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The effect of smoking on the olfactory function*

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SUMMARY

Although smoking is a widely spread habit, its effect on olfaction has not been clearly established. The aim of this study was to investigate the effect of cigarette smoking on the olfactory function, using the "Sniffin' Sticks" test. Sixty-five smokers were studied, with a median period of smoking of 10 years (range: 1–45 years) and a median number of 15 cigarettes smoked per day (range: 5–20). Forty-nine non-smokers were used as controls. Olfactory function was evaluated using the "Sniffin' Sticks" test, which consists of odour threshold (OT), odour discrimination (OD) and odour identification (OI) and its overall results may be presented as a composite threshold-discrimination-identification (TDI) score. Multivariate linear and logistic regression analyses were performed. All OT, OD, OI and TDI scores were statistically significantly lower in smokers compared to non-smokers, even when controlled for gender and age. Low OT, OD, OI and TDI scores were more prevalent among smokers than non-smokers. Multivariate logistic regression analysis, adjusted for gender and age, revealed that smoking remained a strong independent risk factor for low OT, OD, OI and TDI scores. Among smokers, statistically significant negative relationships were found between pack-years and OT, OD, OI and TDI, controlling for age. In conclusion, smoking was found to be adversely associated with the olfactory ability in a dose-related manner. Smokers were found to be nearly six times as likely to evidence an olfactory deficit as non smokers, depending on the duration and the amount of cigarettes smoked.

Key words: olfaction, olfactory thresholds, olfactory discrimination, olfactory identification, smoking, Sniffin' Sticks.

INTRODUCTION

Olfactory evaluation has been often neglected in clinical practice, despite its importance in the otolaryngologic and neurologic clinical examination. The main reason for this was the lack of simple, fast and reliable methods of olfactory testing. Several olfactory tests were introduced during the past two decades, but only a few of them proved successful, including the University of Pennsylvania Smell Identification Test (UPSIT) [(1)] with its down-scaled cross-cultural version (CC-SIT) [(2)] and the Connecticut Chemosensory Clinical Research Center Test (CCCRC) [(3)]. Recently, a new olfactory test developed in Germany by Kobal and Hummel [(4,5)] became commercially available under the name "Sniffin' Sticks".

"Sniffin' Sticks" are odour-dispensing devices that resemble felt-tip pens. The "Sniffin' Sticks" test battery consists of three elaborate tests of olfactory function: odour threshold (OT), odour discrimination (OD), and odour identification (OI) [(4,5)]. Presently, this test is widely used in European Clinics. Previous work has already established its test-retest reliability and its validity in comparison with established measures of olfactory sensitivity obtained by the UPSIT, the CCCRC and the CC-SIT tests [(5,6)]. In our previous work, we provided normative values for olfactory function and examined the effect of age, sex, and side tested in the population in Greece, which is characterized by a mild Mediterranean climate [(7)].

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The effect of smoking on the olfactory funtion is an important issue, which has not been sufficiently investigated [8], although adequate evidence exists supporting the great influence of various chemical substances on the olfactory function [9]. Additionally, research on the effect of smoking on olfaction has focused mainly on threshold sensitivity, and, practically, no information is available about the ability of smokers to identify and discriminate odours, questions of a great concern both in real life and in the clinic [10]. As smoking is a worldwide habit for millions of people, further investigation of its possible effects on the olfactory function is warranted.

The aim of the present study was to determine the effect of smoking not only on OT, but also on OD and OI in the Greek population, using the "Sniffin' Sticks" tests. Another goal of the study was to provide the risk factor for smokers to manifestate problems with their olfactory function, in comparison with non-smokers, according to the dose and the duration of smoking.

MATERIALS AND METHODS

Human Subjects

One hundred fourteen healthy volunteers were studied during one year, from September 2004 to August 2005. Sixty-five of them (57%) were smokers and 49 subjects (43%) had never smoked and did not live with or work with smokers according to the information they provided. Complete smoking histories were taken from all subjects. All the participants were in general good condition. There were no abnormal findings from the nose and the paranasal sinuses, as proven by both nasal endoscopy and computerized tomography scan of the region. Additionally, there was no history of any major olfactory disturbance in any of them. The care of the human subjects for this study was approved by the local Institutional Review Board. All subjects were volunteers and were fully explained the aim, the design and the clinical implications of the study. The investigations were performed in accordance with the principles of the Declaration of Helsinki/HongKong.

Olfactory Testing

Identical olfactory tests were performed in a bilateral and a lateralized mode, using the "Sniffin' Sticks" test package (Burghardt, Wedel, Germany). The sequence of testing the left, right, or both nostrils was randomized across all subjects.

Specific tests for OT, OD and OI were performed. The OT test was performed with n-butanol and was evaluated using a single-staircase, triple-forced choice procedure [11]. A 1:2 dilution series with 16 stages, beginning with 4% was used; dilutions were established in a geometric series, according to previous reports [12]. In the suprathreshold OD test, triplets of pens were presented in a randomized order, with two containing the same odorant and the third a different odorant. The examined was asked to detect which of the three pens smelled differently from the remaining two. For the OI test 16 odorants were presented in suprathreshold intensity. The examined was asked to identify individual odorants from a list of four descriptors, using a multiple-choice procedure. In all three tests, subjects were blindfolded to avoid visual identification of the odorant-containing pens, and the obtained score was an integral, ranging from 0 (no odorant recognized) to 16 (all odorants recognized).

Finally, according to the principles of previous reports [6,13], the results of the three tests were combined to form an overall score called "composite threshold-discrimination-identification score" (TDI). TDI represented the sum of the results obtained for OT, OD and OI tests and might prove useful in daily clinical practice as a single indicator of olfactory performance. The TDI score ranged from 0 to 48, with values ≤ 15 considered consistent with anosmia, because of the probability of obtaining this number of correct results by chance alone [4,14].

All subjects completed the test. The time needed for the complete examination ranged from 20 to 30 min. Their scores for OT, OD and OI tasks were related to age and sex. Cigarette dose was calculated in pack-years by multiplying the number of packs smoked per day by the number of years that smoking occurred.

Statistics

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS), version 13.0 (SPSS, Inc., Chicago, IL). The normality of continuous variables was tested with the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as the mean ± SD (standard deviation), while non-normally distributed variables were expressed as the median and range. Categorical variables were expressed as frequencies (and percentages). The chi-square test was used to evaluate any potential association between categorical variables. Student's t-test was used to assess differences of indices of olfactory function between smokers and non-smokers. Multivariate stepwise linear and logistic regression models were constructed to explore the independent effect of smoking on the indices of olfactory function. Subject's gender and age were the major confounders in all multivariate models. Adjusted odd ratios (aOR) and 95% confidence intervals (CI) were estimated as the measure of association between smoking and the presence of olfactory dysfunction. Pearson's r-correlation coefficient was used to assess the relation between pack-years and the indices of olfactory function. All tests were two-tailed and statistical significance was accepted at the $p < 0.05$ level.

Table 1. Olfactory function (mean values ± SD) in relation to smoking.

	Smokers	Non-smokers	p-value	95% CI of difference
Odor threshold	7.3 ± 0.9	8.5 ± 0.9	< 0.001	-1.6 to -0.9
Odor discrimination	14.8 ± 0.9	15.7 ± 0.7	< 0.001	-1.2 to -0.6
Odor identification	14.2 ± 1.0	14.9 ± 0.8	< 0.001	-1.1 to -0.4
Composite (TDI) score	36.3 ± 2.0	39.1 ± 1.6	< 0.001	-3.5 to -2.2

SD: standard deviation; CI : confidence interval.

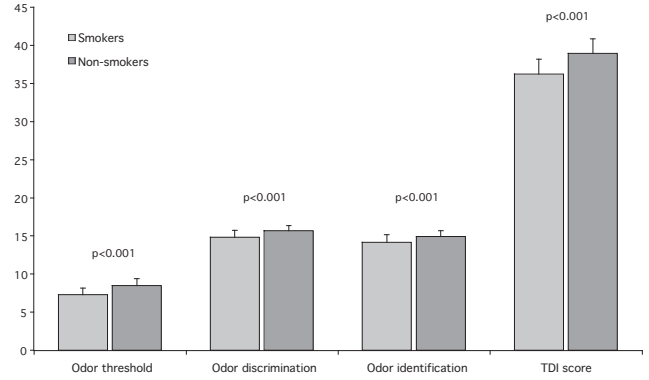

Figure 1. Olfactory function (mean values ± SD) in relation to smoking.

RESULTS

The study population of 114 healthy subjects comprised of 62 (54.4%) males and 52 (45.6%) females, with a median age of 22 years (range 14–72 years). Sixty-five of them (57.0%) were smokers (48 males and 17 females; median age 31 years; range 17-72 years). They were smoking for a median period of 10 years (range 1-45 years), and the median number of cigarettes smoked per day was 15 (range 5-20). Forty-nine (43.0%) subjects (14 males and 35 females; median age 24 years; range 13-70 years) had never smoked. Male sex was more prevalent in smokers compared to non-smokers (73.8% versus 28.6%, $p < 0.001$). Furthermore, smokers were significantly older than non-smokers ($p < 0.001$).

All indices of olfactory function of smokers were statistically significantly lower than non-smokers (all $p < 0.001$; Table 1). The test presented the greatest reduction, approaching 14.1%, while 5.7% and 4.7% reductions were observed in the OD and OI tests, respectively. Overall, the TDI score in smokers was found to be reduced by 7.2% compared with non-smokers (Figure 1). Even when controlled for gender and age in multivariate linear regression analysis, smoking remained independently associated with all indices (OT: $p < 0.001$; OD: $p < 0.001$; OI: $p = 0.003$; TDI: $p < 0.001$; Table 2). The coefficients of the regression equations, which describe quantitatively the exact relationship of gender, age and smoking with OT, OD, OI and TDI scores, are shown in Table 2.

As a cut-off for OT, OD, OI and overall TDI score was considered the 10th percentile of the reference values used in our clinic [7]. We decided on using the 10th percentile rather than the 3rd or 5th percentiles since, when an overlap exists between the distribution of values of healthy and diseased, there is a better chance of detecting abnormal subjects by allowing a narrower range for the healthy subjects. Moreover, our results could be directly compared with the respective

Table 2. Results of multivariate linear regression analysis of olfactory function.

	Coefficient	**Standard error**	**Test statistic**	**p-value**
Odor threshold (OT)				
Constant	8.782	0.124	70.790	< 0.001
Gender	-0.698	0.167	-4.186	< 0.001
Age	-0.760	0.182	-4.186	< 0.001
Smoking	-0.740	0.173	-4.280	< 0.001
Odor discrimination (OD)				
Constant	15.762	0.109	144.515	< 0.001
Age	-0.669	0.173	-3.877	< 0.001
Smoking	-0.705	0.148	-4.754	< 0.001
Odor identification (OI)				
Constant	15.049	0.110	137.157	< 0.001
Age	-1.277	0.174	-7.351	< 0.001
Smoking	-0.447	0.149	-2.999	0.003
Composite (TDI) score				
Constant	39.668	0.220	180.467	< 0.001
Gender	-0.962	0.296	-3.254	0.002
Age	-2.702	0.322	-8.399	< 0.001
Smoking	-1.774	0.306	-5.791	< 0.001

Included in regression were gender (female = 0, male = 1), age (≤55 years = 0, >55 years = 1) and smoking (No = 0, Yes = 1). The R^2 of regression was 48.5% (47.1% adjusted) for OT, 31.8% (30.5% adjusted) for OD, 42.3% (41.2% adjusted) for OI, and 64.2% (63.2% adjusted) for TDI. Only variables that maintained statistical significance in multivariate regression are shown.

Table 3. Association between smoking and the presence of olfactory dysfunction (lower than the 10th percentile of the reference values) expressed as odds ratios with 95% confidence intervals.

	Smokers*	**Non-smokers***	**aOR (95% CI)**	**p-value**
Odor threshold	32 (49.2)	8 (16.3)	3.0 (1.0-7.7)	0.040
Odor discrimination	24 (36.9)	5 (10.2)	3.4 (1.1-11.3)	0.044
Odor identification	20 (30.8)	3 (6.1)	5.0 (1.1-23.7)	0.041
Composite (TDI) score	16 (24.6)	3 (6.1)	5.9 (1.2-28.9)	0.026

* Data are number of cases; percentages are shown in parentheses; aOR: adjusted odds ratio for gender and age; CI: confidence interval.

results of studies from other settings using the same olfactory test [4,5]. In particular, the cut-off for OT score was 7, for OD score it was 14, for OI score it was 13 and for TDI score it was 34.50. Low OT, OD, OI and TDI scores were more prevalent among smokers compared to non-smokers (OT: 49.2% versus 16.3%, $p < 0.001$; OD: 36.9% versus 10.2%, $p = 0.001$; OI: 30.8% versus 6.1%, $p = 0.001$; TDI: 24.6% versus 6.1%, $p = 0.009$). Multivariate logistic regression analysis, adjusted for gender and age (Table 3), revealed that smoking remained a strong independent significant predictor of low OT, OD, OI and TDI scores (OT: aOR = 3.0, 95% CI = 1.0–7.7, $p = 0.040$; OD: aOR = 3.4, 95% CI = 1.1–11.3, $p = 0.044$; OI: aOR = 5.0, 95% CI = 1.1–23.7, $p = 0.041$; TDI: aOR = 5.9, 95% CI = 1.2–28.9, $p = 0.026$).

Based on the number of packs smoked per day and the number of years that smoking occurred, the number of pack-years was calculated for each smoker. The median number of pack-years was 15 (range 0.5–45.0). Among the smokers of our study, statistically significant negative relationships were found between pack-years and OT ($r = -0.544$, $p < 0.001$), OD ($r = -0.501$, $p < 0.001$), OI ($r = -0.573$, $p < 0.001$) and TDI ($r = -0.761$, $p < 0.001$) scores, which remained significant even after controlling for age (OT: $r = -0.479$, $p = 0.002$; OD: $r = -0.341$, $p = 0.045$; OI: $r = -0.282$, $p = 0.024$; TDI: $r = -0.590$, $p < 0.001$) (Figure 2).

DISCUSSION

Olfaction has been characterized as a neglected sense in the past [15] due to the lack of interest in olfactory testing in the clinical practice. This may be attributed to the inconsistency and limited availability of some tests, the lack of normative data and the time needed for performing the examination. This situation has recently changed and renewed interest in olfaction testing was observed, because olfactory evaluation contributes to both accurate medical diagnosis and quality control in the treatment of diseases associated with smell disorders, such as cranial injuries, nasal and paranasal disease and infections [16].

"Sniffin' Sticks" is a modern olfactory test recommended by the German Olfactology and Gustology Association as a standard for olfactory testing [17]. The test has gained wide acceptance in many hospitals in countries of the central and northern Europe. Kobal and co-workers who initially presented this test, participated recently in a multicenter investigation that first provided normative values for routine clinical use of the "Sniffin' sticks" examination [13], emphasizing the need for continuous expansion of the test's normative database, thus expecting to strengthen its usefulness in the diagnosis of olfactory disorders. Recently, we provided normative values for routine clinical use of the "Sniffin' sticks" tests related to subject's age, gender and the nostril being examined [7]. Our data referred to the different climate conditions in Greece and, generally, the mild Mediterranean climate and environmental conditions. Our findings confirmed the weather and environmental effect on olfactory performance, because our subjects obtained better results in all olfactory tests compared to the results obtained in other centers of northern and central Europe [7].

In the present paper, the important issue of the effect of smoking on the olfactory function was studied. In general, the results from various reports have not demonstrated conclusively that smoking affects odour perception. Several studies suggest that cigarette smoking has an adverse effect on the ability to smell [10,18,19], but other studies have failed to find such an influence [20]. It has been also suggested that tobacco smoking only temporarily alters smell function [21]. It appears, thus, that the impact of smoking on the olfactory function still remains a matter of disagreement.

A brief review of the older literature confirms the contradictory views on this issue. First, Fordyce in 1961 [22] did not find any effect of cigarette smoking on olfactory sensitivity. Amoore [23,24] claimed that moderate smokers are not less sensitive than non-smokers provided that they have not smoked in the 15 minutes immediately prior to the test. Furthermore, Venstrom and Amoore [25] suggested that there was a slight non-significant advantage exhibited by non-smokers. However, Joyner [26-27] revealed a statistically significant difference in olfactory acuity between smokers when compared to non-smokers in an investigation of a group of industrial workers.

In a more recent study, Ahlstrom et al. [10] examined the olfactory perception in matched groups of smokers, non-smokers

and passive smokers in butanol and pyridin, and reported that smokers are less sensitive to the odours of both substances than are nonsmokers. Additionally, they found that the scores obtained from passive smokers were similar to those of the smokers. The authors discussed the possibility of habituation to the odour, which a central phenomenon and refers to the cessation of a response because of a learned adjustment to a stimulus situation. However, in our study, although we did not include passive smokers, we found a clear decrease in OT, OD and OI ability of smokers as related to non-smokers. Especially the OT ability in smokers presented a 14.1% reduction, while 5.7% and 4.7% reductions were observed in OD and OI tests, respectively. Therefore, it appears that smokers smell substances in higher concentrations than the non-smokers and they discriminate and identify odours with more difficulty than subjects who don't smoke. This should be attributed to an olfactory deficit rather than habituation, because testing included a wide range of odours and besides threshold sensitivity, OD and OI were examined as well.

In another study [8], a large group of subjects was divided into non-smokers, subjects who had smoked in the past and in current smokers. The authors found a clear adverse effect of cigarette smoking on olfactory function that is dose related and present in past smokers. An interesting point was that this effect was reversible, with the time course of its reversibility being dependent on the duration of abstinence from smoking and the intensity of prior smoking activity. According to the authors, the finding that past smokers evidence dose-related decrements in their OI ability similar with those observed in current smokers, may explain discrepancies observed in previous studies that examined the effect of smoking on olfaction. Such studies categorized past smokers as non-smokers and, additionally, did not control for the effects of cumulative

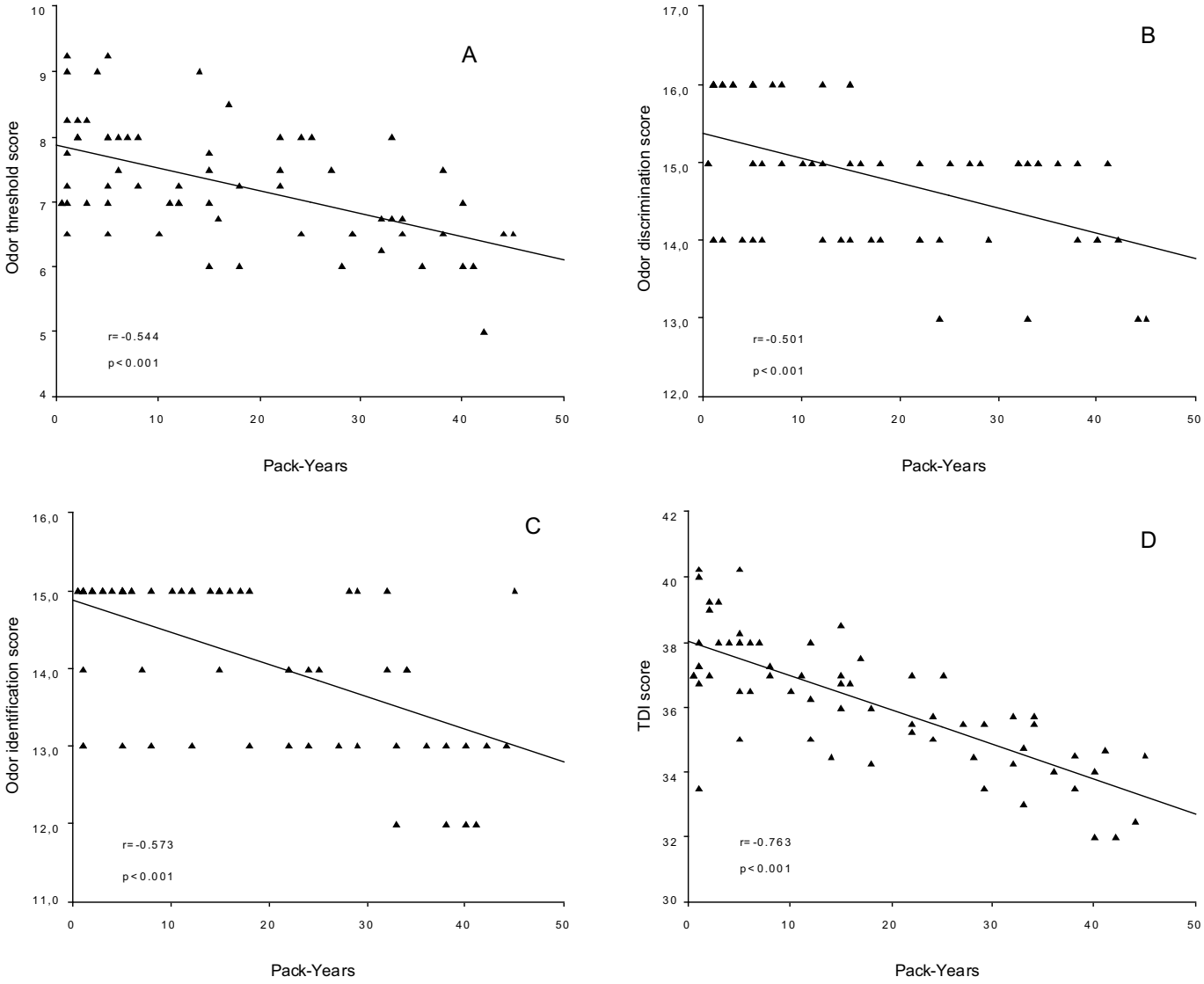

Figure 2. The association between pack-years and (A) odor threshold (OT), (B) odor discrimination (OD), (C) odor identification (OI), and (D) threshold-discrimination-identification (TDI) score, among smokers.

smoking dose. Additionally, Murphy et al. [28] studied high risk factors for olfactory impairment in a large group of older adults and they found that only current smoking was associated with impaired olfaction. They did not find any significant difference between persons who had never smoked and past smokers, implicating reversible effects of tobacco on the olfactory function. On the contrary, in a recent study of odour identification in a Japanese adult population [29], the authors found decreased odour identification to both current and past smokers. They concluded that cessation of smoking may not provide recovery of olfactory function and attributed the discrepancies of their findings with previous reports to the different ethnicity of the sample studied and to the use of CC-SIT as an odour identification test, which might have lower sensitivity than the standard UPSIT.

To avoid this confusing factor, we excluded past-smokers and we calculated cigarette dose in pack-years. We, thus, confirmed that the adverse effect of cigarette smoking on olfactory function is dose and duration related. A statistically significant negative relation was found between pack per years and all olfaction measures, even after controlling for age. Thus, it may be concluded that both cigarette smoking per se and the actual amount of cigarettes smoked can be directly correlated with a diminished olfactory acuity as measured by this test procedure. Age of the subject and sex did not interact with smoking dose, indicating that age and sex did not potentiate or attenuate the smoking dose effect.

Smoking may have a negative impact in olfaction in patients with sinusitis and polyposis, operated by endoscopic sinus surgery. Sugiyama et al. [30,31] found that there was a significant negative correlation between the cumulative dose of cigarette smoking and the postoperative olfaction measures. Smoking-induced olfactory dysfunction might be the result of not only cigarette smoking per se but also the interactive effect of aging and smoking, because the deficit in olfaction was observed only in older smokers. The authors hypothesized that cigarette smoking may cause time-related alterations in the olfactory system via its long-standing intranasal neurotoxicity, inducing dysfunction of olfactory receptor cells and thus, reducing the ability to smell for older patients.

Recently, in a study of olfactory dysfunction in an adult Swedish population [32] no increased risk for current smokers or number of pack-years (including both current and past smokers) was found. The authors explained their findings, which differ from other studies and from the present one, by the fact that there is a substance-specific effect attributable to overexposure to substances in tobacco smoke. It may be thus possible, that smoking affects olfaction of certain substances more than others, and hence, the results of various studies may depend on the type and the number of tested substances. This hypothesis is further supported by Moncrieff who reported that the effect of smoking on odour perception is selective, affecting only the odours of substances contained in tobacco smoke, such as pyridine, but no other odors [18].

In the present study, we examined the association between smoking and the presence of olfactory dysfunction (lower than the 10^{th} percentile of the reference values), and we found that among non-smokers OT ability is affected easier than OD and OI, possibly as a result of the environmental influence. The results of the logistic regression analysis revealed that persons who currently smoke are nearly six times more likely to have an olfactory deficit in comparison with persons who have never smoked (adjusted smoking odds ratio [95% confidence interval] = 5.9 [1.2-28.9]), as we can see from the TDI score.

Moreover, smokers' normal ability to identify the odors is affected more than the OT and OD ability. In the present study we found a 5-fold higher independent risk for dysfunction of their identification ability among smokers compared to non-smokers. Smoking was also associated with 3 and 3.4-fold higher risk for developing low OT and OD, respectively. It should be noted that although olfactory impairment was much more prevalent among smokers, the magnitude of the adverse effect of smoking on olfactory function was not large, although statistically significant. This finding is in agreement with the previous study of Frey et al. [8], in which the authors reported only mild or moderate and not severe olfactory loss from smoking.

Table 2 presents our results of multivariate linear regression analysis of olfactory function that may be analyzed to deduce mathematically the relationship between smoking, age, gender and their OT, OI and OD ability. According to these findings, the relationship given above does form the basis for the following models for olfactory function:

$$OT = 8.782 - 0.698\ \text{Gender} - 0.760\ \text{Age} - 0.740\ \text{Smoking};$$
$$OD = 15.762 - 0.669\ \text{Age} - 0.705\ \text{Smoking};$$
$$OI = 15.049 - 1.277\ \text{Age} - 0.447\ \text{Smoking};$$
$$TDI = 39.668 - 0.962\ \text{Gender} - 2.702\ \text{Age} - 1.774\ \text{Smoking}.$$

The primary finding of this study that cigarette smoking adversely influences olfactory ability, expressed from the TDI score, in a dose-duration related manner suggests that smoking causes long-term changes in the olfactory system. The biological basis for the decreased ability to smell associated with smoking is not clear. Irritation or trigeminal stimulation from exposure to smoke may inhibit activation of the olfactory nerve and consequently, odour perception [10]. However; a direct effect of tobacco on the olfactory epithelium may be implicated, as has been proven by several animal studies. It has been shown that relatively brief exposures to cigarette smoke in mice (once or twice per day for 6 to 9 days) can cause anatomic changes of the olfactory mucosa, including a reduction in the number and size of olfactory vessels and cilia [33].

Additionally, it has been found that animals exposed to a number of chemicals present in cigarette smoke demonstrate damage to the olfactory mucosa and receptor cells, often in a dose related manner [34-35]. Exposure to the heat and toxic by-products of tobacco smoke are presumed to damage the olfactory epithelium in a similar manner to that seen in the respiratory epithelium of the sinuses and lungs [36]. A recent study in rats exposed in ethanol and tobacco revealed increase in respiratory nasal epithelium and decrease in olfactory epithelium, which was thinner, in comparison with the control group [37]. Accordingly, long-term effects of smoking on olfaction could be caused by the adverse influence of the chemicals contained in cigarette smoke on the olfactory receptor cells within the olfactory mucosa [8]. However, the influence of such chemicals might cause short-term effects as well, owed to change of the consistency or nature of the mucus overlying the receptors, and, possibly, adaptation or habituation of the receptor system. Nasal airway constriction might be also implicated, especially when considerable airway obstruction is present [38,39].

The role of apoptosis, the cellular mechanism that is responsible for the efficient removal of aged or damaged cells and may be triggered in response to injury, has been recently studied in the olfactory epithelium [40]. This mechanism is predominant in olfactory sensory neurons, replacing dead cells throughout adult life by mitosis and maturation of progenitors present within the epithelium. Several studies have demonstrated apparent increase in olfactory sensory neuron apoptosis in sinusitis and aging, but also in animals exposed in tobacco smoke [40]. Neuronal apoptosis is mediated through the effector enzyme caspase-3, which shows increased activity in the olfactory epithelium of tobacco exposed animals, reflecting apoptotic cell death of the olfactory neurons [41]. This has been suggested as a common cause for clinical smell loss.

In conclusion, a diminished olfactory sensitivity associated with cigarette smoking was observed, and a direct negative correlation between olfactory sensitivity and amount smoked was demonstrated. The present findings imply long-term general effects of cigarette smoking on smell function and could be explained by the adverse effects of airborne chemicals on the olfactory receptors, resulting in alterations of the olfactory epithelium and increased apoptosis of the olfactory sensory neurons.

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