RHINOSINUSITIS (J MULLOL, SECTION EDITOR)

Olfactory Dysfunction in a Mexican Population Outside of COVID-19 Pandemic: Prevalence and Associated Factors (the OLFAMEX Study)

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Abstract

Purpose of Review To study the prevalence of olfactory loss and its associated factors in a Mexican population a cross-sectional analytical study based on a population interviewed about health, epidemiologic aspects, and sense of smell (tested with four scents: rose, banana, perfume, and gas) was conducted to evaluate olfactory detection, memory, and identification. Levels of sense of smell perception were determined when the participants detected, recognized, or identified all (normosmia), 1–3 (hyposmia), or none (anosmia) of the odorants. Associated factors of olfactory dysfunction were identified by multivariate analysis (odds ratio, 95%CI).

Recent Findings Olfactory dysfunction is a prevalent disorder affecting up to 20% of the general population. In addition to viral infection, including COVID-19, a number of other causes and factors may also be involved.

Summary 1,956 surveys were conducted and 1,921 were analyzed. Most of the participants (62.1%) were women. The general prevalence of olfactory dysfunction, regarding detection, was 7.2% (7.1% hyposmia, 0.1% anosmia). Age-related olfactory deterioration was observed in both sexes from the 5th decade of life (OR 2.74, $p = 0.0050$). Women showed better olfactory identification (OR 0.73, $p = 0.0010$). Obesity (OR 1.97, $p = 0.0070$), low educational level, bad/very bad self-perceived olfactory function (OR 2.74, $p = 0.0050$), olfactory loss for less than one week (OR 1.35, $p = 0.0030$), exposure to toxics/irritants (OR 1.31, $p = 0.0030$), active smoking (OR 1.58, $p < 0.0010$), and type 2 diabetes mellitus (OR 2.68, 95%CI 1.74–4.10, $p < 0.0001$) were identified as factors associated with olfactory dysfunction. These results in a Mexican population suggest better olfactory identification (verbalization) in females. Age was a determining factor in the olfactory deterioration process and obesity and diabetes mellitus were also associated with olfactory disorders. Finally, these findings reinforce the differential diagnosis with other potential causes of sense of smell loss, during the COVID-19 outbreak.

Keywords Olfactory disorders · Prevalence · Survey · Odorants · Anosmia · COVID-19

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Introduction

In the context of the worldwide COVID-19 epidemic, taste and smell disorders have gained public attention due to media diffusion and an increased number of studies [1••, 2] highlighting the relevance of those symptoms in the clinical spectrum of COVID-19 infection. In that context, some authors have proposed the suspicion of COVID-19 upon sudden onset of anosmia, even in the absence of other symptoms [1••, 3]. In recent years, the study of olfaction has become relevant because several analyses have suggested that olfactory dysfunction is a marker of health deterioration [4, 5•, 6].

Anosmia and hyposmia are the results of olfactory system dysfunction at different pathway levels. Normosmia is the ability to detect/recognize/identify all odors, hyposmia is the partial olfactory loss, and anosmia is the total olfactory loss. Odor detection is related to the most peripheral part of the olfactory system [7], whereas identification and recognition memory involve cognitive tasks of central structures, such as the orbitofrontal region and other areas of the limbic system. In addition to viral etiology [8, 9], several other causal factors have been described: posttraumatic events [10–12], neurodegenerative diseases [13–15], sinonasal inflammatory diseases (chronic rhinosinusitis, nasal polyps) [16–19], and allergic rhinitis (in adults [20] or children) [21, 22].

Several epidemiologic studies have focused on the prevalence (from 1 to 20%) of olfactory disorders in the general population, investigating the influence of certain factors on olfactory function [23–28]. Mullol et al. carried out the OLFACAT survey [29] on a Catalan population. Through epidemiologic and health status questionnaires assessing olfaction status, they found a 19.4% general prevalence of olfactory dysfunction (hyposmia 19.1% and anosmia 0.3%).

The OLFAMEX survey was modeled after the OLFACAT survey, adapting the questionnaire to Mexican health conditions to study the prevalence of normal sense of smell (normosmia) and the loss of sense of smell (hyposmia, anosmia), as well as to identify risk factors associated with olfactory dysfunction, before the COVID-19 outbreak.

Material and Methods

Study Design

A cross-sectional analytical study was carried out in Guadalajara (Jalisco, Mexico) from August to October 2017, several years before the COVID-19 outbreak. An epidemiologic and health status survey, together with a smell test (OLFAMEX-4), was conducted on a population from 16 to 100 years of age. Study participants were patients in waiting rooms at a referral hospital center who agreed to be surveyed. Persons with acute upper respiratory infection were excluded.

Age and sex were considered determining factors of olfaction status in the sampling process. The population was stratified by age groups to include females (16–59 years of age), males (16–59 years of age), and older adults of both sexes (> 60 years of age), in a representative proportion of the Mexican population.

The study was approved by the Local Research and Ethics Committee. All patients gave their verbal consent to participate in the survey.

Questionnaire 1—Epidemiologic Data and Health Status

Questionnaire 1 was designed to obtain information on epidemiologic aspects, self-perceived olfactory function, risk exposure history, and specific health conditions. The questionnaire was applied by the research staff and collaborators, with a total of 7 participating physicians. Each investigator carried out an average of 279 surveys over 6 weeks. The epidemiologic data covered the following aspects: sex (male, female), age (years), educational level (none, primary, secondary, university/postgraduate), as well as weight and height, to calculate body mass index (BMI).

Questionnaire 1 contained ten questions (Table 1): two on self-perceived olfactory function: (1) How do you consider your sense of smell? (good, very good, bad, very bad), (2) Have you ever lost your sense of smell? (never, up to 1 week, > 1 week); two on toxic exposure history: (3) Have you ever been exposed to dust, gases, fumes, vapors, and/or volatile toxic compounds at home and/or in the workplace? (yes, no), (4) Do you smoke? (yes, no); four on health conditions: (5) Have you ever suffered a severe face or head trauma? (yes, no), (6) Have you ever been diagnosed with chronic rhinosinusitis? (yes, no), (7) Have you been diagnosed with type 2 diabetes mellitus (DM2)? (yes, no), (8) Have you or a close relative (parents, brothers, sisters) been diagnosed with Parkinson's disease (PD) or Alzheimer's disease? (yes, no). And finally, two questions on women's health (female participants exclusively): (9) Are you currently pregnant? (yes, no) and (10) Are you currently menstruating? (yes, no).

Questionnaire 2—Smell Test (OLFAMEX-4)

Once the epidemiologic questionnaire was answered, the bottles containing the odorants were randomly provided, one by one, to each participant, who then was asked to breathe naturally (approximately 5 s), after which he/she answered the following questions (Questionnaire 2): (1) Can you smell all the scents? (yes, no), to evaluate odor detection; (2) Have you ever smelled that scent? (yes, no), to evaluate odor recognition memory; and (3) Which name best defines the scent you just smelled? (only one correct option), to evaluate forced-choice odor identification. The term "normosmia" was used when a participant was able to correctly detect, recognize (memory),

Table 1 OLFAMEX Survey. Epidemiologic characteristics and comparison by sex of the Mexican population studied

Population characteristic †	Female	Male	Total	p-value*
Population	1192 (62.1)	729 (37.9)	1921 (100)	
Age, years (mean±SD)	35.6 ± 16.7 °°	34.2 ± 16.8 °°	35.73 ± 16.8 °°	
< 20	301 (25.3)	171 (23.5)	472 (24.6)	0.7060
20–39	482 (40.4)	311 (42.7)	793 (41.3)	
40–59	274 (23.0)	170 (23.3)	444 (23.1)	
60 ≥ 60	135 (11.3)	77 (10.6)	212 (11.0)	
Menstruation	154 (12.9)	–	154 (8.0)	
Pregnancy	84 (7.0)	–	84 (4.4)	
Educational level				< 0.0001
No education	52 (4.4)	10 (1.4)	62 (3.2)	
Primary	337 (28.2)	184 (25.2)	521 (27.1)	
Secondary	287 (24.1)	219 (28.8)	497 (25.9)	
University/college	516 (43.3)	325 (44.6)	841 (43.8)	
Body Mass Index				0.8380
Underweight	23 (1.9)	11 (1.5)	34 (1.8)	
Normal	623 (52.2)	390 (53.5)	1013 (52.7)	
Overweight	419 (35.2)	256 (35.1)	675 (35.1)	
Obesity	127 (10.7)	72 (9.9)	199 (10.4)	
Self-perceived olfactory function				0.1240
Very good	254 (21.3)	168 (23.0)	422 (22.0)	
Good	818 (68.6)	467 (64.1)	1285 (66.9)	
Bad	105 (8.8)	85 (11.7)	190 (9.9)	
Very bad	15 (1.3)	9 (1.2)	24 (1.2)	
History of olfactory loss				0.1920
Never	719 (60.3)	469 (64.3)	1188 (61.8)	
≤ 1 week	408 (34.2)	221 (30.3)	629 (32.8)	
> 1 week	65 (5.5)	39 (5.4)	104 (5.4)	
Active smoking	274 (23.0)	255 (34.0)	529 (27.5)	< 0.0001
Exposure to noxious substances	566 (47.5)	448 (61.5)	1014 (52.8)	< 0.0001
History of head trauma	142 (11.9)	114 (15.6)	256 (13.3)	0.0200
History of chronic rhinosinusitis	72 (6.0)	54 (7.4)	126 (6.6)	0.2400
History of type 2 diabetes mellitus	138 (11.6)	74 (10.2)	212 (11.0)	0.3330
History of Parkinson's disease or Alzheimer's disease	186 (15.6)	97 (13.3)	283 (14.7)	0.1680

*Chi-square test

°°Mean value and standard deviation (SD)

†All values (except Age) are expressed as "N (%)"

or identify all four odorants. When the participant could not correctly detect, recognize (memory), or identify one, two, or three of the four odorants, the term "hyposmia" was used. Finally, the term "anosmia" was used when the participant was unable to detect, recognize (memory), or identify any of the four odorants.

Survey Odorants

As in the OLFACAT study (28), four common odorants for our population were selected: rose (Bulgarian rose 2%, phenylethyl alcohol 98%) as a floral scent; banana (isoamyl isobutyrate 50% in diethyl phthalate) as a food scent; musk (1:1 mixture of galaxolide and exaltolide diethyl phthalate) as a perfume scent; and gas (mixture of 30% mercaptan and 70% tetrahydrothiophene) as an industrial scent. A mixture of paraffins and polyethylene glycols with no scent was used as the excipient. Each bottle was numbered from 1 to 4, corresponding to rose (N° 1), banana (N° 2), perfume (N° 3), and gas (N° 4). The distractors for those odors were: rose (banana, perfume, gas), banana (rose, perfume, gas), perfume (rose, banana, gas), and gas (rose, banana, perfume).

Data and Statistical Analysis

Surveys were manually entered into an Excel database. Detection, recognition memory, and forced-choice identification were analyzed individually. Due to the low prevalence of anosmia for detection and recognition, the sample was merged into two groups: normosmia and olfactory dysfunction (hyposmia plus anosmia). Self-perceived olfactory function was re-grouped into "very good" and "good" sense of smell and compared with "very bad" and "bad" sense of smell. The participants were divided into four age groups: younger than 20 years, 20 to 39 years, 40 to 59 years, and 60 years or older. According to BMI, the participants were grouped into low weight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), and obese (BMI > 29.9), as classified by the World Health Organization [30].

The statistical analysis was performed using the PASW Statistics 18 program. The potential risk factors for the prevalence of olfactory disorders were calculated using age-adjusted logistic regression models (multivariate analysis). Olfactory disorders were the dependent variable. Frequencies and means were calculated for the descriptive statistics, as a hypothesis test by p value (significant when $p < 0.0500$) for the chi-square (Chi^2) test. The strength of association was determined by the odds ratio (95% confidence interval), calculated to compare the independent variables considered for olfactory loss. The group with the best olfactory ability was the reference. Surveys with inconsistencies or missing data were excluded.

Results

Characteristics of the Survey Population

In total, 1956 surveys were carried out, of which 35 were excluded due to inconsistencies or missing data. The final sample size was 1921 surveys (Fig. 1). Table 1 describes the epidemiologic characteristics of the population surveyed.

The overall profile of the OLFAMEX Survey was female, 36 years of age, secondary/university educational level, and normal BMI.

Age and Sex The mean age of the population studied was 35.73 ± 16.8 years (range: 16–87). 62.1% ($n = 1192$) were female (age: 35.1 years). Young participants (up to 39 years) accounted for 65.9% (2 out of 3), middle-aged participants (40–59 years) made up 23.1% (1 out of 4), and older participants (≥ 60 years) accounted for 11% (1 out of 10) of the total (Table 1). Regarding females, 7.4% were pregnant and 13.1% were menstruating.

Educational Level 43.8% reported having a university education, 52% primary or secondary education, and 3.2% had no school education. Lack of education was higher in the female group (4.4% vs 1.4%; $p < 0.0010$)

Body Mass Index 52.7% had normal BMI, 35.1% had overweight, 0.4% obesity, and 1.8% low weight or malnutrition. There were no differences between sexes

Self-Perceived Sense of Smell Sense of smell perception was similar between males and females.

Exposure to Tobacco and Toxic Substances 27.5% of the participants were active smokers and 1 out of 2 participants (52.8%) reported exposure to volatile toxic substances, both conditions being more common in males ($p < 0.0001$)

History of Olfactory Loss 61.8% of participants never noticed olfactory loss, whereas 32.7% experienced it for > 1 week, and 5.4% for > 1 week, with no differences between sexes

History of Severe Head Trauma 13.3% reported said condition, which was higher in males (15.6% vs 11.9%; $p = 0.0200$)

Health Status 6.6% of participants had been diagnosed by a physician with chronic rhinosinusitis, 11% with DM2, and 14.7% diagnosed with or having a family history of PD or Alzheimer's disease. There were no differences between sexes

Sense of Smell

Overall Sense of Smell All scents (normosmia) were detected by 92.8%, recognized by 78.6%, and identified by 44.4% of the participants. Detection, recognition, and identification of 1–3 scents (hyposmia) was 7.1%, 20.9%, and 53.8%, respectively. None of the 4 scents (anosmia) were detected by 0.10% of the participants, recognized by 0.5%, and identified by 1.8%. Odor detection (rose 97.5%, banana 98.5%, perfume 97.8%, and gas 97.5%) was greater than recognition (rose 93.4%, banana 96.0%, perfume 93.4%, and gas 88.0%) and forced-choice identification (rose 67.8%, banana 88.9%, perfume 76.3%, and gas 73.0%) of the odorants. The most effectively perceived, recognized, and identified scent was banana for the male and female groups.

Olfaction by Sex and Age Only odor identification, not detection or recognition memory, was higher in females (47.1% vs 39.9%, $p = 0.0030$). Detection, recognition, and identification were higher in participants 20–39 years of age (95%, 83.4%, and 48% respectively), whereas there was a tendency toward deterioration in participants 40 years of age and older ($p < 0.0010$) (Fig. 2). Participants > 60 years of age had the highest prevalence of olfactory disorders (hyposmia/anosmia)
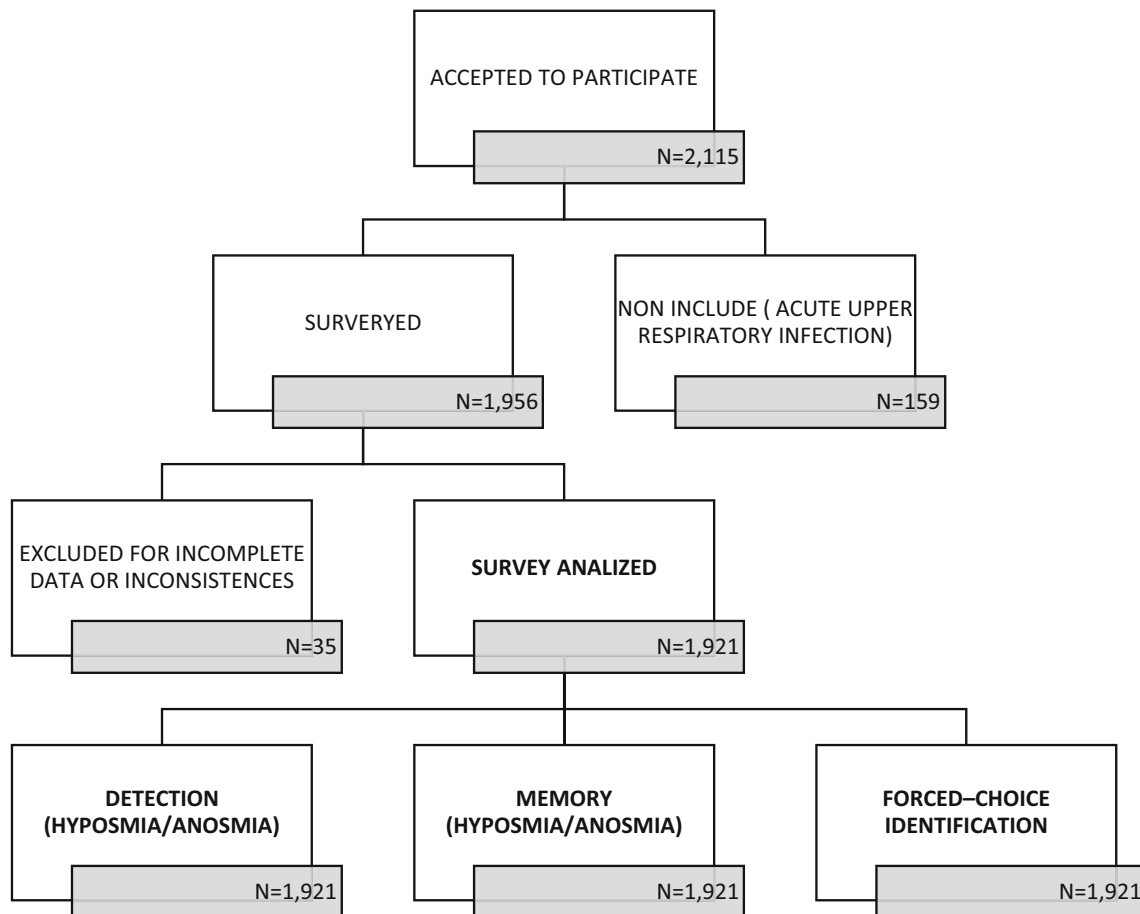
Fig. 1 Flowchart of the OLFAMEX survey participants

for odor detection, recognition, and identification (17.5%, 31.6%, and 63.7% respectively) (Fig. 3).

Olfaction and BMI 95.8% of the participants with normal weight detected all 4 scents (normosmia). That figure dropped to 88.4% ($p = 0.0420$) in the obesity group. No differences in odor recognition memory or identification were found.

Olfaction and Educational Level Detection olfactory disorders were more frequent in the participants with educational levels of no school (16.1%) and primary school (10.4%) ($p < 0.0001$). Recognition memory hyposmia was higher in the group with a primary school education (22.1%). The population with no school education showed a higher prevalence of identification anosmia and hyposmia (4.8%, 67.7%, $p = 0.0180$).
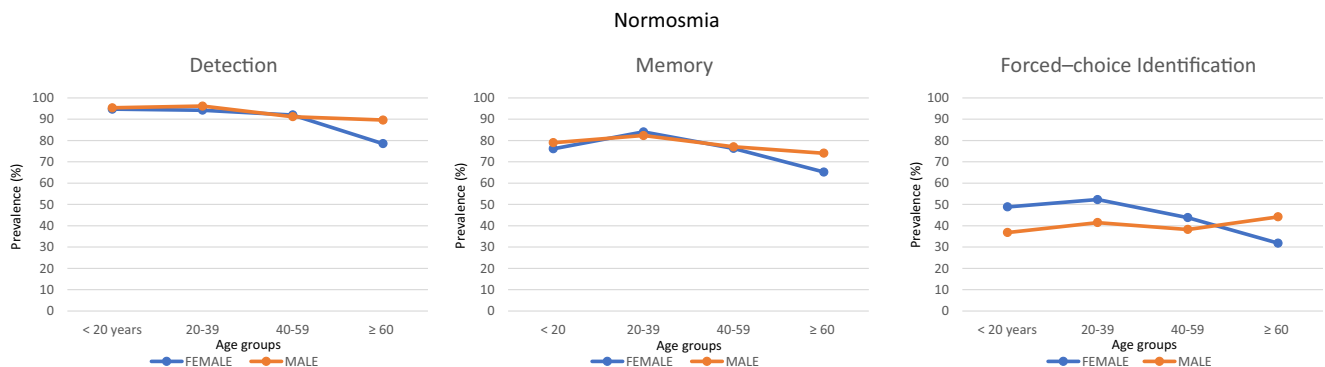

Fig. 2 Lifetime progression of normosmia (perception of all 4 odors). Odor detection, recognition memory, and forced-choice identification reached their highest scores in participants 20 to 39 years of age, with a tendency to deteriorate in participants 40 years of age and older ($p < 0.0010$)
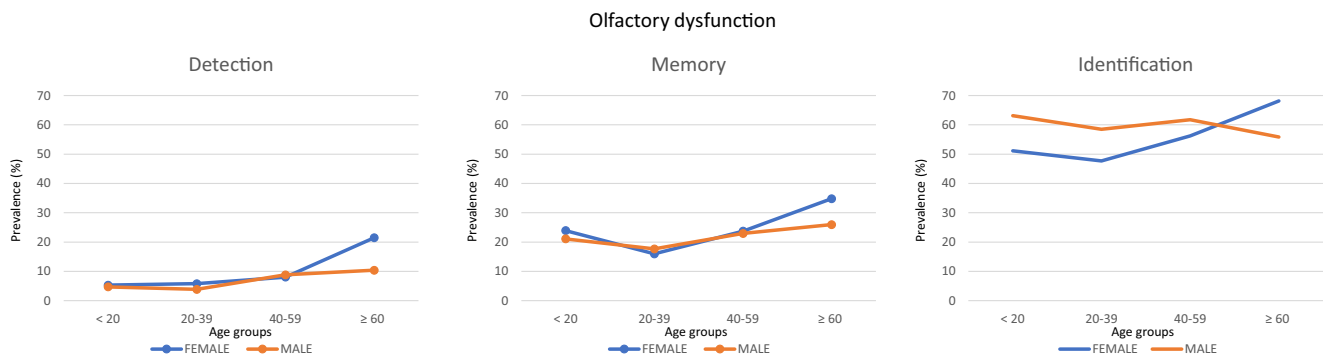
Olfactory dysfunction

Fig. 3 Lifetime progression of olfactory dysfunction (olfactory loss in ≥ 1 more odors). The highest prevalence of olfactory dysfunction in odor detection, recognition memory, and forced-choice identification was observed in participants > 60 years of age. Women showed better identification skills than men ($p = 0.0333$), except in older adults

Self-Perceived Sense of Smell Regardless of sex, most participants (88.9%) reported having a good or very good sense of smell, whereas only 11.1% stated having a bad or very bad sense of smell. Most participants (79.5%) with detection hyposmia reported a good or very good sense of smell, whereas only a few (13.2%) of the subjects with identification hyposmia reported a bad or very bad sense of smell. Finally, only 1 of every 2 participants (50.2%) that reported having a good sense of smell, correctly identified the four odorants ($p < 0.0001$).

Olfaction and History of Olfactory Loss One-third (35.5%) of the participants with identification hyposmia reported having a history of olfactory loss for < 1 week. Regarding the history of olfactory loss for more than a week, the answer was significantly much lower in participants with normosmia than those with anosmia (11.4%) ($p = 0.0100$).

Factors Associated with Olfactory Dysfunction (Hyposmia + Anosmia)

Odor Detection In our Mexican population, sex was not associated with differences in olfactory detection. In contrast, a lack of education (OR 2.74) was associated with a poor sense of smell, and low weight (OR 2.6), obesity (OR 1.97), DM2 (OR 2.69), and bad or very bad self-perceived sense of smell (OR 2.30) were associated with olfactory dysfunction. Additionally, age over 70 years increased the risk for an olfactory dysfunction by almost 4 times (OR 3.98), and to a lesser extent, in the 40 to 59-year age group (OR 1.71) (Table 2).

Odor Recognition Memory The participants 20 and 40 years of age showed the best skills for olfactory recognition, whereas recognition hyposmia/anosmia was associated with those that were younger or older (< 20 years: OR 1.49; 40–59 years: OR 1.53; ≥ 60 years: OR 2.31). Obesity (OR 1.45), bad or very bad self-perceived sense of smell (OR 1.76), and history of

olfactory loss < 1 week (OR 1.36) were also associated with olfactory loss. On the other hand, pregnancy seemed to be associated with better olfactory recognition (OR 0.36). (Table 2).

Odor Identification Females identified odorants better than males (OR 0.73). As in detection and recognition memory, older age (OR 1.51), low educational level (OR 2.08), and poor self-perceived olfactory function (OR 1.84) were associated with odor identification hyposmia.

A personal history of olfactory loss for <1 week (OR 1.35), smoking (OR 1.58), exposure to toxic substances (OR 1.32), and diabetes mellitus (OR 1.78) were also associated with worse odor identification, whereas pregnancy was associated with better odor identification (OR 0.25).

Identification anosmia was found in 1.8% of the participants and older age (OR 5.94), lack of education (OR 4.45), diabetes mellitus (OR 4.06), and poor self-perceived olfactory function (OR 7.16) were also associated with anosmia (Table 3).

Discussion

Highlighting the most important results of our study on the general prevalence of olfactory disorders, first, regarding odor detection, we found hyposmia (7.1%) and anosmia (0.1%) in 7.2% of the Mexican population analyzed. Second, there was a tendency toward age-related olfactory deterioration in both sexes, finding the best olfactory abilities in the 20 to 39 year age group, with progressive deterioration from the 5th decade of life, for odor detection, recognition memory, and forced-choice identification. Third, both sexes showed very similar olfactory abilities for odor detection and recognition, but odor identification was significantly better in females in all age groups, except for the 7th decade of life. Fourth, pregnancy, but not menstruation, was associated with better odor recognition and identification. Fifth, obesity, low school education,

Table 2 Relative risk (OR) for odor detection and recognition/memory olfactory dysfunction (hyposmia + anosmia) using a multivariate logistic analysis of demographic characterisitics and health problems

Covariate	Olfactory dysfunction (detection)					Olfactory dysfunction (recofnition/memory)				
	1921 subjects [136 with hyposmia (7.1, 2 with anosmia (0.1%)%)]					1921 subjects [401 with hyposmia (20.9%), 10 with anosmia (0.5%)]				
	No	Yes	OR	(95% IC)	p value	No	Yes	OR	(95% IC)	p value
Female	1097 (92)	95 (8)	1.38	(0.95–2.00)	0.0880	931 (78.1)	261 (21.9)	1.08	(0.86–1.36)	0.494
Age (years)										
< 20	448 (94.9)	24 (5.1)	1.01	(0.60–1.69)	0.9750	364 (77.1)	180 (22.9)	1.49	(1.12–1.97)	0.006
20–39*	753 (95)	40 (5)	1	_	_	661 (83.4)	132 (16.6)	1	_	_
40–59	407 (91.7)	37 (8.3)	1.71	(1.07–2.71)	0.0220	340 (76.6)	104 (23.4)	1.53	(1.14–2.04)	0.0040
60 or more	175 (82.5)	37 (17.5)	3.98	(2.47–6.40)	< 0.0010	145 (68.4)	37 (31.6)	2.31	(1.63–3.26)	< 0.0010
Menstruation	144 (93.5)	10 (6.5)	0.77	(.39–1.53)	0.4690	123 (79.9)	31 (20.1)	0.88	(.58–1.34)	0.5700
Pregnancy	81 (96.4)	3 (3.6)	0.4	(.12–1.32)	0.1230	76 (90.5)	8 (9.5)	0.35	(.16–.71)	0.0040
Education level										
No education	52 (83.9)	10 (16.1)	2.74	(1.32–5.70)	0.0050	52 (83.9)	10 (16.1)	0.69	(.34–1.39)	0.3060
Primary	466 (89.4)	55 (10.6)	1.68	(1.14–2.49)	0.0080	402 (77.2)	119 (22.8)	1.07	(0.82–1.39)	0.6040
Secondary	479 (96.4)	18 (3.6)	0.53	(.31–.92)	0.0230	397 (79.9)	100 (20.1)	0.91	(.69–1.11)	
University/college*	786 (93.5)	55 (6.5)	1	_	_	659 (78.4)	182 (21.6)	1	_	_
Body mass index										
Under weight	29 (85.3)	5 (14.7)	2.6	(.97–6.94)	0.0480	24 (70.6)	10 (29.4)	1.65	(.77–3.51)	0.1870
Normal	950 (93.8)	63 (6.2)	1	_	_	809 (79.9)	204 (20.1)	1	_	_
Over weight	628 (93)	47 (7)	1.12	(.76–1.66)	0.5440	532 (78.8)	143 (21.2)	1.06	(.83–1.35)	0.6020
Obesity	176 (88.4)	23 (11.6)	1.97	(1.19–3.26)	0.0070	145 (72.9)	54 (27.1)	1.44	(1.04–2.09)	0.0270
Olfactory self-perception										
Very good/good	1598 (93.6)	109 (6.4)	1	_	_	1362 (79.8)	345 (20.2)	1	_	_
Very bad/bad	185 (86.4)	29 (13.6)	2.29	(1.48–3.55)	< 0.0001	148 (69.2)	66 (30.8)	1.76	(1.28–2.40)	> 0.0010
History of olfactory loss										
Never	1104 (92.9)	84 (7.1)	1	_	_	954 (80.3)	234 (19.7)	1		
≤ 1 week	584 (92.8)	45 (7.2)	1.01	(.69–1.47)	0.9470	472 (75)	157 (25)	1.35	(1.07–1.70)	0.0090
> 1 week	95 (91.3)	9 (8.7)	1.24	(.60–2.55)	0.5490	84 (80.8)	20 (19.2)	0.97	(0.58–1.61)	0.9090
Active smoking	485 (91.7)	44 (8.3)	1.25	(0.86–1.81)	0.2350	421 (79.6)	108 (20.4)	0.92	(.72–1.18)	0.5190
Exposure to noxious substances	947 (93.4)	67 (6.6)	0.83	(.58–1.17)	0.3010	797 (78.6)	217 (21.4)	1	(.80–1.24)	0.9550
History of cranial trauma	231 (90.2)	25 (9.8)	1.48	(.94–2.34)	0.0860	197 (77)	59 (23)	1.11	(.81–1.52)	0.4890
Chronic rhinosinusitis	114 (90.5)	12 (9.5)	1.39	(.74–2.59)	0.2930	98 (77.8)	28 (22.2)	1.05	(.68–1.62)	0.8150
Diabetes mellitus II	180 (84.9)	32 (15.1)	2.68	(1.75–4.10)	< 0.0001	162 (76.4)	50 (23.6)	1.15	(.82–1.61)	0.4100
Parkinson or Alzheimer	266 (94)	17 (6)	0.8	(.47–1.35)	0.4060	224 (79.2)	59 (20.8)	0.96	(.70–1.31)	0.9520

* Reference value for OR

bad/very bad self-perceived olfactory function, history of olfactory loss for less than 1 week, exposure to toxins, active smoking, and DM2 were also associated with olfactory disorders. Sixth and last, neither head trauma nor the history of chronic rhinosinusitis was associated with the development of olfactory loss.

By 2015, Mexico had a population of 87 million inhabitants, 15 years of age or older [31]. According to the prevalence of olfactory loss found (7.2%) in our study, we estimate that around 6 million Mexicans have some degree of olfactory dysfunction, of which they are unaware (79.5% of participants with detection hyposmia perceived their sense of smell as good or very good). We based our prevalence study on the Catalan OLFACAT Survey [29] regarding odor detection, recognition memory, and forced-choice identification. Although the prevalence of detection hyposmia in our population was lower than that reported in the OLFACAT survey (7.2% vs 19.4%), odor identification was similar (55.6% vs 48.8%). Those differences can be explained by the demographic characteristics in the two populations, with a tendency

Table 3 Relative risk (OR) for forced-choice identification hyposmia and anosmia using a multivariate logistic analysis of demographic characteristic and health problems

Covariate	Hyposmia (forced-choice identification)					Anosmia (forced-choice identification)				
	1921 subjects (excluding 35 with anosmia), 1033 with hyposmia (53.7%)					1921 subjects (excluding 1033 with hyposmia), 35 with anosmia (1.8%)				
	No	Yes	OR	(95% IC)	p value	No	Yes	OR	(95% IC)	p value
Female	562 (47.1)	605 (50.8)	0.73	(.60–.88)	0.0010	562 (95.7)	25 (4.3)	1.29	(.61–2.73)	0.4970
Age (years)										
< 20	210 (45)	257 (55)	1.16	(.92–1.46)	0.2060	210 (97.7)	5 (2.3)	0.9	(.306–2.689)	0.8600
20–39[*]	381 (48.7)	402 (51.3)	1	_	_	381 (97.4)	10 (2.6)	1	_	_
40–59	185 (42.4)	251 (57.6)	1.28	(1.01–1.62)	0.0370	185 (95.9)	8 (4.1)	1.64	(064–4.24)	0.2960
60 or more	77 (38.5)	123 (61.5)	1.51	(1.10–2.08)	0.0100	77 (86.5)	12 (13.5)	5.93	(2.47–14.23)	< 0.0010
Menstruation	70 (46.4)	81 (53.6)	1.08	(.77–1.53)	0.6350	70 (95.9)	3 (4.1)	0.95	(.28–3.28)	0.9460
Pregnancy	64 (77.1)	19 (22.9)	0.25	(.14–.42)	< 0.0010	64 (98.5)	1 (1.5)	0.32	(.04–2.43)	0.2490
Education level										
No education	17 (27.4)	42 (67.7)	2.08	(1.16–3.72)	0.0110	17 (27.4)	3 (4.8)	4.44	(1.17–16.83)	0.0170
Primary	242 (46.4)	266 (51.1)	0.92	(.74–1.15)	0.5050	242 (46.4)	13 (2.5)	1.35	(.63–2.89)	0.4330
Secondary	216 (43.5)	277 (55.7)	1.08	(.86–1.35)	0.4910	216 (43.5)	4 (0.8)	0.46	(.15–1.42)	0.1710
University/college[*]	378 (44.9)	448 (53.3)	1	_	_	378 (44.9)	15 (1.8)	1	_	_
Body mass index										
Under weight	15 (45.5)	18 (54.5)	1.06	(.53–2.13)	0.8620	15 (93.9)	1 (6.2)	2.08	(.25–16.82)	0.4810
Normal	469 (47)	529 (53)	1	_	_	469 (96.9)	15 (3.1)	1	_	_
Over weight	290 (43.9)	371 (56.1)	1.13	(.93–1.38)	0.2120	290 (95.4)	14 (4.6)	1.5	(.71–3.17)	0.2740
Obesity	79 (40.7)	115 (59.3)	1.12	(.94–1.76)	0.1090	79 (94)	5 (6)	1.97	(.70–5.59)	0.1900
Olfactory self-perception										
Very good/good	788 (46.8)	897 (53.2)	1	_	_	788 (97.3)	22 (2.7)	1	_	_
Very bad/bad	65 (32.3)	136 (67.7)	1.83	(1.34–2.50)	< 0.0001	65 (83.3)	13 (16.7)	7.16	(3.44–14.87)	< 0.0010
History of olfactory loss										
Never	562 (48.2)	605 (51.8)	1	_	_	562 (96.4)	21 (3.6)	1	_	_
≤ 1 week	252 (40.7)	367 (59.3)	1.35	(1.11–1.64)	0.0030	252 (96.2)	10 (3.8)	1.06	(.49–2.28)	0.8780
> 1 week	39 (39)	61 (61)	1.45	(.95–2.20)	0.0780	39 (90.7)	4 (9.3)	2.74	(.89–8.39)	0.0650
Active smoking	192 (37.1)	325 (62.9)	1.58	(1.28–1.94)	< 0.0010	192 (36.3)	12 (2.3)	1.79	(.84–3.67)	0.1050
Exposure to noxious substances	418 (42)	577 (58)	1.31	(1.09–1.58)	0.003	418 (94.1)	19 (5.9)	1.23	(.62–2.43)	0.5400
History of cranial trauma.	113 (44.8)	139 (55.2)	1.01	(.78–1.32)	0.8950	113 (96.6)	4 (3.4)	0.84	(.29–2.43)	0.7550
Chronic rhinosinusitis	46 (37.4)	77 (62.6)	1.41	(.96–2.06)	0.0710	46 (93.9)	3 (6.1)	1.64	(.48–5.57)	0.4200
Diabetes Mellitus II	67 (33)	136 (67)	1.77	(1.30–2.42)	< 0.0010	67 (88.2)	9 (11.8)	4.06	(1.82–9.02)	< 0.0010
Parkinson or Alzheimer	112 (40)	168 (60)	1.28	(.99–1.66)	0.0570	112 (97.4)	3 (2.6)	0.62	(.18–2.05)	0.4310

[*] Reference value for OR

toward a younger population with a lower educational level in the OLFAMEX survey. Detection hyposmia is expected to be lower in a younger population, but its relation to recognition and identification, which depend on cognitive and semantic capability, is less clear. [32] Several studies have focused on olfactory disorders in the general population, reporting a prevalence of 1 to 20%. That wide range is due to the diversity of methods used for assessing olfaction [23–29]. Researchers are currently encouraging the use of universal language and methodological quality so there can be the consistency of results in this field [33].

In recent decades, the world population has shown a tendency toward aging. By the year 2030, there will be 55% more adults reaching the 7th decade of life in Mexico [31]. A significant number of that older population will experience age-related sensory loss and a worsening in general health, well-being, self-sufficiency, and quality of life. In the OLFAMEX study, a strong decrease in olfactory identification was demonstrated in the 6th and 7th decades of life, with more than half of the participants > 65 years of age having significant olfactory disorders [23–25, 27, 29, 34]. Thus, we observed a

higher prevalence of olfactory dysfunction from the 6th decade of life.

In our Mexican study population, aging was associated with detection, recognition memory, and identification of olfactory dysfunction. Different agents, acting alone or together, can potentially explain that deterioration. An increase in the number of patches of respiratory epithelium, which represents a loss of primary olfactory receptor neurons, has been found in the olfactory zone in the older adult population [35], as well as a decrease in the expression of olfactory receptors in olfactory mucosa, predominating in men [36]. Similarly, exposure to harmful agents, the risk of head trauma from falls, the prevalence of diseases, such as diabetes mellitus and neurodegenerative diseases, increase with aging. The National Social Life and Aging Project (NSHAP) study [4], conducted in the US from 2005 to 2011 on an older adult population, found that 5-year mortality was associated with hyposmia (OR 1.54) and highly associated with anosmia (OR 3.24). They concluded that olfactory dysfunction is one of the strongest 5-year predictors (together with heart failure, diabetes, and stroke) of mortality and can serve as a marker of accumulated toxic environmental exposures.

A majority of studies have found that females have better olfactory identification than males, both in free and forced-choice responses [27, 29, 37, 38]. In the OLFACAT survey, Mullol et al. reported that women had higher detection, recognition memory, and forced-choice identification skills than men [29]. However, the findings on olfactory sensitivity are inconclusive. In a study involving 154 adults, Gouveri et al. [39] found no differences in detection skills and olfactory discrimination between males and females. In our study, females showed a higher capacity for forced-choice identification (OR 0.73) but, as in Gouveri's study, we found no differences for detection and recognition. It is well-known that olfactory identification involves a semantic memory task that requires individual knowledge of a specific odor [40]. Larsson et al. [32] also found that olfactory information verbalization was higher in females, suggesting a better olfactory identification capacity, as well.

Traditionally, pregnancy has been associated with a sharper sense of smell and most pregnant females report an increase in odor detection. However, Ochsenbein-Kolble et al. [41] objectively evaluated olfactory function, finding no increase in olfactory sensitivity during pregnancy. In fact, they found a decrease in olfactory sensitivity detected in late pregnancy, which remained even after delivery. Contrastingly, we observed a lower prevalence of olfactory disorders for recognition memory and a greater ability to identify odorants in the Mexican female population. That phenomenon could be explained by the evidence that pregnant females can better identify certain odors than controls [42–45] but further comparative studies are needed to establish a clear association between pregnancy and olfactory identification.

Mexico is the second country worldwide with the highest prevalence of obesity, at 30% in the adult population [46]. The impact of obesity on cardiovascular (cerebral vascular disease, blood hypertension) and metabolic (diabetes mellitus) systems have been widely studied. The olfactory and endocrine systems appear to be connected, with important roles played by insulin, ghrelin, and leptin. Similarly, a high-fat diet can affect the general neuro-architecture of the olfactory system by reducing the number of olfactory receptor neurons and their axonal projection [47]. The lower the olfactory function, the higher the emotional consumption of food and the consequent increase in BMI [48]. In our study, obesity was associated with odor detection loss by 97% and recognition memory by 44%. That situation is a great challenge for the comprehensive management of obesity and partially explains the difficulty of adhering to a healthy diet, since obesity may be a significant cause-effect in olfactory disorders. Said event is even more relevant in older adults, in whom olfactory impairment plays a role in poorer diet quality [49••].

Several studies have shown an independent association between olfactory loss and DM2. Patients with the microvascular disease caused by DM2 exhibit a particularly severe deterioration in olfaction [38, 50]. Similarly, an association between low olfactory scores and DM2 complications has been found [51]. Gascon et al. [52] described a decrease in the percentage of correct responses indirectly related to increased albuminuria and low glomerular filtration rate. Those findings suggest that olfactory tests may be used for the early recognition of DM2 complications. In our study, DM2 was associated with the detection and identification of hyposmia, and even with anosmia.

The impact of formal education on neurodegenerative diseases and behavioral functions has been widely studied. The theory of cognitive reserve posits that highly educated individuals suffering from brain diseases are more likely to use strategies to recruit brain structures other than those normally used in cognitive tasks [32]. The identification of an odorant requires semantic memory, which is a cognitive ability that is increased by formal education [53]. Some studies [29, 32] have reported that a high educational level improves the capacity of odor recognition memory and identification. Similarly, in the OLFAMEX survey, we found higher skills for odor detection, recognition memory, and identification in the middle/high educational level groups. The participants that could not read or write had a 2 to 3-times higher association with recognition and identification of olfactory disorders.

Exposure to toxins, as potential olfactory disorder-inducing agents, is the cause in 1–5% of those conditions and its impact is clearly underestimated, especially in individuals with chronic long-term exposure [54]. In the OLFAMEX survey, exposure to toxic/harmful substances was associated with identification hyposmia. The impact of smoking on the respiratory tract and its inflammatory, mutagenic, and carcinogenic

effects are well known. Despite contradictory study results, structural or functional changes have been found in the olfactory neuroepithelium, suggesting that smoking may impact odor detection and recognition memory [55]. Bramerson et al. [27] found no differences between the threshold and discriminative capacity in smokers and non-smokers but Mullol et al. [29] found that smoking was associated with better odor recognition memory. In our study, as in previous studies, active smoking and olfactory dysfunction were associated.

Neurodegenerative diseases are relevant to olfactory disorders. Early olfactory deficits have been observed in patients with Alzheimer's disease. The first to be altered [35] is odor identification because certain medial temporal lobe structures involved are affected in the early stages of Alzheimer's disease [56]. Similarly, olfactory deficits can be found early on in patients with PD. Olfactory dysfunction is the second most common characteristic after rigidity and akinesia and could even be the most frequent early alteration [14]. A study involving 48 relatives of persons with PD (25 individuals with hyposmia and 23 with normosmia) found that 8% of individuals with hyposmia developed PD compared with 0% of individuals with normosmia, indicating that olfactory disorders precede the classic clinical motor signs of the disease [57]. Our results showed that participants with a personal or family history of those diseases had difficulty correctly identifying odorants, and 28% had hyposmia. Taking into account the significant number of dopaminergic neurons lost at the time of clinical diagnosis of PD, the detection of patients in the prodromal period of clinical parkinsonism is very important for the development of treatment strategies that reduce or prevent motor PD [14, 58, 59].

Although chronic rhinosinusitis [60] and head trauma have been associated as frequent causes of olfactory deficit [11, 61], we found no associations with an increased prevalence of hyposmia/anosmia. Nevertheless, a personal history of olfactory loss for < 1 week appears to be associated with olfactory loss, with respect to both memory and identification. Post-viral etiology is frequently associated with olfactory loss in the course of acute manifestations, such as nasal blockage and rhinorrhea [8, 9]. In the COVID-19 epidemic, evidence has emerged that reveals the appearance of olfactory alterations as one of the most common signs of that viral infection [1••, 2, 60, 62]. Some authors suggest that anosmia could be the only clinical presentation, without any other significant symptoms [3], or even an early sign of COVID-19 infection [62]. In the context of post-viral olfactory loss, the mechanism of lesion development is unclear, and even though most patients in our study experienced spontaneous recovery, we observed the persistence of a certain degree of injury manifested by alterations in olfactory recognition and identification. Accordingly, we must be aware of possible permanent sequelae in olfactory function, as consequences of COVID-19.

The OLFAMEX survey is the first to investigate the prevalence of olfactory disorders in a Mexican, as well as Latin American, population. The study's significant strengths include the large size of the sample population, the face-to-face collection of data by trained personnel, and the ability to identify persons with acute respiratory infections. Its limitations or weaknesses were the lack of control over the self-described level of education, which tended to be higher than known characteristics in Mexico, as well as not distinguishing participants with a neurodegenerative disease from those that had only a direct family history, preventing a separate evaluation of those two groups. Nevertheless, our results about the olfactory condition are very revealing in our Mexican population and the association with olfactory loss paves the way for further investigations in that direction. Given the relevant prevalence of diabetes mellitus in Mexico [63], as well as in many other developed countries worldwide, there is an important unmet need to deeply investigate the impact of DM2 and obesity on the sense of smell, and in consequence, their potential roles in early mortality.

Conclusions

In agreement with previously reported epidemiologic studies, the OLFAMEX survey of a general Mexican population indicated an age-related deterioration in odor detection, recognition memory, and identification, as well as better forced-choice identification in females. Pregnancy was associated with better odor recognition and identification. Low educational level, active smoking, and DM2 were associated with olfactory disorders. Although we are still a long way from establishing the role of olfaction and its impact on health, current efforts to standardize protocols and methodology for diagnosis and treatment [34], including cases of post-viral and COVID-19-induced loss of smell, will help increase the quality of continuing research.

Finally, these findings are also of scientific interest regarding the differential diagnosis, given that the loss of the sense of smell during the COVID-19 outbreak could already have been present at the time of the SARS-CoV-2 infection, and been caused by different etiologies or associated factors.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no conflicts of interest.

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•• Of major importance

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