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Smoking and Olfactory Dysfunction: a Systematic Literature Review and Meta-Analysis

Gaurav S. Ajmani, M.H.S.¹, Helen H. Suh, Sc.D², Kristen E. Wroblewski, M.S.³, Jayant M. Pinto, M.D.⁴

¹Pritzker School of Medicine, The University of Chicago, Chicago, IL, United States

²Department of Civil and Environmental Engineering, Tufts University, Medford, MA, United States

³Department of Public Health Sciences, The University of Chicago, Chicago, IL, United States

⁴Section of Otolaryngology-Head and Neck Surgery, Department of Surgery, The University of Chicago, Chicago, IL, United States

Abstract

Objective: A systematic review and meta-analysis of the literature examining the association between tobacco smoking and olfactory function in humans.

Data Sources: PubMed and Web of Science (1970–2015).

Review Methods: A database review of studies of smoking and olfaction with a focus on identifying high quality studies (based on modified Newcastle-Ottawa scales) using validated olfactory tests among the generally healthy population.

Results: We identified 11 studies meeting inclusion criteria. Of 10 cross-sectional studies, 2 were excluded from meta-analysis as the cohorts they studied were included in another paper in the review. In meta-analysis, current smokers had substantially higher odds of olfactory dysfunction compared to never smokers (OR 1.59, 95% CI 1.37–1.85). In contrast, former smokers were found to have no difference in risk of impaired olfaction compared to never smokers (OR 1.05, 95% CI 0.91–1.21). The single longitudinal study reviewed found a trend towards increased risk of olfactory decline over time in ever smokers; this trend was stronger in current as compared to former smokers.

Conclusion: Current smoking, but not former smoking, is associated with significantly increased risk of olfactory dysfunction, suggesting that the effects of smoking on olfaction may be reversible. Future studies that prospectively evaluate the impact of smoking cessation on improvement in olfactory function are warranted.

Keywords

smoking; cigarette smoke; tobacco smoke; smell; olfaction

Corresponding Author: Jayant M. Pinto, MD, Section of Otolaryngology-Head and Neck Surgery, Department of Surgery, The University of Chicago Medicine and Biological Sciences, MC1035, 5841 South Maryland Avenue, Chicago, Illinois 60647 USA, jpinto@surgery.bsd.uchicago.edu, Telephone: 773-702-6727, Fax: 773-702-6809.

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INTRODUCTION

Olfactory dysfunction affects millions of adults worldwide, with prevalence estimated around 19%^{1,2}. This sensory disorder is associated with major decreases in quality of life³, poor mental and physical health⁴, increased mortality^{5,6}, and impending neurodegenerative disease⁷. Major risk factors for olfactory impairment include older age, male sex, head trauma, upper respiratory infections, and toxic exposures⁸. Although smoking is commonly considered a risk factor for poor olfaction⁹, several studies have also found no association with smoking^{2,10,11}. Furthermore, while the study of smoking and olfaction goes back decades¹², to our knowledge these data have yet to be thoroughly reviewed as in olfactory decline associated with other toxic exposures^{13–15}. Given that effective methods exist for tobacco cessation and control¹⁶, understanding whether exposure to tobacco smoke affects olfaction would be of use in clinical practice with a potentially large public health impact.

METHODS

Literature Review

We performed a literature search to find all potentially relevant studies of smoking and olfaction, with the assistance of a professional academic reference librarian. PubMed was searched on January 16, 2016 for papers published between 1970–2015, using both Medical Subject Headings (MeSH) terms and keywords. Web of Science was searched on the same day using keywords only. Papers were required to include at least one term from Group A and at least one term from group B (Table 1). As we were interested in human studies, we used MeSH terms in PubMed to restrict results to exclude studies tagged with “Animals” but to include papers tagged with both “Animals” AND “Humans”. Papers in PubMed not yet indexed in MEDLINE and those in Web of Science were manually examined using the same criteria. Results were limited to English language. We excluded case studies, reviews, and other non-original research. Papers were also excluded if they only employed a subjective measure of olfactory function (e.g., self-report, odor annoyance), did not evaluate differences in olfaction associated with smoking (excluding environmental tobacco smoke [ETS, secondhand smoke]), or did not study a generally otherwise healthy population. Studies meeting these initial criteria were then reviewed in full and scored using a modified version of the Newcastle-Ottawa Scale for cohort studies (Table S1)¹⁷. All studies were required to present actual effect sizes (and corresponding standard errors or confidence intervals) for smoking and olfaction in a generally healthy population. Using these criteria, we identified studies to be included in this review (Table 2), using a standard cutoff for high quality (Newcastle-Ottawa Scale ≥ 7 points)^{18,19}.

Meta-Analysis

Effect sizes and corresponding standard errors or confidence intervals were pulled from individual papers and used in meta-analysis. Analyses were structured as odds ratios of olfactory dysfunction for smoking vs. non-smoking and presented separately for current smoking (vs. never) and former smoking (vs. never). Results for ever smoking (vs. never) are presented in the supplemental material. One paper presented data as former vs. current smokers and never vs current smokers—we were able to compute coefficients and

confidence intervals for current vs. never smokers from these results and include in the meta-analysis²⁰. However, as we could not estimate standard errors/confidence intervals for former vs. never smokers from these results, this was omitted from our results and meta-analysis.

We had planned to also group analyses by the olfactory domain tested (odor identification or threshold), but no papers were found which assessed odor threshold.

If multiple papers were found studying the same cohort, all were reported as included in our review results, but only one paper was included in meta-analysis, per standard protocol²¹. This was determined by the paper with the highest modified Newcastle-Ottawa Scale score or with the larger sample size if scores were equal. In our own prior work¹¹, smoking status was treated as current vs. non-current. As we had access to this dataset these analyses were re-run treating smoking as ever/never and current/former/never. These re-analyses used standard logistic regression with olfactory dysfunction as the dependent variable, as described in the supplementary material and presented in Table S2. For papers presenting results as linear regression with the number of odors correctly identified as the dependent variable, results were converted to binary outcomes with odds ratios (ORs) using the following validated formula²², also recommended per guidelines from the Cochrane Collaboration²³:

$$OR = e^{SMD * \left(\frac{\pi}{\sqrt{3}}\right)}, \text{ where } SMD \text{ (standardized mean difference)} = \frac{\text{difference in means}}{\text{standard deviation of outcome}}$$

For linear regression papers presenting effects with the corresponding 95% confidence interval (CI), this method was used to convert the CIs as well. One paper²⁴ presented linear regression results as effects with the corresponding standard error (SE); we first computed a 95% CI (effect size $\pm t * SE$), where t = t-statistic for a two-sided $P = .05$ with $n - p$ degrees of freedom, where n = the sample size in regression and p = the number of coefficients estimated (including the intercept). These values were then converted as above into ORs. As a sensitivity analysis, we re-ran the meta-analysis excluding studies with linear regression results.

Resultant ORs and 95% CIs were used to generate forest plots and compute pooled odds ratios for olfactory dysfunction using fixed effects models with individual studies weighted according to the inverse variance method. Corresponding I^2 tests evaluated whether variability of results between studies could be explained by chance alone or was driven in part by heterogeneity. Publication bias was assessed using funnel plots, separately for studies of current and former smokers. All analyses were conducted using the *metan* package in Stata Version 14.2²⁵.

RESULTS

We found 464 English papers in PubMed and 1018 in Web of Science; there were 1046 unique studies. These were reviewed on the basis of title or abstract, from which 993 studies were excluded because they were not pertinent. The remaining 53 papers were reviewed in

detail, and after evaluation using our modified Newcastle-Ottawa Scale, 11 studies were included in this review (Figure 1). A detailed description of our modified Scale scoring for each of these 11 studies is presented in the supplemental material (Table S1). Among these 11 papers, 2 were excluded from meta-analysis because the cohort they studied was also studied in another paper. Only 1 longitudinal study was found²⁶; this will be discussed separately.

Key cohort characteristics from all 11 papers are summarized in Table 2. Six studies were conducted in the United States, the remainder in China (1), Germany (3), and Denmark (1). Sample sizes ranged from 173–2,928, the mean age of participants ranged from 43–82 years, and the sex composition ranged from 13- to 100% female. Descriptions of each study cohort are also provided in Table 2. Cohort characteristics from our re-analysis of Pinto et al. (2014) are omitted here, as they are identical to those reported for the original paper.

Analytic methods and results from all 11 studies are summarized in Table 3. All studies used a validated, objective measure of odor identification, ranging from 5–40 items in length. For studies dichotomizing olfaction, the prevalence of dysfunction ranged from 3.8–24.5%. Only Pinto et al. (2014) used an objective measure of current smoking (serum cotinine) in addition to self-report. In no studies were detailed smoking parameters provided (e.g. cumulative pack-years smoked, current cigarettes per day, etc.), thus we were unable to consider how these factors may have differed between study cohorts and explained any observed heterogeneity in results. For statistical analysis, all studies used a form of multivariate regression with olfaction as the dependent variable, controlling for age and sex (Ranft et al. [2009] did not control for gender but their study cohort was women only). All but one study (10/11) controlled for at least one additional factor, most often education (4/11), cognition (3/11), and specific health characteristic(s) (7/11). Four studies used linear regression to evaluate the association of smoking with numerical score on an olfactory function test. These results were converted to ORs for olfactory dysfunction, a binary outcome, as described above (see Methods: Meta-Analysis). Original linear regression results and converted ORs for these studies are also presented in Table 3. The data from Pinto et al. (2014) were re-analyzed as described in the supplemental material; we present these results separately in Table 3 (“Present Study, 2016”).

Current Smokers

Data on the risk of olfactory dysfunction for current smokers compared to never smokers was available from 6 included papers and re-analysis of data from Pinto et al. (2014). These 7 studies included 11,771 subjects and a forest plot of a meta-analysis of extracted results is presented in Figure 2. 6/7 studies found current smokers to have higher odds of olfactory impairment compared to never smokers. This increase was significant in 3 of the 6 studies. 1 study found a negative association between smoking and olfaction that was non-significant²⁷. Of note, this was a cohort of elderly females only with only 3% of participants currently smoking. This is substantially lower than current smoking rates in the other cohorts studied here (10–28%), except one for which this data was unavailable²⁰. The low percentage of current smokers may also explain the wide confidence interval for this

estimate, reflecting a high degree of uncertainty and thus the smallest weight among the 7 studies.

When pooling data in meta-analysis, current smoking was associated with a significant 59% increased odds of olfactory dysfunction compared to never smoking (OR 1.59, 95% CI 1.37–1.85). There was minimal heterogeneity of results between studies ($I^2 = 11.8\%$, $P = 0.340$) despite substantial differences in cohort composition with respect to mean age (between 43–82 years) and sex composition (between 0–87% male) (Table 2). Further, there was no clear association between effect size for current smoking and study cohort age- or sex- composition.

Former Smokers

Data comparing former and never smokers was available in 5 studies as well as the re-analysis of data from Pinto et al. that included the addition of a former smoking category. Among these 6 studies, totaling 7,884 subjects, 4 found higher odds of olfactory impairment among former smokers compared to never smokers, however this increase was not significant in any study (Figure 3). Former smoking was not associated with increased odds of olfactory dysfunction compared to never smoking in meta-analysis (OR 1.05, 95% CI 0.91–1.21). There was no heterogeneity of results between studies ($I^2 = 0\%$, $P = 0.731$), despite similarly substantial differences in the age and sex composition of the study cohorts as with current smokers (Table 2).

Longitudinal Data

Only one longitudinal cohort study was found, a follow-up of a cross-sectional cohort included in our literature review. Schubert et al. (2014) found, in a 5-year follow-up that current and former smokers appeared to be more likely to experience a decline in olfactory function over time, compared to never smokers. These differences were, however, not significant. Of note, the effect size in current smokers (OR 1.68, 95% CI 0.84–3.38) was greater than that in former smokers (OR 1.46, 95% CI 0.81–2.63).

Secondary and Sensitivity Analyses

Meta-analysis of three studies demonstrated that ever smokers had significantly greater odds of olfactory dysfunction than never smokers (OR 1.19, 95% CI 1.02–1.40), although the magnitude of this association was far less than for current smokers (Supplemental Material, Figure S1).

Excluding data from the 4 studies that used linear regression and limiting results to studies using regular logistic regression resulted in similar findings and did not change any of our conclusions.

Funnel plots for both groups of studies are included in the Supplemental Material (Figures S2a, b) and demonstrate no overt publication bias, but some evidence of a lack of studies with larger standard errors and stronger smoking-olfaction findings, and a lack of studies with smaller standard errors and weaker findings. However, as the number of studies identified for both groups was below the threshold of 10 generally recommended for reliable

analysis of funnel plots²⁸, we are unable to draw any strong conclusions regarding publication bias.

DISCUSSION

We present here the first systematic review and meta-analysis of studies examining smoking and risk of impaired olfaction. These analyses demonstrate that current smokers are significantly more likely to suffer from olfactory dysfunction compared to never smokers. This finding is important to patients who smoke and to the clinicians caring for them. The effect size observed here, that current smokers are at approximately 60% increased risk of olfactory dysfunction, roughly corresponds with the effect size for men compared to women, one of the largest risk factors for olfactory dysfunction^{2,11,20,24}. The magnitude of this association also correlates to aging approximately 5–10 years, in terms of risk of impaired olfaction^{11,29,30}.

In contrast to current smoking, we did not find any increase in risk for former smokers in our meta-analysis, perhaps informing the mechanism by which smoking may impact olfaction. One such potential mechanism is squamous metaplasia, in which the normal pseudostratified columnar epithelium of the airways is *reversibly* replaced by squamous epithelium^{31,32} in response to insults from tobacco smoke. The olfactory mucosa (another columnar epithelia) of smokers has also been found to contain increased squamous metaplasia, compared to non-smokers³³. The clinical differences observed between current and former smokers may be a manifestation of the reversibility of metaplastic changes. Indeed, studies of respiratory mucosa of current and former smokers have found substantially greater metaplasia in current smokers³⁴ and have found that the degree of squamous metaplasia in smokers decreases within 6 months of cessation³⁵. Some studies have also linked tobacco smoke exposure to increased apoptosis in olfactory neurons³⁶. As the olfactory epithelium has high cell turnover, regenerating approximately every 60–90 days³⁷, it is possible that continued regeneration with smoking cessation allows restoration of the epithelium and, consequently, olfactory function.

Another potential explanation for these results is that smoking is associated with reversible sinonasal inflammation³⁸. Inflammation in the olfactory mucosa is associated with olfactory dysfunction and treatment of this is associated with improvement³⁹. Cessation of smoking may result in the resolution of acute or chronic inflammation, which would result in improved olfaction, consistent with the results of this study. The effect of smoke may also be indirect, leading to increased susceptibility to other insults that can damage the olfactory epithelium through similar inflammatory mechanisms, such as ambient air pollutants and heavy metals^{14,15}.

There is also evidence that smoking may impact olfaction through effects on central neural pathways directly involved in olfactory function. For example, smokers have been found to have significantly smaller olfactory bulb volumes compared to non-smokers⁴⁰. Notably, this study found no differences in olfactory function between the smokers and non-smokers, suggesting that morphologic changes may predate frank olfactory dysfunction. Similarly, current smokers' brains have been found to have significantly less gray matter volume in the

olfactory gyrus, a tissue associated with the primary olfactory cortex, compared to never smokers⁴¹. It is unclear to what extent these changes are directly associated with olfactory function and whether they are reversible. Importantly, odor identification tasks (used in all of the studies reviewed here) have a cognitive component⁴², thus the results observed here may be driven at least in part by neurotoxic effects of tobacco smoke on cognition⁴³ in addition to any direct effect on the peripheral olfactory system in the nose.

Our differing findings in comparing current and former smokers may also be due to exposure error resulting from the rather crude measures of exposure, which does not account for the number of pack-years smoked, a potentially more accurate measure of smoking exposure for studies of olfaction. Consistent with this, Frye et al. (1990) found a significant dose-response relationship between pack-years smoked and score on the UPSIT among current and former smokers. However, this study did not evaluate whether this explained their finding that current smokers, but not former smokers, were at increased risk of olfactory dysfunction.

More granular smoking data, such as pack years for ever smokers or cigarettes per day for current smokers would also allow for more robust analyses, such as dose-response relationships. Evidence for such an association in smoking and olfaction overall remains unclear. For example, Vennemann et al. (2008) found that, among current smokers, crude rates of olfactory dysfunction increased with increasing numbers of cigarettes smoked per day. In contrast, Siderowf et al. (2007) found a slight trend towards improved olfaction among former smokers with >10 pack-year history compared to never smokers but found a slight trend towards poorer olfaction for former smokers with 1–10 pack-year history compared to never smokers. Another potentially important factor among former smokers is time since quitting smoking, which we would also anticipate to potentially affect olfactory ability, as former smokers who have only recently quit may not yet have undergone repair or reversal of smoking-induced damage to the olfactory system. Indeed, Frye et al. (1990) found time since cessation to be significantly related to olfactory performance. Studies with this level of detail are particularly important given the body of evidence suggesting some reversibility of smoking-associated pathology. Of note, however, these analyses were not conducted prospectively, and olfactory improvement has not to our knowledge been evaluated as an outcome in any longitudinal studies of tobacco use cessation.

This search did identify one longitudinal study, which found current and former smokers to be at elevated risk of decline in olfactory performance, with a stronger association among current smokers²⁶. Our own prior longitudinal examination of olfactory decline also found no effect of smoking status⁴⁴. Although no effect size was presented in the paper (and thus, this study excluded from our meta-analysis), in a re-analysis of the data, current smoking (vs. non-current smoking) was found to have no association with change in score on a repeated olfactory function measure over 5 years ($P = 0.26$). Additional longitudinal studies are needed, with a focus on evaluating effects of smoking dose, timing, and cessation on change in olfactory function.

The studies discussed here have measured olfactory ability only through multi-item odor identification tasks. Future studies should consider the impact of smoking on identification

of specific odorants, with specific attention given to how closely these odorants overlap with tobacco smoke. Prior research has suggested that smokers may have particularly poor ability to detect overlapping odorants⁴⁵, perhaps due to de-sensitization. Research is also needed that includes assessment of olfaction through other domains (i.e., odor threshold and discrimination).

Although not evaluated here, environmental tobacco smoke (ETS, secondhand smoke) is another potential source of exposure. Two studies identified in this review evaluated ETS and olfaction: one found a non-significant increased risk of dysfunction in non-smokers exposed to high levels of ETS compared to those not exposed³⁰, while the other found no association²⁷. Others have shown that children not exposed to ETS at home out-perform exposed children on an olfactory test⁴⁶. Additional study is needed to synthesize the literature evaluating ETS and olfaction.

An important limitation to this review is that it largely identified only cross-sectional studies, with only one longitudinal analysis of changes in olfaction. As these are observational studies, they cannot define causal relationships between smoking and olfaction. For example, it is possible that individuals who smoke tend to be of lower socioeconomic status (SES), an independent risk factor for olfactory dysfunction and one that is difficult to adequately account for in population surveys¹¹. However, our meta-analysis showed generally consistent results between studies, several of which controlled for some component of SES. The reviewed studies also all controlled for age and sex, the two most important potential confounders affecting olfaction⁸. However, as odor identification has a cognitive component⁴², these effects could also be confounded by cognitive function. Only a minority of studies reviewed here controlled for cognition, and these relied on simple measures that are easy to conduct and useful in identifying dementia but insufficient to detect milder cognitive impairment⁴⁷. Future studies should incorporate more robust cognitive measures, especially when using an odor identification task.

Overall, given that effective behavioral and pharmacologic strategies exist for smoking cessation¹⁶, clinicians working with anosmic/hyposmic patients who smoke should consider the role that smoking may have played in their olfactory impairment and that patients may benefit significantly from cessation. Such recommendations are particularly important given that few effective treatments exist for a majority of patients with diminished smell. Smoking cessation will of course also be of substantial health and quality of life improvement beyond olfactory loss.

CONCLUSION

There is significant evidence that current smokers are at a higher risk of olfactory dysfunction than never smokers. In contrast, no such increase in risk appears to exist for former smokers, possibly an indication that the effects of smoking on olfaction are reversible. Future studies are needed to prospectively evaluate the impact of smoking cessation on improvement in olfaction. Clinicians treating patients with olfactory loss should advise patients of the potential impact of smoking and that quitting may be associated with improvements in sense of smell.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Summary of literature review.

Figure 2.

Forest plot of meta-analysis of current smokers. ES = effect size, the odds ratio of olfactory dysfunction for current smokers vs. never smokers.

Figure 3.

Forest plot of meta-analysis of former smokers. ES = effect size, the odds ratio of olfactory dysfunction for former smokers vs. never smokers.

Table 1.

Search terms.

Search terms and Databases		Group A terms	Group B terms
MeSH Terms	PubMed only	Smoking	Olfaction disorders
			Smell
			Olfactory nerve diseases
			Olfactory pathways
Keywords	PubMed and Web of Science		Olfactory nerve
		Smok [*]	Olfact [*]
			Smell
			“Odor identification” “Odor threshold” “Odor discrimination”

^{*} End-truncated search terms

Table 2.

Summary of cohorts from included studies.

Author, year	Cohort description	Country	N	Age range (mean)	% Male	NOS Score
Cross-Sectional						
Frye et al., 1990 ⁴⁸	Employees of a chemical manufacturing plant, tested as part of a study of chemical exposure on olfactory function.	United States	638	17–69 (43)	87	7/9
Liu et al., 1995 ²⁴	460 community members on Kinnmen island (off coast of China), tested as part of a dementia survey (those with dementia, stroke, or PD excluded). 50 visitors to an outpatient neurology clinic in Taipei, Taiwan.	China	510	50–92 (68)	47	7/9
Murphy et al., 2002 ⁴⁹	Beaver Dam Eye Study in 1988–90 was a population-based study of adults 43–84 years age in Beaver Dam, WI ⁵⁰ . Those surviving 5 years invited to participate in EHLS baseline study of sensory function, 1993–95. Data in this study from 5-year follow-up of EHLS, 1998–2000.	United States	2491	53–97 (69)	42	8/9
Siderowf et al., 2007 ⁵¹	First-degree relatives of patients with PD who were diagnosed at University of Pennsylvania (Philadelphia, PA) or the Institute for Neurodegenerative Disorders (New Haven, CT). Participants >50 years age or within 10 years of age of onset of PD in relative, excluding current smokers and those with any neurodegenerative disorder, history of nasal trauma, sinusitis, or known olfactory problem.	United States	173	31–87 (58)	31	7/9
Vennemann et al., 2008 ¹	DHS was a population study of adults 25–75 years age in Dortmund, Germany with a focus on studying the prevalence of headaches and other chronic conditions, 2003–4 ⁵² .	Germany	1277	25–75 (52)	47	8/9
Ranft et al., 2009 ²⁷	SALIA in 1985–94 was a population study of women 54–55 living in the Ruhr district and 2 nearby rural towns, Germany, focused on health effects of ambient air pollution. Data in this study from a 2007–08 follow-up.	Germany	377	68–79 (74)	0	7/9
Doty et al., 2011 ³⁰	Study included subjects from 2 separate nationwide elderly population cohorts. LSADT included twins 70+ years in 2001 and still in Denmark in 2005. The Danish 1905-Cohort 2005 survey included people born in 1905 and still alive in Denmark in 2005.	Denmark	1222	74 (82)	43	8/9
Schubert et al., 2012 ³⁰	BOSS cohort, a study of sensory function in adult children of EHLS cohort participants, 2005–08.	United States	2838	21–84 (49)	46	7/9
Khil et al., 2015 ²⁹	DHS was a population study of adults 25–75 years age in Dortmund, Germany with a focus on studying the prevalence of headaches and other chronic conditions, 2003–4 ⁵² .	Germany	1208	25–74 (52)	47	8/9
Present study, 2016	NSHAP cohort, a national population study of older adults age 57–85 across the United States, with a focus on social determinants of health, 2005–6.	United States	2928	57–85 (68)	49	9/9
Longitudinal						
Schubert et al., 2014 ²⁶	5-year follow-up of the BOSS cohort, a study of sensory function in adult children of EHLS cohort participants, 2010–13.	United States	2302	21–84 (49)	46	9/10

EHLS = Epidemiology of Hearing Loss Study; DHS = Dortmund Health Study; SALIA = Study on the Influence of air pollution on Lung function, Inflammation and Aging; LSADT = Longitudinal Study of Aging Danish Twins; BOSS = Beaver Dam Offspring Study; NSHAP = National Social Life, Health, and Aging Project; NOS = Newcastle-Ottawa Scale; PD = Parkinson's disease

Table 3.

Summary of results from included studies.

Author, year	Olfaction test (# of items)	Prevalence of olfactory dysfunction ^d	Regression method	Model covariates	Results, organized by smoking status: effect size (95% CI) ^a
Cross-Sectional					
<i>h</i> _{Frye et al., 1990⁴⁸}	UPSIT (40)	10.5% (in cohort of 731 participants, from which sample of 638 for this study was obtained ⁵³).	Logistic	Age, sex, education, workplace chemical exposure	<i>Current</i> : OR 1.9 (1.0, 3.8) <i>Former</i> : OR 0.7 (0.3, 1.5)
<i>h</i> _{Liu et al., 1995²⁴}	MODSIT (12)	N/A	Linear	Age, sex, education, cognition	<i>Ever</i> : -0.32 (-0.68, 0.04) Converted: OR 1.22 (0.98, 1.53)
<i>h</i> _{Murphy et al., 2002⁴⁹}	SDOIT (8)	24.5%	Logistic	Age, sex, nasal congestion or URI, stroke, epilepsy	<i>Current</i> : OR 1.93 (1.33, 2.81) <i>Former</i> : OR 1.05 (0.83, 1.33)
<i>h</i> _{Siderowf et al., 2007⁵¹}	UPSIT (40)	N/A	Linear	Age, sex, caffeine consumption	<i>Former</i> (>10 pack- <i>ys</i>): 1.1 (-1.2, 3.4) Converted: OR 0.72 (0.36, 1.43)
<i>h</i> _{Vennemann et al., 2008¹}	Sniffin' Sticks (12)	22.2%	Logistic	Age, sex, education, DM, MI, head trauma	<i>Current</i> : OR 1.71 (1.19, 2.47) <i>Former</i> : OR 1.01 (0.72, 1.43)
<i>h</i> _{Raafit et al., 2009²⁷}	Sniffin' Sticks (16)	N/A	Linear	Age, traffic exposure, ambient air pollution, urban/rural residence, ETS, indoor air pollution exposure, depression, respiratory disease, DM, hypertension, high cholesterol, MI, stroke, activity, obesity	<i>Current</i> : 0.8 (-0.8, 2.4) Converted: OR 0.57 (0.19, 1.75) <i>Former</i> : -0.2 (-0.9, 0.6) Converted: OR 1.15 (0.66, 1.87)
<i>h</i> _{Doty et al., 2011³⁰}	B-SIT (12)	N/A	Linear	Age, sex, cognition	<i>Current</i> : -0.66 (-1.01, -0.31) Converted: OR 1.65 (1.26, 2.15)
<i>h</i> _{Schubert et al., 2012³⁰}	SDOIT (8)	3.8%	Logistic	Age, sex	<i>Ever</i> : OR 1.11 (0.74, 1.87) <i>Current</i> (vs. Non-smokers with none/little ETS exposure): OR 1.64 (0.99, 2.72)
Pinto et al., 2014 ¹¹	Sniffin' Sticks (5)	N/A	Ordinal logistic	Age, sex, race, education, cognition, household assets, self-rated health, comorbidity, depressive and anxiety symptoms, stressors, alcohol	<i>Current</i> (vs Non-current): OR 0.94 (0.75, 1.19)
Khil et al., 2015 ²⁹	Sniffin' Sticks (12)	21.5%	Logistic	Age, sex, social status, diabetes, alcohol	<i>Current</i> (vs Non-current): OR 1.63 (1.15, 2.32)
<i>h</i> _{Present study, 2016}	Sniffin' Sticks (5)	22.0%	Logistic	Age, sex, race, education, cognition, comorbidity	<i>Ever</i> : OR 1.18 (0.91, 1.54) <i>Current</i> : OR 1.24 (0.88, 1.74) <i>Former</i> : OR 1.16 (0.89, 1.51)
Longitudinal					
Schubert et al., 2014 ²⁶	SDOIT (8)	1.7% (5-year incidence of olfactory dysfunction)	Logistic	Age, sex, hypertension, BMI, alcohol, atherosclerosis	<i>Current</i> : OR ^c 1.68 (0.84, 3.38) <i>Former</i> : OR ^c 1.46 (0.81, 2.63)

^aComparison group is never smokers unless otherwise stated;

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q Study included in meta-analysis;

o Odds ratio for decline in olfactory function from baseline to follow-up;

p For studies treating olfactory function as binary (logistic regression)

UPSIT = University of Pennsylvania Smell Identification Test; MODSIT = Modular Smell Identification Test; SDOIT = San Diego Odor Identification Test; B-SIT = Brief Smell Identification Test; URI = upper respiratory tract infection; DM = diabetes mellitus; MI = myocardial infarction; ETS = environmental (secondhand) tobacco smoke; BMI = body mass