

## Original Article

# Factors influencing olfactory function in an adult general population sample: the CHRIS study

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The sense of smell allows for the assessment of the chemical composition of volatiles in our environment. Different factors are associated with reduced olfactory function, including age, sex, as well as health and lifestyle conditions. However, most studies that aimed at identifying the variables that drive olfactory function in the population suffered from methodological weaknesses in study designs and participant selection, such as the inclusion of convenience sample or only of certain age groups, or recruitment biases.

We aimed to overcome these issues by investigating the Cooperative Health Research in South Tyrol (CHRIS) cohort, a population-based cohort, by using a validated odor identification test. Specifically, we hypothesized that a series of medical, demographic and lifestyle variables is associated with odor identification abilities. In addition, our goal was to provide clinicians and researchers with normative values for the Sniffin' Sticks identification set, after exclusion of individuals with impaired nasal patency.

We included 6,944 participants without acute nasal obstruction and assessed several biological, social, and medical parameters. A basic model determined that age, sex, years of education, and smoking status together explained roughly 13% of the total variance in the data. We further observed that variables related to medical (positive screening for cognitive impairment and for Parkinson's disease, history of skull fracture, stage 2 hypertension) and lifestyle (alcohol abstinence) conditions had a negative effect on odor identification scores. Finally, we provide clinicians with normative values for both versions of the Sniffin' Sticks odor identification test, i.e. with 16 items and with 12 items.

**Key words:** smell, odor identification, dementia, age, sex, traumatic brain injury.

## Introduction

The sense of smell allows for the assessment of the chemical composition of volatiles in our environment. We perceive odorants from outside our body, via the air inhaled through the nostrils (orthonasal olfaction) and from the oral cavity via the nasopharynx (retronasal olfaction). The sense of smell is sensitive to disturbances: quantitative olfactory dysfunctions include hyposmia (a partial loss of olfactory sensitivity) and anosmia (a complete loss of olfactory sensitivity). Qualitative olfactory dysfunction, on the other hand, include parosmia (smell distortion) and phantosmia (perception of odors in the absence of an odorant source) (Hummel et al. 2017).

Quantitative olfactory dysfunction is widespread. Several studies from different countries used subjective self-reporting and estimated the rate of olfactory dysfunction between 1.4% and 23% (Hoffman et al. 1998; Hastan et al. 2011; Bhattacharyya and Kepnes 2015; Rawal et al. 2016; Hirsch et al. 2017). However, this huge variation may be explained by the fact that self-reports are often unreliable, especially when the individuals in question are not formally tested psychophysically (Landis et al. 2003; Lotsch and Hummel, 2019). When psychophysical methods using an odor identification task are used, studies estimate the percentage of individuals suffering from hyposmia and anosmia in the overall

adult population at roughly 15% and 5%, respectively. In other words, roughly 1 in 5 suffers from reduced olfactory abilities (Murphy et al. 2002; Bramerson et al. 2004; Landis et al. 2004; Vennemann et al. 2008).

Different factors are associated with reduced olfactory function, according to the available literature. They include age (younger individuals typically outperform older ones) and sex (female typically outperform male participants) as well as health and lifestyle conditions. This includes (i) inflammatory processes, e.g. in sinusal disease, (ii) traumatic events, e.g. traumatic brain injury, (iii) neurodegeneration such as Parkinson's disease or Alzheimer's disease, (iv) metabolic disturbances such as diabetes or kidney failure, and (v) exposure to toxins and drugs as well as smoking and alcohol consumption (Hummel et al. 2017). However, most of the available data on causes of olfactory dysfunction stems from clinics and labs specialized in smell problems. These data from these labs may have an important selection bias. For example, chronic rhinosinusitis (CRS) can be found in 10% of the general population (Hastan et al. 2011), and is thus very common. However, patients with CRS are typically managed by their GP or an ENT surgeon and do not necessarily consult in a specialized clinic (Hummel et al. 2017); they may therefore be underrepresented at a specialized clinic, even if CRS is

amongst the most important causes of olfactory dysfunction (Deems et al. 1991; Temmel et al. 2002; Damm et al. 2004). On the other hand of the spectrum, individuals with rare conditions but little to no additional symptoms, e.g. isolated congenital anosmia, may directly consult at the specialized clinic and therefore be overrepresented (Temmel et al. 2002).

To overcome these issues, one needs to carry out studies with large sample sizes; such studies that used odor identification tasks to investigate olfactory function are available from countries on different continents, e.g. Asia (Iran (Jalali et al. 2020)), Australia (Karpa et al. 2010), Europe (Germany (Landis et al. 2004), Spain (Mullol et al. 2012), Sweden (Larsson et al. 2004; Seubert et al. 2017; Ekstrom et al. 2020)), and North America (Mexico (Castillo-Lopez et al. 2020), the United States (Boesveldt et al., 2011; Schubert et al. 2012; Pinto et al. 2015; Hoffman et al. 2016)). By including between 1,200 and 9,300 participants, common determinants of the ability to identify odors could be established such as age (a reduction typically starting from the 4th or 5th decade of life), sex (female participants typically outperforming male) and education (more years of education typically being associated with better scores). Health-related conditions such as Parkinson's disease, dementia, history of head trauma, nasal polyposis, acute rhinitis, diabetes, or hypertension were inconsistently found, similarly to lifestyle factors such as smoking and drinking habits. These differences between studies may be due to differences in study designs and participant selection between the studies. In fact, some authors tested convenience samples (e.g. patients in waiting rooms at a hospital center (Landis et al. 2004; Castillo-Lopez et al. 2020)), limited themselves to older participants (e.g. above 40, 45, or 60 years (Larsson et al. 2004; Karpa et al. 2010; Boesveldt et al. 2011; Hoffman et al. 2016; Seubert et al. 2017)), included descendants of a population-based cohort (Schubert et al. 2012) or recruited amongst the readers of a newspaper (Mullol et al. 2012). All this may be associated with potential biases.

We aimed to overcome these issues by investigating a population-based cohort by using a validated odor identification test. We therefore set out to investigate olfactory function in the Cooperative Health Research in South Tyrol (CHRIS) cohort, a study sample of adult participants from the Vinschgau district in Northern Italy. Specifically, we aimed

at understanding to what extent (i) medical and (ii) lifestyle conditions impact olfactory function. We hypothesized that a series of medical, demographic and lifestyle variables is associated with odor identification abilities. In addition, our goal was to provide clinicians and researchers with normative values for the Sniffin' Sticks identification set, after exclusion of individuals with acutely impaired nasal patency.

## Material and methods

### Study participants

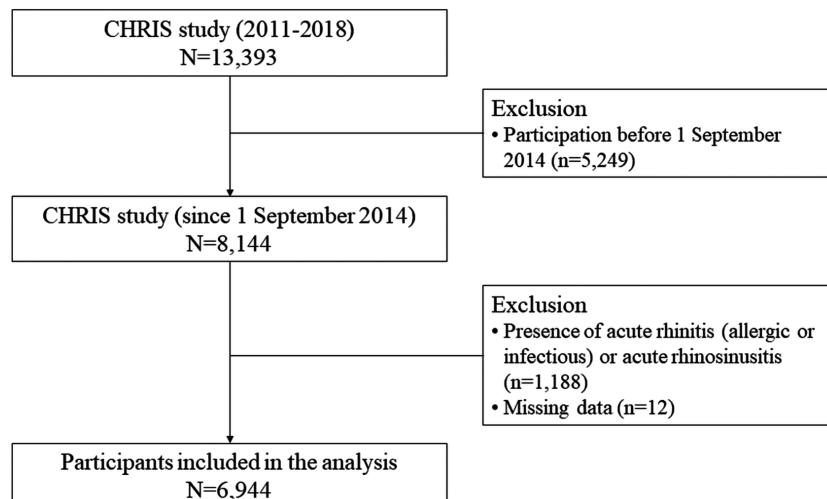
The Cooperative Health Research in South Tyrol (CHRIS) study is a population-based study which recruited 13,393 adults in the Vinschgau district (South Tyrol, Italy) between 2011 and 2018 (for details, see Pattaro et al. (2015)). The CHRIS study was approved by the Ethical Committee of the Healthcare System of the Autonomous Province of Bolzano (protocol number 21/2011, 19 April 2011). Each participant provided written informed consent.

Participants were invited to the study center in the morning following overnight fasting, underwent blood drawing, urine collection, anthropometric measurements, clinical examinations, as well as self- and interviewer-administered interviews based on standardized questionnaires on medical history and lifestyle. Since September 2014, an examination battery with focus on prodromal neurodegenerative symptoms including an odor identification test was added to the study workflow. Overall, 8,144 participants underwent the extended workflow. However, we excluded participants with nasal conditions potentially interfering with olfactory function from olfactory testing. This included acute rhinitis (allergic or infectious), acute rhinosinusitis, and other conditions hindering nasal patency. Therefore, these conditions were not analyzed in this study (Fig. 1).

## Methods

### Olfactory assessment

The CHRIS study used the Sniffin' Sticks odor identification test. This test is based on felt-tip pen-like odor dispensing devices that contain odorants instead of ink (Hummel et al. 1997). The odor identification test consists of 16 pens.



**Fig. 1.** Flowchart illustrating the selection of participants.

Participants smelled 1 pen after the other and had to choose the best descriptor from a list of 4 (forced choice) (Kobal et al. 1996; Hummel et al. 1997). We counted the sum of correct response as a sum score (total score) (Oleszkiewicz et al. 2019). In addition to this score based on 16 items, we calculated another score (SS12), based on the 12 items that are used for the Sniffin' Sticks 12 items screening test. For this, the items *turpentine*, *garlic*, *apple*, and *anise* are not used for the sum score, as they have low identification rates (Hummel et al. 2001).

The Sniffin' Sticks tests were carried out by 8 different technicians. We included the executing technician as a covariate into the model. Further, the Sniffin' Sticks test has a shelf life of one year. Therefore, it was renewed on a regular basis and a total of four batches of the test were used. We therefore added the batch number as a covariate into the model. Further, we used the days until stick expiration date as a covariate into the model.

### Assessment of variables of interest

#### Basic model variables

We first assessed 5 variables to be included in the basic model. In addition to (1) *age* and biological (2) *sex*, we defined (3) *education* quantitatively as number of school years (interview question “In total, how many years did you attend school?”). We then assessed (4) *smoking status* using the European Community Respiratory Health Survey (ECRHS) III questionnaire (Janson et al. 2001). Accordingly, we classified participants were classified as (i) “never smoker,” (ii) “past smoker,” (iii) “current smoker who reduced,” or (iv) “current smoker who did not reduce” (Murgia et al. 2019). Further, participants were asked to bring the boxes of medication which they took during the last 7 days to the study center. Barcodes were scanned and the Anatomical Therapeutic Chemical classification system (ATC) code identified. We accordingly entered the (5) *number of drugs* with different ATC codes taken as a variable (Pattaro et al. 2015).

We then defined a total of 15 variables to be included into the extended model. They were selected according to Hummel et al. (2017).

#### Self-reported diagnoses

More specifically, we used self-reported diagnoses of (1) *diabetes* (yes/no), (2) *epilepsy* (yes/no), (3) history of *nasal polyp surgery* (yes/no), (4) history of *skull fracture* (yes/no), (5) *kidney diseases* (yes/no), (6) *liver diseases* (yes/no), and (7) *stroke or transient ischemic attack* (TIA) (yes/no) from the computer assisted personal interview (CAPI).

#### Questionnaires

Next, we used responses to screening questionnaires for several medical conditions. More specifically, to assess the presence of (8) *Parkinson's disease* (PD), we used the questionnaire for parkinsonism (Pramstaller et al. 1999) which screens for 9 PD symptoms and results in a score ranging from 0 to 9. Next, we assessed (9) *migraine* through a questionnaire based on the International Classification of Headache Disorders 2nd edition (ICHD-II) criteria. Participants were classified as having (i) no migraine, (ii) migraine with aura, (iii) or migraine without aura (Zanigni et al. 2014). Then, to assess (10) *REM sleep behavior disorder* (RBD) we used the self-administered 13-item RBD screening questionnaire

(Stiasny-Kolster et al. 2007), yielding scores from 0 to 13. We considered scores of  $\geq 8$  as being RBD-positive (Marelli et al. 2016). Finally, to screen for (11) *cognitive impairment*, we used the Mini-Mental State Examination (MMSE) (Folstein et al. 1975), a 30-point questionnaire. A high MMSE score is an indication for normal cognition function. We used the MMSE score as a quantitative trait.

It is important to point out that these diagnoses were not additionally confirmed during the medical examination.

#### Self-reported exposure

We next assessed exposure to alcohol and other substances which were collected using CAPI. More specifically, we assessed (12) the frequency of *alcohol consumption* with the questions “Have you ever drunk alcoholic drinks?” (yes/no) and “During the last 12 months, on average how often have you drunk alcoholic drinks?” with the response options (i) “Never,” (ii) “At special occasions only,” (iii) “Once a month or less,” (iv) “2–4 times per month,” (iv) “2–3 times per week,” (v) “4 or more times per week but not daily,” and (vi) “Daily.” We collapsed “no alcohol consumption ever” and “never during the last 12 months” into one category. We next assessed (13) *exposure to other substances* with the question “Does your work or your hobbies frequently expose you to the following substances?” for (i) detergent/disinfectant; (ii) engine exhaust; (iii) wood dust; (iv) grain dust; (v) glass wool/mineral wool; (vi) asbestos; (vii) metals; (viii) heavy metals/arsenic; (ix) solvents; (x) petroleum products; (xi) X-rays/microwaves/radioactive materials; (xii) pesticides. We collapsed the responses to exposure to any category into a single variable (positive if “yes” to at least one substance, otherwise negative).

#### Anthropometric measures

Finally, a series of measurements was carried out during the visit to the study center. More specifically, to calculate the (14) *body mass index* (BMI), height (to 0.1 cm) and weight in light clothing (to 0.1 kg) was measured. We classified participants according to the definition of the World Health Organization as (i) underweight ( $BMI < 18.5$ ), (ii) normal ( $18.5$ – $24.9$ ), (iii) overweight ( $25.0$ – $29.9$ ), or (iv) obese ( $\geq 30.0$ ). Then, we assessed blood pressure (BP) either (a) with 3 measurements at 2-minute distance in supine position at the end of a 20-minute resting electrocardiogram (ECG) using an Omron Monitor M10-IT or (b) at 10-minute distance at the start, middle and at the end of the 20-minute ECG using a CNAP Monitor 500 system. We defined (15) the *hypertension status* of the participants as (i) normal (systolic BP  $< 130$  mm/Hg/ diastolic BP  $< 85$  mm/Hg), (ii) prehypertension (130–139/85–89), (iii) stage 1 hypertension (140–159/90–99), or (iv) stage 2 hypertension or higher ( $\geq 160/\geq 100$ ) according to ESH/ESC Guidelines for the management of arterial hypertension. See Table 1 for the frequencies of the selected predictor variables.

#### Statistical analysis

We performed the statistical analysis using Stata version 17.0 (StataCorp LLC). We present continuous variables as a mean  $\pm$  standard deviation (SD) or a median with interquartile range (IQR). Categorical variables are presented as a number (percentage).

We built a basic linear regression model in 3 steps with the Sniffin' Sticks total score as dependent variable: First, we

**Table 1.** Frequencies of selected predictor variables.

	CHRIS olfaction test subsample N = 6,944
Chronic rhinosinusitis	
Polyp surgery (n = 6,860) – n (%)	719 (10.5)
Neurodegenerative diseases	
MMSE score (n = 6,760) – median (IQR)	30 (29, 30)
PD screening score (n = 6,616) – median (IQR)	0 (0, 0)
Metabolic diseases	
Diabetes (n = 6,935) – n (%)	171 (2.5)
Liver disease (n = 6,903) – n (%)	329 (4.8)
Kidney disease (n = 6,914) – n (%)	569 (8.2)
BMI classification (n = 6,934) – n (%)	
Underweight (<18.5)	111 (1.6)
Normal (18.5 to <25)	3,241 (46.7)
Overweight (25 to <30)	2,388 (34.4)
Obese (≥30)	1,194 (17.2)
BP classification (systolic/diastolic BP, mm/Hg) (n = 6,938) – n (%)	
Normal (<130/<85)	4,422 (63.7)
Prehypertension (130–139/85–89)	1,229 (17.7)
Stage 1 hypertension (140–159/90–99)	1,029 (14.8)
Stage 2 hypertension or higher (≥160/≥100)	258 (3.7)
Neurological diseases	
Migraine (n = 6,942) – n (%)	
No migraine	6,410 (92.3)
Migraine without aura	344 (5.0)
Migraine with aura	188 (2.7)
Epilepsy (n = 6,925) – n (%)	70 (1.0)
TIA or stroke (n = 6,902) – n (%)	59 (0.9)
RBD score (n = 6,876) – median (IQR)	2 (1, 4)
Skull fracture (n = 6,901) – n (%)	111 (1.6)
Drugs and toxins	
Exposure to any of the selected substances (n = 6,877) – n (%)	4,156 (60.4)
Alcohol consumption, last 12 months (question) (n = 6,944) – n %	
Never	357 (5.1)
At special occasions only	1,375 (19.8)
Once a month or less	652 (9.4)
2–4 times per month	2,082 (30.0)
2–3 times per week	1,195 (17.2)
Four or more times per week but not daily	370 (5.3)
Daily	672 (9.7)

Abbreviations: BMI, body-mass-index; BP, blood pressure; MMSE, Mini-Mental State Examination; PD, Parkinson disease; RBD, REM sleep behavior disorder; TIA, transient ischemic attack.

included (1 a) *examiner*, (1 b) *batch number*, and (1 c) *days until sticks expiration date* as independent variables to account for study design-related factors. Second, we added (2 a) *sex*, (2 b) *age*, (2 c) *age<sup>2</sup>*, and a (2 d) *sex \* age* interaction term to the model to account for basic individual characteristics of

the participants. Third, we added the lifestyle-related factors (3 a) *education*, (3 b) *smoking status*, and (3 c) *number of medications* to the model. We assessed the goodness-of-fit of these models using the adjusted *R<sup>2</sup>* as an indicator of the total variance explained by all variables included in the model.

Based on this basic model, we tested the impact of the 15 selected medical and lifestyle conditions on olfactory function. We set statistically significant results at a nominal *P*-value < 0.05. To correct for possible false positives due to multiple comparisons during the individual linear regression analyses, we applied a 2 layered correction. First, we used the Bonferroni-Holm procedure for the 15 variables. In contrast to the Bonferroni method (in which *P*-values are multiplied by the number of tested conditions), this adaptation allows for a reduction of false rejections (Holm 1979). If any variable required multiple comparisons (e.g. between 4 possible hypertension statuses), we applied an appropriate second Bonferroni correction for it.

To derive normative values, we computed mean, SD, minimum, and maximum values and the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of the total score and SS12 score, respectively, over 7 age strata for the overall sample and for males and females separately.

## Results

After exclusion of participants with acute conditions hindering nasal patency, 6,944 participants were included in the analysis (Table 2).

We provide normative data per age groups and sexes for the olfactory identification test (total score: all 16 items; SS12: 12 items) in Table 3.

The first iteration of the model including *examiner*, *batch number*, and *days until stick expiration date* as variables had an adjusted *R<sup>2</sup>* of 0.0602. There were significant differences between the scores obtained by the individual *examinators*, and there were significant differences in the scores obtained with the individual *batches*. Finally, *days until stick expiration date* had a small but significant positive effect. See Table 4 for an overview.

In the second iteration, we added *sex*, *age*, *age<sup>2</sup>*, *sex \* age* as variables to the model. All these variables had a significant effect on the identification scores. Female sex and a younger age were associated with higher scores. Being female was associated with 0.47 additional points at the odor identification total score at age 45 years with smaller differences between sexes at younger age and increasing differences at higher age. This model had an *R<sup>2</sup>* of 0.1957. See Fig. 2 for the relationship between sex, age, and total score.

In the third iteration, we added *education*, *smoking status*, and *number of medications* as variables to the model. Both *education* and *smoking status*, but not the *number of medications* yielded significant effects. With regards to *education*, the number of school years had a significant positive effect on the total score. With regard to *smoking status*, belonging to the categories “past smoker” or “current smoker with reduced consumption” was associated with significantly higher total score compared to the category “never smoker.” This model had an *R<sup>2</sup>* of 0.2064.

Subsequently, we added the 15 predictors individually to the model (see Table 4). Negative effects that remained significant after correction for multiple comparisons include

**Table 2.** Sample description.

	Male <i>n</i> = 3,232	Female <i>n</i> = 3,712	Total <i>n</i> = 6,944
Age (years) – mean (SD)	45.1 (16.5)	44.2 (16.6)	44.6 (16.6)
Smoking status— <i>n</i> (%)			
Never smkr	1,624 (50.3)	2,175 (58.6)	3,799 (54.7)
Past smkr	1,000 (30.9)	866 (23.3)	1,866 (26.9)
Curr smkr/reduced	172 (5.3)	185 (5.0)	357 (5.1)
Curr smkr/non-Reduced	424 (13.1)	472 (12.7)	896 (12.9)
Missing	12 (0.4)	14 (0.4)	26 (0.4)
School years—mean (SD)	12.2 (2.9)	12.1 (3.1)	12.1 (3.0)
Median (IQR)	12 (11, 13)	12 (10, 14)	12 (10, 13)
No. of drugs—mean (SD)	0.73 (1.40)	1.11 (1.42)	0.93 (1.42)
Median (IQR)	0 (0, 1)	1 (0, 2)	0 (0, 1)

(i) *cognitive impairment* ( $P < 0.001$ ,  $P_{\text{adj}} < 0.001$ ), a (ii) *skull fracture* ( $P < 0.001$ ,  $P_{\text{adj}} < 0.001$ ), (iii) *alcohol consumption* (“abstinence” category being significantly different from the reference category;  $P = 0.001$ ,  $P_{\text{adj}} = 0.004$ ), (iv) *Parkinson’s disease* ( $P = 0.003$ ,  $P_{\text{adj}} = 0.012$ ), and (v) *blood pressure* (“stage 2 hypertension” category being significantly different from the reference category;  $P = 0.004$ ,  $P_{\text{adj}} = 0.022$ ). Further, correction for multiple comparisons rendered the following effects non-significant: (1) *body mass index* (“obese” category being different from the reference category;  $P = 0.009$ ,  $P_{\text{adj}} = 0.053$ ), (ii) *liver disease* ( $P = 0.014$ ,  $P_{\text{adj}} = 0.100$ ) and (iii) *stroke* ( $P = 0.019$ ,  $P_{\text{adj}} = 0.152$ ). Importantly, the latter 2 were associated with increased scores. Results obtained for the SS12 score were in line with those of the total score. See Table 5 for an overview.

## Discussion

Here we provide information on olfactory function, as measured with an odor identification test, in a cohort of nearly 7,000 adult individuals, by excluding individuals suffering from acute conditions interfering with nasal patency. The main findings are: (i) female and younger people have better odor identification scores; (ii) education is positively associated with odor identification scores; (iii) smoking status is a minor contributor to odor identification scores; (iv) (a) positive screening for cognitive impairment, (b) positive screening for Parkinson’s disease as well as (c) a history of traumatic brain injury were associated with reduced odor identification scores; (v) alcohol abstinence had a significant negative effect on odor identification scores.

Here, we examined the influence of health-related factors on odor identification abilities. It is important to remind the reader that participants with acutely impaired nasal breathing (e.g. due to viral rhinitis or allergic rhinitis) were excluded from olfactory testing. First, scoring high on screening tests for both (i) cognitive impairment and (ii) Parkinson’s disease was significantly associated with a reduction of odor identification. Specifically, scoring 1 point less on the MMSE, a screening tool for cognitive impairment, was associated with a reduction of 0.18 on the odor identification score. In fact, performance in memory tasks, particularly semantic memory, is associated with olfactory function

and more specifically with odor identification tests (Hedner et al. 2010; Jobin et al. 2023). Consequently, scoring low on screening tests for cognitive impairment is associated with lower odor identification (Xu et al. 2020). As a matter of fact, Alzheimer’s disease is strongly associated with olfactory dysfunction (Rahayel et al. 2012). Olfactory dysfunction is one of the earliest signs of Alzheimer’s disease and can precede Alzheimer’s diagnosis by several years (Devanand et al. 2015; Jobin et al. 2021). Accordingly, patients suffering from preclinical and early stages of Alzheimer’s disease such as subjective cognitive decline (Jobin et al. 2021) and mild cognitive impairment (Roalf et al. 2017) exhibit reduced odor identification that parallels the cognitive decline. In analogy to screening for cognitive impairment, scoring high on a screening test for Parkinson’s disease was significantly associated with a reduction of odor identification. Scoring 1 point more was associated with a reduction of 0.10 on the odor identification score. Similarly to Alzheimer’s disease, Parkinson’s disease is associated with olfactory dysfunction (Rahayel et al. 2012), and olfactory dysfunction precedes diagnosis by several years (Hawkes et al. 2010). In contrast to Alzheimer’s disease, Parkinson-related olfactory dysfunction is manifest from early stages and does not decline further (Haehner et al. 2011).

Second, we observed that a history of skull fracture, i.e. traumatic brain injury, was associated with a significant reduction of odor identification scores. Here it is important to point out that traumatic brain injury can also exist without a skull fracture, and that a skull fracture is more likely to be associated with moderate to severe traumatic brain injury than with mild traumatic brain injury such as a concussion. In fact, traumatic brain injury is one of the main causes of olfactory dysfunction (Mullol et al. 2012; Liu et al. 2016; Hummel et al. 2017). In both the acute (Lecuyer Giguere et al. 2019) and the chronic phase (Charland-Verville et al. 2012), individuals with a history of traumatic brain injury exhibit reduced olfactory function. Potential pathomechanisms include (i) stretching/shearing of the olfactory nerve or (ii) contusion/cerebral hemorrhage (Reiter et al. 2004). Our study design does not allow us to differentiate between injuries to different locations, but earlier studies suggest that damage to the basal frontal areas to the brain are particularly susceptible to

**Table 3.** Normative values per age groups for the Identification test total score (16 items) and SS12 score (12 items).

	Total score			SS12 score		
	Females	Males	Total	Females	Males	Total
Age group 18 to 25 years						
N	692	548	1240	692	548	1240
Mean	13.37	13.28	13.33	10.83	10.76	10.80
SD	1.46	1.69	1.56	1.08	1.19	1.13
Minimum	5	6	5	5	5	5
Maximum	16	16	16	12	12	12
Percentiles						
5	11	10	11	9	8	9
10	12	11	11	9	9	9
25	12.5	12	12	10	10	10
50	14	13	14	11	11	11
75	14	14	14	12	12	12
90	15	15	15	12	12	12
95	15	16	16	12	12	12
Age group 26 to 35 years						
N	631	527	1158	631	527	1158
Mean	13.52	13.40	13.47	10.84	10.81	10.82
SD	1.40	1.60	1.50	1.05	1.19	1.11
Minimum	7	3	3	6	3	3
Maximum	16	16	16	12	12	12
Percentiles						
5	11	11	11	9	9	9
10	12	11	12	10	9	9
25	13	13	13	10	10	10
50	14	14	14	11	11	11
75	15	14	14	12	12	12
90	15	15	15	12	12	12
95	16	16	16	12	12	12
Age group 36 to 45 years						
N	650	566	1216	650	566	1216
Mean	13.60	13.25	13.44	10.79	10.55	10.68
SD	1.58	1.70	1.64	1.25	1.30	1.28
Minimum	3	5	3	2	3	2
Maximum	16	16	16	12	12	12
Percentiles						
5	11	10	11	9	8	8
10	12	11	11	9	9	9
25	13	12	13	10	10	10
50	14	13.5	14	11	11	11
75	15	14	15	12	11	12
90	15	15	15	12	12	12
95	16	15	16	12	12	12
Age group 46 to 55 years						
N	796	696	1,492	796	696	1,492
Mean	13.32	12.89	13.12	10.52	10.21	10.38
SD	1.73	1.92	1.83	1.32	1.50	1.42
Minimum	4	2	2	4	2	2
Maximum	16	16	16	12	12	12
Percentiles						
5	10	9	10	8	7	8
10	11	11	11	9	9	9

**Table 3.** Continued

	Total score			SS12 score		
	Females	Males	Total	Females	Males	Total
25	12	12	12	10	10	10
50	14	13	13	11	10	11
75	15	14	14	11	11	11
90	15	15	15	12	12	12
95	16	15	16	12	12	12
Age group 56 to 65 years						
N	542	524	1,066	542	524	1,066
Mean	12.91	12.29	12.61	10.17	9.61	9.90
SD	1.87	2.25	2.09	1.48	1.77	1.65
Minimum	5	4	4	4	3	3
Maximum	16	16	16	12	12	12
Percentiles						
5	9	8	9	7	6	7
10	10	9	10	8	7	8
25	12	11	11	9	9	9
50	13	13	13	10	10	10
75	14	14	14	11	11	11
90	15	15	15	12	12	12
95	16	15	15	12	12	12
Age group 66 to 75 years						
N	292	272	564	292	272	564
Mean	12.05	11.46	11.77	9.55	8.98	9.27
SD	2.28	2.35	2.33	1.80	1.95	1.89
Minimum	4	3	3	3	2	2
Maximum	16	16	16	12	12	12
Percentiles						
5	8	7	7	6	5	6
10	9	8	9	7	6	7
25	11	10	10	9	8	8
50	12	12	12	10	9	10
75	14	13	13	11	10	11
90	15	14	14	12	11	11
95	15	15	15	12	12	12
Age group over 75 years						
N	109	99	208	109	99	208
Mean	10.87	9.70	10.31	8.53	7.59	8.08
SD	2.68	3.03	2.90	2.15	2.44	2.34
Minimum	2	2	2	2	1	1
Maximum	15	16	16	12	12	12
Percentiles						
5	6	4	4	5	3	4
10	7	5	5	5	4	5
25	10	8	8	7	6	7
50	11	10	10	9	8	8
75	13	12	12	10	9	10
90	14	13	13	11	10	11
95	15	14	14	12	12	12

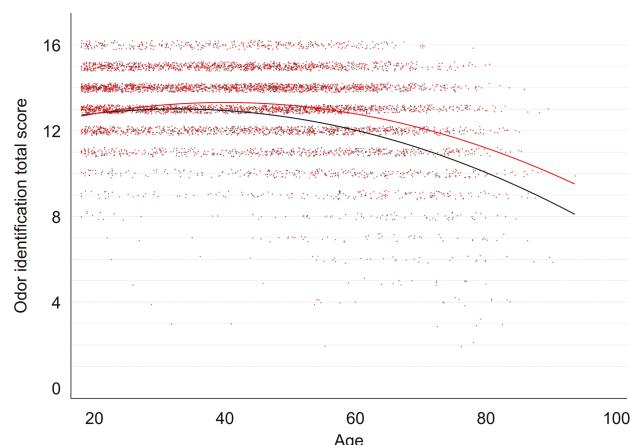
cause olfactory dysfunction (de Guise et al. 2015). These damages may be linked to reduced memory function, as they can be observed in survivors of even mild traumatic brain injury (Fortier-Lebel et al. 2021), as reduced memory

is associated with worse odor identification scores (Hedner et al. 2010).

We further observed that stage 2 hypertension/( $\geq 160/\geq 100$ ) was significantly associated with a reduction in odor

**Table 4.** Construction of the basic (linear regression) model M0 for the total score (16 items) and equivalent M0-3 estimates for the SS12 score (12 items).

	Total score			SS12 score				
	M0-1	M0-2	M0-3	M0-3	M0-3	M0-3	P-value	
	Coef. (95%CI)	P-value	Coef. (95%CI)	Coef. (95%CI)	P-value	Coef. (95%CI)	P-value	
Examinator								
#1	-0.953 (-1.125, -0.780)	<0.001	-0.959 (-1.118, -0.799)	<0.001	-0.952 (-1.111, -0.794)	<0.001	-0.705 (-0.828, -0.582)	<0.001
#2	0.300 (0.133, 0.466)	<0.001	0.332 (0.178, 0.486)	<0.001	0.370 (0.215, 0.525)	<0.001	0.232 (0.111, 0.352)	<0.001
#3	0.286 (0.118, 0.455)	0.001	0.152 (-0.004, 0.308)	0.056	0.149 (-0.006, 0.304)	0.06	0.101 (-0.020, 0.222)	0.1
#5	0.114 (-0.033, 0.260)	0.129	0.022 (-0.114, 0.157)	0.755	0.015 (-0.120, 0.150)	0.827	0.097 (-0.008, 0.202)	0.069
#6	0.422 (0.249, 0.596)	<0.001	0.335 (0.174, 0.496)	<0.001	0.320 (0.160, 0.480)	<0.001	0.184 (0.059, 0.308)	0.004
#8	0.518 (0.339, 0.697)	<0.001	0.488 (0.322, 0.654)	<0.001	0.464 (0.299, 0.628)	<0.001	0.256 (0.128, 0.384)	<0.001
#9	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
#10	-0.652 (-0.829, -0.476)	<0.001	-0.671 (-0.835, -0.508)	<0.001	-0.717 (-0.880, -0.555)	<0.001	-0.508 (-0.635, -0.381)	<0.001
Batch								
#1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
#2	0.210 (0.095, 0.324)	<0.001	0.127 (0.021, 0.233)	0.019	0.100 (-0.006, 0.205)	0.064	0.143 (0.061, 0.225)	0.001
#3	0.235 (0.120, 0.351)	<0.001	0.218 (0.110, 0.326)	<0.001	0.209 (0.101, 0.317)	<0.001	0.248 (0.164, 0.332)	<0.001
#4	0.574 (0.370, 0.780)	<0.001	0.556 (0.366, 0.747)	<0.001	0.542 (0.352, 0.732)	<0.001	0.586 (0.439, 0.734)	
Days until stick expiration date								
Sex (female)								
Age, centered (years)								
Age, centered <sup>2</sup>								
Sex * Age								
Smoking status								
Never smkr								
Past smkr								
Curr smkr/R								
Curr smkr/NR								
School years, centered (years)								
School years, centered <sup>2</sup>								
No. of drugs								
Adjusted R-squared	0.0602		0.1957		0.2064		0.2357	



**Fig. 2.** The relationship of the odor identification total score with age and sex. The scatter plot shows the total score results obtained by female and male (black dots) CHRIS study participants, with addition of a jitter effect to avoid the overlapping of dots. The age-dependent relationship for females (top line) and males (black line) is estimated from the linear regression model including all covariates. For color figures, refer to the online version.

identification abilities. This contrasts with earlier reports who described hypertension not to be associated with odor identification (Landis et al. 2004; Karpa et al. 2010; Arsiwala-Scheppach et al. 2022). However, individuals suffering from hypertension reported subjective olfactory dysfunction significantly more often (Roh et al. 2021). It is important to point out that in contrast to some earlier report, rather than self-reported values we included actual blood pressure test results on the day of testing into our analysis.

Another factor, obesity—but not overweight—was associated with a reduction of olfactory function. However, this association did not survive correction for multiple comparison. Earlier reports have shown that obesity is associated with reduced olfactory function, and particularly with odor identification (Karpa et al. 2010; Micarelli et al. 2022; Velluzzi et al. 2022). The exact link between obesity and impaired odor identification is not well understood, but different potential mechanisms have been put forward including (a) alterations in insulin sensing by the olfactory bulb, (b) ghrelin resistance, and (c) modulation of leptin actions with potential impact on different parts of the olfactory system (Faour et al. 2022). Further research is needed to clarify the link between obesity and odor identification.

In addition to medical conditions, we show that different demographic factors influence odor identification scores. Being female was associated with an increase of 0.47 points in the identification score compared to being male. We further observed a link between age and the olfactory identification score. This was significant with both a linear and a quadratic association. Finally, there was a significant interaction between sex and age. At a younger age, the gap between male and female is relatively small, and it grows with increasing age. The link between both sex and age on the one hand and odor identification ability is very robust and described in many previous population-based studies (Landis et al. 2004; Larsson et al. 2004; Karpa et al. 2010; Boesveldt et al. 2011; Mullol et al. 2012; Schubert et al. 2012; Hoffman et al. 2016; Liu et al. 2016; Seubert et al. 2017; Castillo-Lopez et al. 2020; Jalali et al., 2020; Xu et al. 2020). Especially odor

identification tests show superiority of female participants (Sorokowski et al. 2019), mainly in younger adults (Wang et al. 2019). Different potential causes have been put forward to why this is the case, including superior naming abilities in women compared to men ((Larsson et al., 2004) although see (Wallentin 2009)), as well as hormonal or anatomical differences (Sorokowski et al. 2019).

Further, higher education was associated with better scores in the olfactory identification task. Our results compare well with earlier research that showed that more years of formal education are correlated with better scores in an odor identification task (Frye et al. 1990; Larsson et al. 2004; Boesveldt et al. 2011; Hoffman et al. 2016; Seubert et al. 2017; Castillo-Lopez et al. 2020). In fact, odor identification scores are associated with linguistic capacity and semantic memory (Larsson et al. 2004; Hedner et al. 2010; Jobin et al. 2023), which both are related to the level of education. However, one must be careful with this conclusion since this result may be confounded by socio-economic status (Fornazieri et al. 2019; James et al. 2021).

We also observed the influence of lifestyle on odor identification. First, we show that smoking status has a minor impact on olfactory identification. Existing literature on the topic is mixed. While some studies showed a deleterious effect of smoking on odor identification abilities (Karpa et al. 2010; Duffy et al. 2019; Castillo-Lopez et al. 2020; Jalali et al. 2020) – in one study this effect was limited to women (Schubert et al. 2012) – other studies did not find an effect of smoking (Landis et al. 2004; Pinto et al. 2015), and one study even found a mild protective effect of smoking on odor identification abilities (Mullol et al. 2012). Especially in the context of increasing alternative nicotine consumption such as vaping (AlMatrouk et al. 2021), it will be important to continue investigating the effect of smoking on the sense of smell.

Alcohol consumption is another lifestyle variable with effects on odor identification. We observed that the group of participants that never drank alcohol had significantly worse scores than the reference group (2–4 times a month). This group was selected to be the reference group as it had the most members. This is in line with an earlier report, which described light-to-moderate alcohol consumption to be associated with reduced risk to suffer from smell dysfunction (Liu et al. 2016). While there may be huge intercultural differences in alcohol consumption making comparisons of studies from different countries difficult, one may speculate that certain medical conditions that may impact the sense of smell on their own may be associated with teetotaling for health reasons (Pinto et al. 2014). On the other hand, although this is very speculative, exposure to a variety of alcoholic drinks with moderate frequency may be associated with improved olfactory function due to olfactory training (Al Ain et al. 2019). Finally, one could speculate that individuals with reduced olfactory function may be less stimulated by alcoholic beverages and therefore less interesting and consequently consume less (Rawal et al. 2021).

It is interesting to note that we did not observe a reduction of olfactory function in several other conditions that are typically thought to be associated with a reduction of olfactory function. This includes a history of surgery for nasal polyposis (Qureshi and Lane 2023), kidney disease including kidney failure (Frasnelli et al. 2002), diabetes (Faour et al. 2022), epilepsy (Khurshid et al. 2019), and migraine (Kandemir et al. 2022). Similarly, self-reported exposure to a variety of

**Table 5.** Results of the linear regression analysis adding one of the selected predictors (as continuous, binary, or categorical variable) to the basic model for the total score (16 items) and the SS12 score (12 items), respectively.

	Total score (SS16)		SS12 score	
	Coef. (95%CI)	P-value	Coef. (95%CI)	P-value
1 – Chronic rhinosinusitis (polyp surgery)	-0.108 (-0.244, 0.028)	0.119	-0.092 (-0.198, 0.014)	0.089
2 – Cognitive function (MMSE score)	0.177 (0.144, 0.210)	<0.001	0.123 (0.097, 0.149)	<0.001
3 – PD screening score	-0.097 (-0.162, -0.033)	0.003	-0.081 (-0.131, -0.031)	0.002
4 – Diabetes diagnosis	0.094 (-0.183, 0.372)	0.505	0.007 (-0.209, 0.223)	0.951
5 – Liver disease diagnosis	0.245 (0.049, 0.442)	0.014	0.121 (-0.031, 0.274)	0.119
6 – Kidney disease diagnosis	0.093 (-0.060, 0.246)	0.233	0.038 (-0.081, 0.157)	0.535
7 – Body-mass-index				
Underweight (<18.5)	-0.273 (-0.606, 0.060)	0.108	-0.335 (-0.594, -0.076)	0.011
Normal (18.5 to <25)	Ref.	Ref.	Ref.	Ref.
Overweight (25 to <30)	-0.028 (-0.125, 0.068)	0.565	-0.035 (-0.110, 0.040)	0.362
Obese ( $\geq 30$ )	-0.163 (-0.286, -0.041)	0.009	-0.131 (-0.226, -0.036)	0.007
8 – Blood pressure				
Normal (<130/<85)	Ref.	Ref.	Ref.	Ref.
Prehypertension (130 to 139/85–89)	-0.018 (-0.135, 0.099)	0.763	-0.037 (-0.128, 0.055)	0.432
Stage 1 hypertension (140 to 159/90 to 99)	-0.065 (-0.197, 0.067)	0.334	-0.053 (-0.155, 0.050)	0.317
Stage 2 hypertension or higher ( $\geq 160/\geq 100$ )	-0.337 (-0.568, -0.106)	0.004	-0.243 (-0.423, -0.063)	0.008
9 – Migraine				
No migraine	Ref.	Ref.	Ref.	Ref.
Migraine without aura	0.176 (-0.018, 0.369)	0.075	0.066 (-0.085, 0.216)	0.393
Migraine with aura	0.054 (-0.202, 0.309)	0.682	-0.017 (-0.216, 0.182)	0.870
10 – Epilepsy	-0.304 (-0.717, 0.110)	0.150	-0.175 (-0.497, 0.147)	0.286
11 – TIA or stroke	0.544 (0.089, 0.998)	0.019	0.420 (0.067, 0.774)	0.020
12 – RBD score	0.012 (-0.009, 0.032)	0.259	0.007 (-0.009, 0.023)	0.390
13 – Skull fracture	-0.593 (-0.922, -0.264)	<0.001	-0.552 (-0.808, -0.296)	<0.001
14 – Exposure to any of the selected substances	0.029 (-0.060, 0.118)	0.527	0.022 (-0.048, 0.091)	0.542
15 – Alcohol consumption, last 12 months				
None	-0.280 (-0.451, -0.110)	0.001	-0.142 (-0.275, -0.009)	0.036
At special occasions only	-0.083 (-0.209, 0.043)	0.195	-0.049 (-0.147, 0.0485)	0.323
Once a month or less	-0.105 (-0.260, 0.050)	0.185	-0.0648 (-0.186, 0.056)	0.293
2–4 times per month	Ref.	Ref.	Ref.	Ref.
2–3 times per week	0.044 (-0.083, 0.171)	0.496	0.017 (-0.082, 0.116)	0.741
4 or more times per week but not daily	0.140 (-0.058, 0.337)	0.165	0.036 (-0.118, 0.189)	0.647
Daily	0.074 (-0.096, 0.244)	0.396	0.081 (-0.052, 0.213)	0.231

relatively common potential toxins such as detergents, exhausts, wood dust, pesticides, and others was also not associated with a reduction of odor identification abilities.

Finally, it is important to point out that olfactory identification scores dependent weakly but significantly on the test administrator and the olfactory test kit that was used. It is therefore of utmost importance to normalize the testing methods and take these variables into consideration. This observation shows the importance of sticking to protocol guidelines, particularly in a clinical context.

There are a few limitations to this study. One of it is that some of the included clinical conditions were based self-reports. Accordingly, participants may misreport leading to an over- or underestimation of the effect. Further, although we carried out a population-based study, certain groups will be underrepresented, such as hospitalized/ institutionalized individuals or populations living in nursing homes. The effects of

medical conditions associated with these factors—most importantly, dementia—will therefore be underestimated by our model. Finally, we only assessed olfactory identification; it may be that other olfactory tasks, e.g. odor detection thresholds or olfactory memory are affected in a different fashion.

In conclusion, we describe a study on odor identification in 6,944 participants without acute nasal obstruction. Age, sex, and education together explained roughly 13% of the total variance in the data. We further observed that variables related to medical (positive screening for cognitive impairment, Parkinson's disease, history of skull fracture, stage 2 hypertension) and lifestyle (alcohol abstinence) conditions had a negative effect on odor identification scores. These factors should be considered when clinicians evaluate olfactory abilities. Finally, we provide clinicians with normative values for both versions of the Sniffin' Sticks odor identification test, i.e. with 16 items and with 12 items.

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## Conflict of interest statement

JF received speaker fees from Aromainfo, Brauerei Forst AG, Bio-Paradies Eppan, SABES, Speikboden AG and royalties from Styriabooks and TopHat.

## Data Availability

Data can be made available upon request and according to Italian law. CHRIS study data can be requested for research purposes by submitting a dedicated request to the CHRIS Access Committee. Please contact access.request.biomedicine@eurac.edu for more information on the process.

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