging, male gender, and nasal polyps, but not with diabetes or smoking, reporting an olfactory dysfunction prevalence of 19.1%.[6]

Approximately two thirds of smell dysfunction cases are likely due to prior upper respiratory infections, head trauma, or sinonasal diseases.[7] Toxic chemical exposure, epilepsy, pollution, drugs, nutritional disturbances, and neurodegenerative diseases may also cause olfactory disorders.[8,9] Smoking may cause a reversible reduction in the ability to smell[10,11] while chronic rhinosinusitis/nasal polyps may result in a partial or total loss of smell.[12]

The aims of this study were to investigate the current status of olfaction in the general population while determining the prevalence of olfactory dysfunction and its related risk factors.

METHODS

Study Design

The OLFACAT (Olfaction in Catalonia) survey was carried out in the general population of Catalonia in Spain. Two questionnaires, olfaction and demography-health status, and a set of four microencapsulated odorants were distributed in the 250,000 daily issues of the newspaper *El Periódico de Catalunya* on December 23rd, 2003. The survey was presented in both Catalan and Spanish languages to facilitate the choice of the preferred language. The present manuscript has followed the STROBE checklist guidelines.

The study was approved by the Institutional Ethics and Clinical Research Committee of Hospital Clínic de Barcelona (reference 1295).

Measurements

Survey Odorants**.** Four common odorants were included in the survey: rose (2% of Bulgarian rose in 98% of phenyl-ethyl alcohol) as a floral odour; banana (amyl-isobutirate at 50% in dietyl-phtalate) as a food odour; musk (1:1 mixture of galaxolide and diethyl-phtalate exaltolide) as a perfume odour; and gas (mixture of 30% mercaptan and 70% tetrahydrothiophene) as an industrial odour. Each compound was prepared following established formulas and the solution magnetically homogenized. Rose, banana, and musk odorants were elaborated by Antonio Puig SA (Barcelona, Catalonia, Spain) and gas odorant by ENAGAS (Saragossa, Spain). Stability test protocols were performed by accelerating the olfactory aging of products at 40ºC for 2 months, following their smell evolution after 1 to 8 weeks. The micro-encapsulation process was done by ARCADE Europe (Paris France) as follows: essential oil component was contained and delivered from highly durable synthetic microcapsules manufactured using a proprietary polycondensated polymerization method.

The microcapsules were blended with a water-based polymer adhesive to form printable slurry. Odorants were adhered to a smell-less paper and dispatched using a folded-form design so as to prevent direct contact between odour samples.

Smell questionnaire. Participants were asked to scratch and sniff each odour and then answer three questions: First) odour detection: did you smell any scent? (yes, no); Second) odour recognition/memory: have you ever smelt this scent? (yes, no); and third) forced-choice odour identification: which name defines the scent you have smelt?, whereby only one of the four given options was correct. The term "normosmia" was used when a participant was able to detect, recognize (memory), or correctly identify all four tested odours; the term "hyposmia" was used when a participant was not able to detect, recognize (memory), or correctly identify one, two, or three tested odours; and the term "anosmia" was used when a participant was unable to detect, recognize (memory), or correctly identify any of the four tested odours.

Epidemiological and health-status questionnaire. From the twelve-question questionnaire, four questions were on demography: first) gender (male, female); second) age (years); third) current educational level (primary school, secondary school, high school, University or College); and fourth) residential area (city, postcode). Two questions described smell self-perception: fiftth) how do you consider your current sense of smell? (very good, good, poor, very poor); and sixth) have you ever lost the sense of smell? (never, up to one week, over one week). Two questions were on exposure to toxic or noxious substances: seventh) have you ever been exposed to dust, gases, fumes, vapours, or/and volatile toxics at home and/or at work? (yes, no); and eighth) do you smoke? (no, ex-smoker, smoker). Two questions were on health-status: ninth) have you ever had a severe face and/or head trauma? (yes, no); and tenth) have you ever been diagnosed with chronic rhinosinusitis? (yes, no). Finally, two questions

were on women's health: eleventh) are you currently pregnant? (yes, no); and twelfth) are you currently menstruating? (yes, no).

Data Management and Statistical Analysis

The returned surveys were read using an optical system (BV Scan system, Voxpublica), the data were transferred to an electronic database, and then statistically analysed using Stata version 8 (Stata Statistical Software: Release 8.0 College Station, TX: *Stata Corporation* 2003).[13] The data cleaning process was based on programmed queries to identify records containing inconsistent or uncertain data. The corrupt or inaccurate values identified by these queries were subsequently recorded as missing values in the data set.

Only those surveys fully and consistently answered were considered for statistical analysis. Differences between gender in epidemiological and health-status characteristics were evaluated by Chi-square test. Adjusted (multivariate) logistic regression models for anosmia and hyposmia were estimated (Tables 2, 3 and 4). To estimate the multivariate models for anosmia, the covariates that do not have any events (anosmia cases) in any of its categories were not included. Results from estimated models were expressed as adjusted Odd Ratio (OR) and 95% Confidence Interval (CI). The reference category used to calculate the OR for each level of variables measured on an ordinal scale was the immediately previous category, starting with the second. Results from estimated models were expressed as Odd Ratio (OR) and 95% Confidence Interval (CI). All tests were performed using a two-tailed significance level of 0.05.

RESULTS

Characteristics of the surveyed population

Following the data cleaning process, 5.6% of answers from the 10,783 received surveys were identified as inconsistent. After the exclusion of both these inconsistent questionnaire returns and the incomplete epidemiological and health-status questionnaires (7.7%), the sample size for analysis was 9,348 questionnaires (Figure 1).

Age and gender. The mean age of the surveyed population was 43.3 years, ranging from 5 to 91 years. The analysis was performed in seven age groups to ensure a reasonable sample size for each age and gender group. Almost two thirds of participants were women (65.7%), of which 2.1% were pregnant and 12.7% were menstruating (Table 1).

Education and residential zone. Most participants (83.8%) had a high educational level (high school or University/College) and were living (93.9%) in an urban area, with no differences between gender.

Exposure to tobacco and noxious substances. More than one fifth (21.4%) of participants were smokers, 28·3% were ex-smokers, while almost a third (29.9%) reported to be regularly exposed to toxic or noxious substances, either at home or at work. Men reported a higher exposure to both tobacco smoke (24.8%, $p<0.0001$) and noxious substances (33.9%, $p<0.0001$) than women (19.7% and 27.7%, respectively).

Health status. 4.4% of participants had received a diagnosis of chronic rhinosinusitis, with similar prevalence in women and men, while 5.0% reported a history of face/head trauma, this prevalence being higher in men than in women (6.2% versus 4.3%, $p<0.0001$).

Sense of smell. All four odours (normosmia) were detected by 80.6%, recognised by 56.0%, and identified by 50.7% of the surveyed population. One to three odours (hyposmia) were detected by 19.1%, recognised by 43.3%, and identified by 48.0%. None of the four odours (anosmia) were detected by 0.3%, recognised by 0.2%, and identified by 0.8%. Individual odours were more highly detected (rose 99.4%, banana 98.9%, gas 96.9%, musk 84.4%) than recognised (rose 94.8%, banana 96.2%, gas 94.9%, musk 66.2%) or correctly identified (rose 91.8%, banana 89.8%, gas 92.1%, musk 65.4%). Moreover, individual odours were always better detected, recognised, and identified by women than by men, except for rose and banana recognition.

Smell by gender and age

Within the population experiencing normosmia, there was a significant and progressive age-related decline of smell detection while smell recognition and identification increased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and declined thereafter. Significant but opposite findings were found for hyposmia and anosmia. Normosmia was higher in women than in men ($p<0.0001$) either in smell detection (82.8% versus 76.5%), recognition/memory (58.0% versus 51.9%), or identification (54.1% versus 44.3%) (Figure 1). Hyposmia was higher in men than in women ($p<0.0001$) either in smell detection (22.8% versus 17.1%), recognition/memory (47.1% versus 41.4%), and identification (54.0% versus 44.9%) (Figure 2). Finally, anosmia was higher in men than in women in both smell detection (0.9% versus 0.1%; $p<0.0001$) and identification (1.2% versus 0.6%; p=0·0057), but not in smell recognition/memory (0.2% versus 0.2%, p=0.9569) (Figure 3). In the oldest group (over 70 years), the prevalence for anosmia of detection (4.4%) and identification (6.6%) was especially higher in men than in women (0% and 1·4%, respectively).

Smell self-perception

Subjective description of smell. Regardless of gender and age, 93.1% of participants subjectively rated their sense of smell as good or very good, while 6.9% of them reported their smell as poor or very poor, the smell score being better in women than in men (p<0.0001).

Loss of smell history. A past history of loss of smell was reported by almost one third (30.4%) of participants, predominantly for less than one week (25.1%). The smell loss for over one week was more frequent in men (6.4% vs 4.8%, p=0.0042).

Risk factors for smell impairment

Smell detection. Women detected odours more frequently than men (82.8% versus 76.5%, p<0.0001). The risk for anosmia of detection was lower in women (OR=0.22) and higher in subjects reporting a loss of smell history for over one week (OR=9.26); and anosmia was also associated with a worse smell self-perception (Table 2). The risk for hyposmia of detection was lower in women (OR=0.78) and associated with older age (>50 years old), a lower educational level, and a worse smell self-perception (Table 2).

Smell recognition / memory**.** Women showed a better capability to recognise odours than men (58.0% versus 51.9%; p<0.0001). The risk for anosmia of recognition was higher in pregnant women (OR=6.94) and associated with a lower educational level and a worse smell self-perception (Table 3). The risk for hyposmia of recognition was lower in women (OR=0.79) and higher in subjects reporting a loss of smell history for over one week (OR=1.23); and it was associated with older age (>70 years old), a lower educational level, and a worse smell self-perception. Smoking (both ex-smokers and smokers) (OR=0.80 and 0.68, respectively) and frequent contact with noxious substances (OR=0.83) were found to have a mild but significant protective effect on odour recognition/memory (Table 3).

Forced-choice smell identification. Women performed better than men on odour identification (54.1% versus 44.3%, p<0.0001). The risk for anosmia of identification was higher in subjects reporting a history of head trauma (OR=3.38) and a loss of smell for over one week (OR=2.79), and it was associated with older age (>60 years old) and a worse smell self-perception (Table 4). The risk for hyposmia of identification was lower in women (OR=0.76) and higher in subjects reporting a loss of smell history for over one week (OR=1.28), and it was associated with older age (>60 years old), a lower educational level, and a smell worse self-perception (Table 4).

DISCUSSION

The most important findings of the OLFACAT survey were: First) the overall prevalence of olfactory dysfunction in the case of detection was 19.4%, with a total loss of smell (anosmia) of 0.3%. Despite this high prevalence of smell impairment, only 6.9% of the subjects considered having a poor or very poor sense of smell. Second) there was a significant age-related decline in smell detection for both genders. However, cognitive smell (recognition and identification) was increased and/or was maintained up to the sixth decade of life, declining thereafter. Third) besides women having a better self-perception of smell capabilities than men, women also scored better than men in smell detection, recognition, and identification, and did so throughout their lifetime. Fourth) pregnancy, but not menstruation was associated with a partial loss (hyposmia) of smell recognition. Fifth) male gender, poor smell self-perception, low educational level, and ageing, but not chronic rhinosinusitis, were risk factors related to smell impairment whether in terms of detection, recognition, or identification. Subjects with a history of persistent olfactory loss or head trauma were also at higher risk of smell impairment. Sixth) finally and surprisingly, persistent exposure to noxious substances and smoking showed to be protective factors for cognitive smell impairment in either recognition or identification.

Approximately 39.5 million Spaniards and 425 million EU citizens are aged 15 years or older, according to Catalan, Spanish, and European Statistic Institutes. Our survey therefore estimates that 1.2 million adult Catalans, 7.7 million Spaniards, and over 82 million EU citizens suffering from olfactory dysfunction, of which 20,000 Catalans, 120,000 Spaniards, and 1.5 million EU citizens have a total loss of sense of smell.

Brämerson et al.[6] reported an overall prevalence of olfactory impairment of 19.1% in a Swedish population which was very similar to our 19.4%. This prevalence is considerably

higher than self-reported loss of smell in the NGSS[2] (1.4%) and in our own survey where 6.9% of participants were considered to have a poor or very poor sense of smell, suggesting a low sensitivity for the subjective assessment of smell loss. The fact that many people may be unaware of their smell dysfunction, especially the elderly and/or those living alone, implies an increased risk for both nutritional problems[14] and safety in the face of a potential domestic fire or gas leak.[15]

In accordance with the OLFACAT survey data, previous studies have indicated that sense of smell detection is impaired with ageing, even in healthy individuals[16] and from the second to the eighth decade of life.[17] Our data also aligns with the NGSS and other studies in that the age decline in odour perception is universal across subjects regardless of gender odorants, outcome measures, or cultural diversity.[2,6] Smell changes observed across the survey's age span are similar to a previous study reporting a progressive decline in odour.[18] Concerning cognitive smell (memory and identification), we observed an increase in performance in the first decades of life, reaching a plateau during the third through to fifth decades of life and declining thereafter. Larsson et al.[4] reported that age was associated with an increased ability to identify banana odour (amylacetate). Our survey, in agreement with the NGSS findings, found not only an increased ability to recognise and identify banana, but rose and gas also, with increase indicated up to the fifth decade of life but decreasing thereafter. Due to the fact that repeated exposure to odorants and olfactory training may increase olfactory identification skills without modifying odour detection,[18] these age-increased abilities for smell identification but not for detection, could be explained by the acquisition of cognitive smell skills through learnt experience.

Among the potential mechanisms proposed for age-related olfactory loss are the replacement of olfactory mucosa with respiratory epithelium caused by disease or pollutant exposure,[19]

cribiform plate calcification,[20] olfactory bulb atrophy,[21] decreased number of glomeruli/mitral cells in the olfactory tract,[22] and/or volume loss in temporal lobe areas.[23]

In accordance with other studies,[2,6,8] our survey found that women performed better in olfactory tasks compared with men of the same age group as well as self-reporting a better perception of smell sense. This gender difference was maintained across the life span, and increased considerably after the seventh decade of life. However, other studies have not found gender differences in olfactory sensitivity and identification, although women were slightly better.[4] We have to note that the rates of correctly identified odours (54.1% by women, 44.3% by men) are lower than those found in the BAST-24 validation,[24] in which the present survey is based, and a potential explanation could be that the OLFACAT study was done in the general population, with both healthy and diseased participants, when in the BAST-24 validation all participant were healthy.

Interestingly, our survey found than pregnancy but not menstruation was associated with a lack of odour recognition/memory. Changes in odour perception during pregnancy have been investigated in small studies and with controversial findings,[25] with olfactory dysfunction being more linked to changes in nasal sensitivity than in real smell perception.[26] Clearly but not significantly, our survey showed that women had an increased risk for anosmia of smell recognition/memory during pregnancy (n=125, OR=6.94).

In addition to male gender and ageing, we found that a history of transient olfactory loss for more than one week was associated to impairment in odour detection, recognition, and identification. Post-viral olfactory dysfunction has been found among the common causes of olfactory disorders of which spontaneous recovery might occur within two years.[21,27]

Moreover, survey participants with a history of head trauma had a higher risk of anosmia in the forced-choice identification task. One of the major causes of smell dysfunction, affecting all ages, is traumatic brain injury, secondary to a partial or total damage of olfactory bulbs and

tracts. This can involve frontal and temporal brain poles, as anosmia usually correlated with trauma severity.[28]

Although severe chronic rhinosinusitis with nasal polyps usually has a negative impact on smell function,[12] our data did not identify chronic rhinosinusitis as being a risk factor for the loss of smell. This controversial finding, also described in other surveys,[26] may be due either to possible mild levels of severity or self-misdiagnosis of the disease among survey participants.

Studies on the impact of smoking on the sense of smell are not conclusive, specially when different smell qualities are considered. Some studies have shown adverse effects on smell detection, identification, and intensity for some odours[8,10,11] whereas others have found no effect on smell detection and discrimination for other odorants.[9,26,29] In our survey, data showed that smoking might be a mild but significant protective factor for cognitive smell. An explanation for this contradictory finding could be the activation of subtype-selective nicotinic receptors in the olfactory bulb. For instance, in neurodegenerative disorders such as Parkinson Disease olfactory loss is being considered as a significant early symptom that correlates with the progression of disease.[30] In addition to the current evidence for the protective effect of smoking in PD,[31] recent studies suggest that therapy with nicotine receptor agonists mediate enhancement of olfactory working memory in rats[32] and could delay the progress of neurodegeneration in PD.[33] However, further epidemiologic and mechanistic studies need to be done taking in account the different smell qualities (detection, memory, identification) to bring definitive light to the impact of smoking in the sense of smell.

Another interesting finding showed that odour performance was positively related to a level of education superior to primary school. It is known that odour identification and semantic memory proficiency tap the same domain,[34] and that educational background is one of the most important predictors of cognitive decline with age, with cognitive deficits occurring

earlier and more extensively in people with a low educational level.[35] From an olfactory perspective, education and training may help to develop a wider repertoire of cognitive strategies to assist performance in verbal memory tasks, such as odour identification.[36]

As with all epidemiological studies, the OLFACAT survey may have some weaknesses. One) the survey population cannot be considered a random sample since there was no control over who and how the survey was performed or whether participants were preferentially motivated to answer the survey. Two) the survey's data may not be fully representative of the general population since the readership survey (2003) shows that the newspaper's readers belong to a higher socio-cultural class (85.1% middle class) and have a higher educational level (31.1% finished secondary school) than the general Catalan population (65.0% and 25.6%, respectively, 2002 census). Three) although other studies have not found smell differences among different ethnic groups, the lack of ethnic diversity in our sample (mainly Caucasians) could limit the generalisation to other ethnic groups. Four) cognitive disturbances in elderly individuals are characterised by impaired smell function but also potentially accounting for unwillingness to participate in the survey. Five) subjects with smell impairment could have been more/less interested in participating in the survey leading to an over/underestimation of the prevalence of dysfunction. Six) observations were based on cross-sectional data, making it impossible to disentangle true ageing effects from cohort membership. Seven) the survey could have a positive female response bias since almost two thirds of participants who returned the surveys were women (65.7%).

In agreement with earlier findings in other cultures, the present survey on the general population indicates an age-related deterioration in odour detection, recognition, and identification, with a higher prevalence and a more manifest age decline in men than in women. Pregnancy, head trauma, and a transient olfactory loss history are absolute risk

factors for olfactory dysfunction while having a higher educational level and smoking may be protective factors for smell. In order to understand the role of smell in human behaviour and determine the potential influence of cognitive, sensorial, and environmental factors, there is however an obvious need for well-designed longitudinal population-based studies, which deploy validated smell tests and consider the characteristics of the populations studied.

CONTRIBUTORSHIP STATEMENT

JM is the guarantor of the study, and has contributed with the conception and design of the study, literature search, acquisition of data, analysis and interpretation of data, and writing the manuscript. IA and FM have contributed through literature research, interpretation of data, and by drafting the manuscript; they approved the final version. LQ has contributed with the study design, acquisition of data, statistical analysis and interpretation of data, and drafting the manuscript; and approved the final version. JH has contributed with the conception and design of the study, acquisition and interpretation of data, and a critical reading of the manuscript; and approved the final version. CP, AV, and MB have contributed with the study design, interpretation of data, a critical reading of the manuscript, and approved the final version. CM has contributed with the conception and design of the study, acquisition of data, analysis and interpretation of data, and a critical reading of the manuscript; and approved the final version. All authors had full access to all of the data of the study including statistical reports and tables.

COMPETING INTERESTS STATEMENT

None.

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

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sponsors participated in the analysis and interpretation of data, writing of the report and the decision to submit the report for publication.

DATA SHARING

Data from this study are not in the public domain.

FIGURE LEGENDS

Figure 1. Flow-chart of participants in the OLFACAT (Olfaction in Catalonia) survey.

Figure 2. Evolution of normosmia (smell of all four odours) during lifetime. Smell detection showed a progressive decrease during the life span, while smell recognition/memory and identification increased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and declined thereafter. For detection, recognition/memory, or identification, normosmia was significantly higher (p<0.0001) in women (blue line) than in men (red line).

Figure 3. Evolution of hyposmia (smell of one to three odours) during lifetime. For detection, hyposmia showed a progressive increase during the life span, while for recognition/memory and identification hyposmia decreased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and increased thereafter. For detection, recognition/memory, or identification, hyposmia was significantly lower (p<0.0001) in women (blue line) than in men (red line).

Figure 4. Evolution of anosmia (smell of none of the four odours) during lifetime. Anosmia showed a progressive mild increase during the life span but being more significant after the sixth decade of life. For detection, recognition/memory, or identification, anosmia was significantly lower (p<0.0001) in women (blue line) than in men (red line), with a maximal difference after the seventh decade of life.

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Table 1. OLFACAT epidemiological characteristics and gender comparison: age, women's health, education level, smoking and toxic exposure, subjective description of smell, residential zone, history of head trauma, chronic rhinosinusitis, and loss of smell history.

Population characteristics [1]		Male 3,211 (34.3)	Female 6,137 (65.7)	Total 9,348 (100)	p-value
Age (years) [1]	< 20	127 (3.9)	315 (5.1)	442 (4.7)	< 0.0001 [2]
	20 - 29	241 (7.5)	878 (14.3)	1,119 (12.0)	
	30 - 39	668 (20.8)	1,487 (24.2)	2,155 (23.1)	
	40 - 49	861 (26.8)	1,673 (27.3)	2,534 (27.1)	
	50 - 59	766 (23.9)	1,181 (19.3)	1,947 (20.8)	
	60 - 69	355 (11.1)	454 (7.4)	809 (8.6)	
	> 70	193 (6.0)	149 (2.4)	342 (3.7)	
Menstruation [1]			781 (12.7)		
Pregnancy [1]			128 (2.1)		
Educational level [1]	elementary school	7 (0.2)	26 (0.4)	33 (0.3)	< 0.0001 [2]
	secondary school	508 (15.8)	978 (15.9)	1,486 (15.9)	
	high school	1,505 (46.9)	2,568 (41.9)	4,073 (43.6)	
	university/college	1,191 (37.1)	2,565 (41.8)	3,756 (40.2)	
Smoking [1]	non-smokers	1,185 (36.9)	3,513 (57.2)	4,698 (50.3)	< 0.0001 [2]
	ex-smokers	1,231 (38.3)	1,418 (23.1)	2,649 (28.3)	
	smoker	795 (24.8)	1,206 (19.7)	2,001 (21.4)	
Subjective description of sense of smell [1]	very good	407 (12.7)	1,576 (25.7)	1,983 (21.2)	< 0.0001 [2]
	good	2,472 (77.0)	4,243 (69.1)	6,715 (71.9)	
	poor	315 (9.8)	305 (5.0)	620 (6.6)	
	very poor	17 (0.5)	13 (0.2)	30 (0.3)	
Residential zone [1]	rural	57 (1.8)	109 (1.8)	166 (1.8)	0.9535 [2]
	semi-rural	142 (4.4)	263 (4.3)	405 (4.3)	
	urban	3,012 (93.8)	5,765 (93.9)	8,777 (93.9)	
History of head trauma [1]		200 (6.2)	264 (4.3)	464 (5.0)	< 0.0001 [2]
Exposure to noxious substances [1]		1,090 (33.9)	1,703 (27.7)	2,793 (29.9)	< 0.0001 [2]
Chronic rhinosinusitis [1]		137 (4.3)	277 (4.5)	414 (4.4)	0.5814 [2]
Loss of smell history [1]	never	2,217 (69.0)	4,289 (69.9)	6,506 (69.6)	0.0042 [2]
	≤ 1 week	789 (24.6)	1,555 (25.3)	2,344 (25.1)	
	> 1 week	205 (6.4)	293 (4.8)	498 (5.3)	

1: number of subjects (percentage)
2: Chi-square test

Table 2. Distribution and relative risk for hyposmia (smell of one to three odours) or anosmia (smell of none of the four odours) in the case of smell detection using a multivariate logistic analysis of demographic and health problems. Data presented as adjusted OR (Odd Ratio), 95% CI (Confidence Interval).

Covariable		Hyposmia (detection) 8,601 subjects, 1,639 with hyposmia (19%)					Anosmia (detection) 9,251 subjects, 25 with anosmia (0.3%)				
		No	Yes	Adjusted OR	(95% CI)	p-value	No	Yes	Adjusted OR	(95% CI)	p-value
Female		4,686 (67.3%)	967 (59.0%)	0.78	(0.69, 0.88)	< 0.0001	6,077 (65.9%)	7 (28.0%)	0.22	(0.07, 0.71)	0.0111
Educational level [1]	elementary school	23 (0.3%)	7 (0.4%)	-	-	0.0352	32 (0.3%)	0 (0.0%)	-	-	-
	middle school	1,061 (15.2%)	247 (15.1%)	0.76	(0.32, 1.81)		1,436 (15.6%)	8 (32.0%)	-	-	
	high school	3,053 (43.9%)	683 (41.7%)	1.02	(0.86, 1.21)		4,020 (43.6%)	11 (44.0%)	-	-	
	university	2,825 (40.6%)	702 (42.8%)	1.18	(1.05, 1.34)		3,738 (40.5%)	6 (24.0%)	-	-	
Subjective description of sense of smell [1]	very good	1,563 (22.5%)	275 (16.8%)	-	-	< 0.0001	1,968 (21.3%)	2 (8.0%)	-	-	< 0.0001
	good	4,990 (71.7%)	1,167 (71.2%)	1.24	(1.08, 1.44)		6,636 (71.9%)	2 (8.0%)	0.20	(0.03, 1.48)	
	bad	388 (5.6%)	188 (11.5%)	1.94	(1.58, 2.37)		608 (6.6%)	5 (20.0%)	9.69	(1.58, 59.30)	
	very bad	21 (0.3%)	9 (0.5%)	0.75	(0.33, 1.70)		14 (0.2%)	16 (64.0%)	109.54	(30.51, 393.35)	
Loss of smell history [1]	never	4,829 (69.4%)	1,130 (68.9%)	-	-	0.0935	6,429 (69.7%)	5 (20.0%)	-	-	0.0172
	≤ 1 week	1,796 (25.8%)	384 (23.4%)	0.88	(0.78, 1.01)		2,324 (25.2%)	1 (4.0%)	0.71	(0.08, 6.35)	
	> 1 week	337 (4.8%)	125 (7.6%)	1.25	(0.97, 1.62)		473 (5.1%)	19 (76.0%)	9.26	(0.98, 87.07)	
Exposure to noxious substances		2,023 (29.1%)	491 (30.0%)	1.02	(0.91, 1.16)	0.7025	2,749 (29.8%)	9 (36.0%)	2.00	(0.67, 5.92)	0.2117
Chronic rhinosinusitis		296 (4.3%)	75 (4.6%)	0.99	(0.76, 1.30)	0.9662	410 (4.4%)	3 (12.0%)	0.59	(0.09, 3.96)	0.5887
Menstruation		616 (8.8%)	116 (7.1%)	0.97	(0.78, 1.20)	0.7655	777 (8.4%)	0 (0.0%)	-	-	-
Age (years) [1]	< 20	374 (5.4%)	54 (3.3%)	-	-	< 0.0001	441 (4.8%)	1 (4.0%)	-	-	-
	20 - 29	914 (13.1%)	163 (9.9%)	1.12	(0.80, 1.57)		1,118 (12.1%)	1 (4.0%)	-	-	
	30 - 39	1,667 (23.9%)	356 (21.7%)	1.17	(0.95, 1.44)		2,150 (23.3%)	0 (0.0%)	-	-	
	40 - 49	1,893 (27.2%)	456 (27.8%)	1.14	(0.97, 1.33)		2,514 (27.2%)	2 (8.0%)	-	-	

	50 - 59	1,360 (19.5%)	386 (23.6%)	1.17	(1.00, 1.37)		1,909 (20.7%)	7 (28.0%)	-	-	
	60 - 69	528 (7.6%)	162 (9.9%)	1.08	(0.88, 1.34)		779 (8.4%)	6 (24.0%)	-	-	
	> 70	226 (3.2%)	62 (3.8%)	0.85	(0.61, 1.19)		315 (3.4%)	8 (32.0%)	-	-	
Residential zone [2]	rural *(reference)*	121 (1.7%)	31 (1.9%)	1	-	0.0821	165 (1.8%)	0 (0.0%)	-	-	-
	semi-rural	294 (4.2%)	85 (5.2%)	1.15	(0.72, 1.83)		403 (4.4%)	1 (4.0%)	-	-	
	City	6,547 (94.0%)	1,523 (92.9%)	0.87	(0.58, 1.30)		8,658 (93.8%)	24 (96.0%)	-	-	
Smoking [2]	non-smoker *(reference)*	3,535 (50.8%)	789 (48.1%)	1	-	0.9331	4,646 (50.4%)	10 (40.0%)	1	-	0.9608
	ex-smoker	1,939 (27.9%)	498 (30.4%)	1.00	(0.88, 1.14)		2,603 (28.2%)	11 (44.0%)	1.10	(0.34, 3.57)	
	smoker	1,488 (21.4%)	352 (21.5%)	1.03	(0.89, 1.19)		1,977 (21.4%)	4 (16.0%)	0.88	(0.19, 4.12)	
History of head trauma		343 (4.9%)	75 (4.6%)	0.85	(0.66, 1.11)	0.2298	456 (4.9%)	1 (4.0%)	0.33	(0.03, 3.98)	0.3832
Pregnancy		99 (1.2%)	19 (1.2%)	1.00	(0.60, 1.65)	0.9893	128 (1.4%)	0 (0.0%)	-	-	-

1: OR relative to the previous category
2: OR relative to the reference category

Table 3. Relative risk for hyposmia (smell of one to three odours) or anosmia (smell of none of the four odours) in the case of smell recognition/memory using a multivariate logistic analysis of demographic characteristics and health problems. Data presented as adjusted OR (Odd Ratio), 95% CI (Confidence Interval).

Covariable		Hyposmia (recognition/memory) 6,778 subjects, 2,936 with hyposmia (43%)					Anosmia (recognition/memory) 9,079 subjects, 18 with anosmia (0.2%)				
		No	Yes	Adjusted OR	(95% CI)	p-value	No	Yes	Adjusted OR	(95% CI)	p-value
Female		2,663 (69.3%)	1,885 (64.2%)	0.79	(0.71, 0.88)	< 0.0001	5,986 (66.1%)	12 (66.7%)	1.26	(0.41, 3.81)	0.6879
Educational level [1]	elementary school	14 (0.4%)	14 (0.5%)	-	-	0.0200	31 (0.3%)	2 (11.1%)	-	-	0.0005
	middle school	536 (14.0%)	505 (17.2%)	1.20	(0.56, 2.60)		1,387 (15.3%)	4 (22.2%)	0.05	(0.01, 0.29)	
	high school	1,671 (43.5%)	1,272 (43.3%)	0.84	(0.72, 0.97)		3,942 (43.5%)	11 (61.1%)	1.18	(0.34, 4.08)	
	university	1,621 (42.2%)	1,145 (39.0%)	0.93	(0.83, 1.04)		3,701 (40.8%)	1 (5.6%)	0.09	(0.01, 0.73)	
Subjective description of sense of smell [1]	very good	961 (25.0%)	532 (18.1%)	-	-	< 0.0001	1,939 (21.4%)	3 (16.7%)	-	-	0.0039
	good	2,690 (70.0%)	2,164 (73.7%)	1.45	(1.28, 1.64)		6,510 (71.8%)	12 (66.7%)	1.13	(0.31, 4.10)	
	Bad	187 (4.9%)	234 (8.0%)	1.62	(1.30, 2.01)		600 (6.6%)	1 (5.6%)	0.75	(0.08, 7.40)	
	very bad	4 (0.1%)	6 (0.2%)	0.98	(0.26, 3.66)		12 (0.1%)	2 (11.1%)	65.35	(4.60, 927.55)	
Loss of smell history [1]	never	2,620 (68.2%)	2,087 (71.1%)	-	-	0.0020	6,303 (69.6%)	11 (61.1%)	-	-	0.7159
	≤ 1 week	1,050 (27.3%)	685 (23.3%)	0.81	(0.73, 0.91)		2,299 (25.4%)	4 (22.2%)	1.22	(0.38, 3.91)	
	> 1 week	172 (4.5%)	164 (5.6%)	1.23	(0.95, 1.59)		459 (5.1%)	3 (16.7%)	1.76	(0.23, 13.60)	
Exposure to noxious substances		1,201 (31.3%)	803 (27.4%)	0.83	(0.74, 0.93)	0.0010	2,694 (29.7%)	4 (22.2%)	0.58	(0.18, 1.82)	0.3497
Chronic rhinosinusitis		168 (4.4%)	127 (4.3%)	1.02	(0.80, 1.30)	0.8574	404 (4.5%)	1 (5.6%)	0.72	(0.08, 6.40)	0.7720
Menstruation		347 (9.0%)	249 (8.5%)	1.08	(0.90, 1.29)	0.4244	774 (8.5%)	1 (5.6%)	1.14	(0.13, 9.87)	0.9070
Age (years) [1]	< 20	175 (4.6%)	214 (7.3%)	-	-	< 0.0001	437 (4.8%)	1 (5.6%)	-	-	0.7500
	20 - 29	494 (12.9%)	405 (13.8%)	0.80	(0.62, 1.03)		1,108 (12.2%)	1 (5.6%)	1.06	(0.06, 18.62)	
	30 - 39	956 (24.9%)	663 (22.6%)	0.81	(0.68, 0.96)		2,115 (23.3%)	4 (22.2%)	1.29	(0.14, 11.82)	
	40 - 49	1,088 (28.3%)	689 (23.5%)	0.91	(0.79, 1.04)		2,475 (27.3%)	2 (11.1%)	0.46	(0.08, 2.66)	
	50 - 59	775 (20.2%)	564 (19.2%)	1.06	(0.92, 1.24)		1,881 (20.8%)	3 (16.7%)	1.74	(0.28, 10.81)	
	60 - 69	268 (7.0%)	257 (8.8%)	1.22	(0.99, 1.50)		755 (8.3%)	4 (22.2%)	1.84	(0.37, 9.12)	

	> 70	86 (2.2%)	144 (4.9%)	1.64	(1.19, 2.26)		290 (3.2%)	3 (16.7%)	1.73	(0.35, 8.63)	
Residential zone [2]	rural *(reference)*	73 (1.9%)	49 (1.7%)	1	-	0.4187	164 (1.8%)	0 (0.0%)	-	-	-
	semi-rural	157 (4.1%)	139 (4.7%)	1.27	(0.82, 1.96)		390 (4.3%)	2 (11.1%)	-	-	
	City	3,612 (94.0%)	2,748 (93.6%)	1.10	(0.76, 1.59)		8,507 (93.9%)	16 (88.9%)	-	-	
Smoking [2]	non-smoker *(reference)*	1,857 (48.3%)	1,648 (56.1%)	1	-	< 0.0001	4,567 (50.4%)	12 (66.7%)	-	-	-
	ex-smoker	1,081 (28.1%)	766 (26.1%)	0.80	(0.71, 0.91)		2,537 (28.0%)	6 (33.3%)	-	-	
	smoker	904 (23.5%)	522 (17.8%)	0.68	(0.60, 0.78)		1,957 (21.6%)	0 (0.0%)	-	-	
History of head trauma		201 (5.2%)	134 (4.6%)	0.86	(0.68, 1.08)	0.1917	446 (4.9%)	0 (0.0%)	-	-	-
Pregnancy		60 (1.6%)	35 (1.2%)	0.84	(0.55, 1.29)	0.4243	125 (1.4%)	1 (5.6%)	6.94	(0.74, 65.52)	0.0907

1: OR relative to the previous category
2: OR relative to the reference category

Table 4. Relative risk for hyposmia (smell of one to three odours) or anosmia (smell of none of the four odours) in the case of smell identification using a multivariate logistic analysis of demographic characteristics and health problems. Data presented as adjusted OR (Odd Ratio), 95% CI (Confidence Interval).

Covariable		Hyposmia (identification) 8,107 subjects, 3,894 with hyposmia (48%)					Anosmia (identification) 9,195 subjects, 75 with anosmia (1%)				
		No	Yes	Adjusted OR	(95% CI)	p-value	No	Yes	Adjusted OR	(95% CI)	p-value
Female		2,911 (69.1%)	2,368 (60.8%)	0.76	(0.69, 0.84)	< 0.0001	6,008 (65.9%)	38 (50.7%)	0.96	(0.55, 1.67)	0.8850
Educational level [1]	elementary school	8 (0.2%)	18 (0.5%)	-	-	0.0007	31 (0.3%)	0 (0.0%)	-	-	-
	middle school	654 (15.5%)	608 (15.6%)	0.49	(0.21, 1.16)		1,419 (15.6%)	24 (32.0%)	-	-	
	high school	1,881 (44.6%)	1,636 (42.0%)	1.01	(0.88, 1.15)		3,970 (43.5%)	28 (37.3%)	-	-	
	university	1,670 (39.6%)	1,632 (41.9%)	1.21	(1.09, 1.34)		3,700 (40.6%)	23 (30.7%)	-	-	
Subjective description of sense of smell [1]	very good	1,034 (24.5%)	667 (17.1%)	-	-	< 0.0001	1,948 (21.4%)	8 (10.7%)	-	-	< 0.0001
	good	2,979 (70.7%)	2,841 (73.0%)	1.42	(1.27, 1.58)		6,567 (72.0%)	38 (50.7%)	1.27	(0.59, 2.76)	
	poor	183 (4.3%)	374 (9.6%)	2.06	(1.69, 2.51)		592 (6.5%)	13 (17.3%)	2.16	(1.00, 4.66)	
	very poor	17 (0.4%)	12 (0.3%)	0.26	(0.12, 0.56)		13 (0.1%)	16 (21.3%)	36.06	(13.12, 99.13)	
Loss of smell history [1]	never	2,895 (68.7%)	2,741 (70.4%)	-	-	0.0005	6,361 (69.7%)	38 (50.7%)	-	-	0.0415
	≤ 1 week	1,130 (26.8%)	901 (23.1%)	0.82	(0.74, 0.91)		2,301 (25.2%)	12 (16.0%)	0.93	(0.48, 1.81)	
	> 1 week	188 (4.5%)	252 (6.5%)	1.28	(1.02, 1.62)		458 (5.0%)	25 (33.3%)	2.79	(1.14, 6.88)	
Exposure to noxious substances		1,255 (29.8%)	1,132 (29.1%)	0.98	(0.89, 1.08)	0.6930	2,716 (29.8%)	23 (30.7%)	1.03	(0.60, 1.77)	0.9111
Chronic rhinosinusitis		187 (4.4%)	170 (4.4%)	0.96	(0.77, 1.20)	0.7290	403 (4.4%)	5 (6.7%)	0.80	(0.28, 2.29)	0.6824
Menstruation		390 (9.3%)	304 (7.8%)	1.03	(0.87, 1.22)	0.7157	772 (8.5%)	2 (2.7%)	0.49	(0.11, 2.14)	0.3421
Age (years) [1]	< 20	203 (4.8%)	194 (5.0%)	-	-	< 0.0001	438 (4.8%)	3 (4.0%)	-	-	0.0006
	20 - 29	551 (13.1%)	466 (12.0%)	0.82	(0.64, 1.04)		1,106 (12.1%)	8 (10.7%)	0.76	(0.19, 2.96)	
	30 - 39	1,032 (24.5%)	839 (21.5%)	0.94	(0.80, 1.10)		2,131 (23.4%)	11 (14.7%)	0.65	(0.25, 1.68)	
	40 - 49	1,198 (28.4%)	1,004 (25.8%)	1.05	(0.93, 1.19)		2,490 (27.3%)	10 (13.3%)	0.68	(0.28, 1.65)	
	50 - 59	822 (19.5%)	831 (21.3%)	1.20	(1.05, 1.37)		1,886 (20.7%)	12 (16.0%)	1.40	(0.58, 3.38)	

	60 - 69	302 (7.2%)	371 (9.5%)	1.19	(0.99, 1.43)		763 (8.4%)	17 (22.7%)	3.38	(1.51, 7.55)	
	> 70	105 (2.5%)	189 (4.9%)	1.43	(1.07, 1.91)		306 (3.4%)	14 (18.7%)	1.24	(0.51, 3.01)	
Residential zone [2]	rural *(reference)*	76 (1.8%)	71 (1.8%)	1	-	0.3585	162 (1.8%)	1 (1.3%)	1	-	0.9858
	semi-rural	176 (4.2%)	181 (4.6%)	1.11	(0.75, 1.65)		400 (4.4%)	3 (4.0%)	0.87	(0.08, 8.95)	
	city	3,961 (94.0%)	3,642 (93.5%)	0.95	(0.68, 1.33)		8,558 (93.8%)	71 (94.7%)	0.85	(0.12, 6.21)	
Smoking [2]	non-smoker *(reference)*	2,118 (50.3%)	1,968 (50.5%)	1	-	0.5326	4,594 (50.4%)	30 (40.0%)	1	-	0.2814
	ex-smoker	1,169 (27.7%)	1,131 (29.0%)	0.96	(0.86, 1.07)		2,567 (28.1%)	30 (40.0%)	1.61	(0.88, 2.93)	
	smoker	926 (22.0%)	795 (20.4%)	0.94	(0.83, 1.06)		1,959 (21.5%)	15 (20.0%)	1.41	(0.70, 2.82)	
History of head trauma		204 (4.8%)	193 (5.0%)	0.97	(0.79, 1.20)	0.7963	442 (4.8%)	12 (16.0%)	3.38	(1.69, 6.74)	0.0006
Pregnancy		62 (1.5%)	48 (1.2%)	1.02	(0.69, 1.51)	0.9157	126 (1.4%)	1 (1.3%)	1.72	(0.22, 13.33)	0.6017

1: OR relative to the previous category
2: OR relative to the reference category

Figure 1

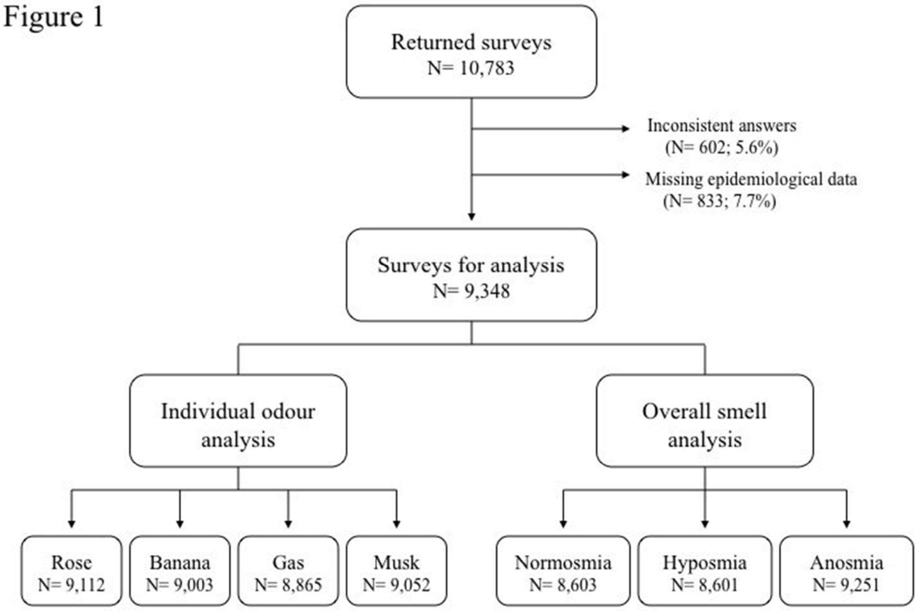

Figure 1. Flow-chart of participants in the OLFACAT (Olfaction in Catalonia) survey.
66x45mm (300 x 300 DPI)

Figure 2

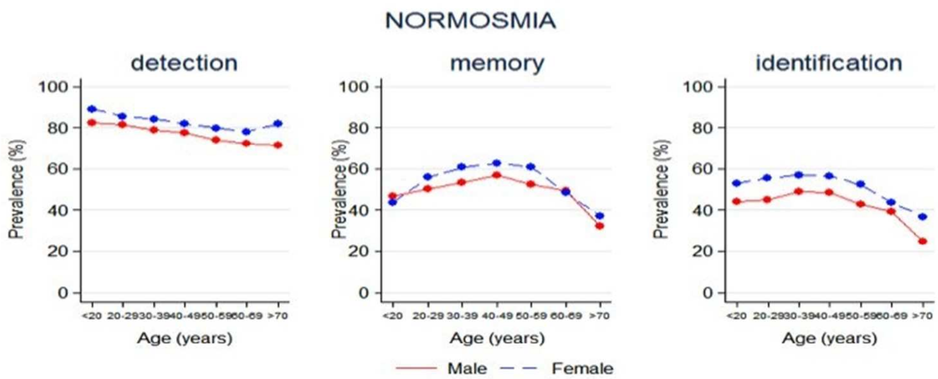

Figure 2. Evolution of normosmia (smell of all four odours) during lifetime. Smell detection showed a progressive decrease during the life span, while smell recognition/memory and identification increased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and declined thereafter. For detection, recognition/memory, or identification, normosmia was significantly higher ($p<0.0001$) in women (blue line) than in men (red line).
66x45mm (300 x 300 DPI)

Figure 3

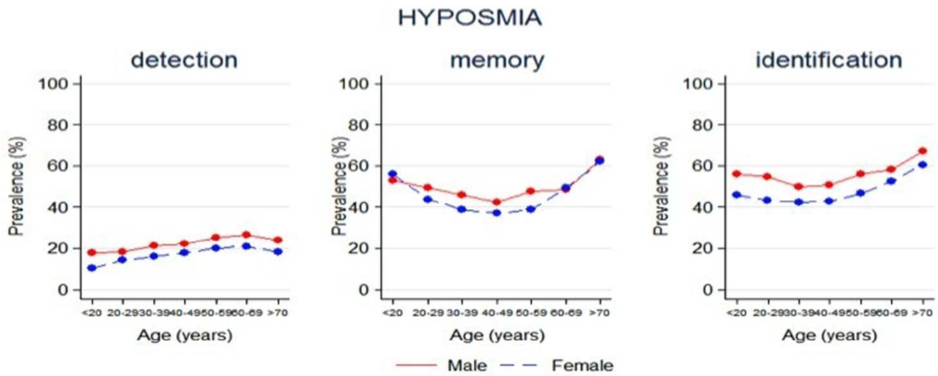

Figure 3. Evolution of hyposmia (smell of one to three odours) during lifetime. For detection, hyposmia showed a progressive increase during the life span, while for recognition/memory and identification hyposmia decreased up to the fourth decade of life, continued to plateau throughout the fifth and sixth decades, and increased thereafter. For detection, recognition/memory, or identification, hyposmia was significantly lower ($p<0.0001$) in women (blue line) than in men (red line).
66x45mm (300 x 300 DPI)

Figure 4

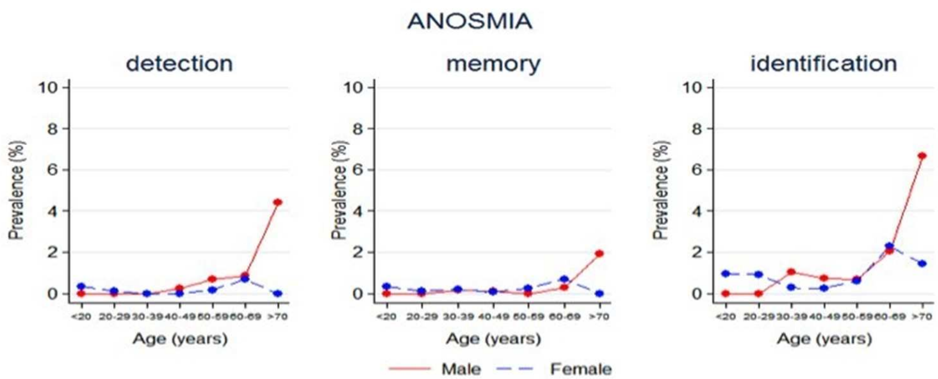

Figure 4. Evolution of anosmia (smell of none of the four odours) during lifetime. Anosmia showed a progressive mild increase during the life span but being more significant after the sixth decade of life. For detection, recognition/memory, or identification, anosmia was significantly lower (p<0.0001) in women (blue line) than in men (red line), with a maximal difference after the seventh decade of life.
66x45mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

YOU MUST NOTE THE PAGE NUMBER WHERE EACH ITEM IS REPORTED INSIDE THE BRACKETS [ ]. IF NOT APPLICABLE WRITE N/A

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Page 1]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[Page 3]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[Pages 5 and 6]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[Page 6]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Page 7]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Page 7]**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[Pages 7 to 9]** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **[N/A]** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **[N/A]**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **[Pages 7 to 9]** *Case-control study*—For matched studies, give matching criteria and the number of controls per case **[N/A]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Pages 7 to 9]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Pages 7 to 9]**
Bias	9	Describe any efforts to address potential sources of bias **[Pages 17 and 18]**
Study size	10	Explain how the study size was arrived at **[Page 9, Figure 1]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Page 9]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Page 9]**
		(*b*) Describe any methods used to examine subgroups and interactions **[Page 9]**
		(*c*) Explain how missing data were addressed **[Page 9, Figure 1]**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **[N/A]** *Case-control study*—If applicable, explain how matching of cases and controls was addressed **[N/A]** *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy **[N/A]**
		(*e*) Describe any sensitivity analyses **[N/A]**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Pages 10 to 13, Figure 1, Table 1]**
		(b) Give reasons for non-participation at each stage **[Figure 1]**
		(c) Consider use of a flow diagram **[Figure 1]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Pages 10 and 11, Table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[Pages 10 to 13, Figure 1]**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **[Page 10]**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **[N/A]**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure **[N/A]**
		Cross-sectional study—Report numbers of outcome events or summary measures **[N/A]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Pages 10 to 13, Figure 2 to 4, Tables 2 to 4]**
		(*b*) Report category boundaries when continuous variables were categorized **[Pages 10 to 13, Tables 2 to 4]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[Page 14]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[N/A]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Page 14]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Pages 17 and 18]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Page 18]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Pages 14 to 18]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[Pages 20 and 21]**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Once you have completed this checklist, please save a copy and upload it as part of your submission. When requested to do so as part of the upload process, please select the file type: *Checklist*. You will NOT be able to proceed with submission unless the checklist has

been uploaded. Please DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.