

Occupational exposure to diesel exhaust and head and neck cancer: a systematic review and meta-analysis of cohort studies

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Exposure to diesel exhaust (DE) and other fossil fuels in the workplace can cause several health effects including cancer. We conducted a systematic review and meta-analysis of cohort studies examining the association between occupational DE exposure and the risk of head and neck cancer (HNC), including cancer of the oral cavity, pharynx and larynx. We included cohort studies mentioned in the Monograph of the International Agency for Research on Cancer, 2014, on DE. Forest plots of relative risk (RR) were constructed for HNC overall and its anatomical subtypes. A random-effects model was used to address heterogeneity between studies. Fifteen articles were included after removing duplicates and irrelevant reports. The summary RR for DE exposure was 1.08 [95% confidence interval (CI) = 1.01–1.17, P heterogeneity = <0.001] for HNC overall, 0.98 (95% CI = 0.87–1.11) for oral cavity, 1.05 (95% CI = 0.77–1.43) for pharyngeal, 1.15 (95% CI = 0.96–1.38) for oral cavity and pharyngeal combined, and 1.13 (95% CI = 1.03–1.24) for laryngeal cancer. There were elevated RRs for incidence studies of HNC (RR = 1.13; 95% CI = 1.05–1.22,

$P = 0.001$), European studies (RR = 1.13; 95% CI = 1.05–1.23, $P = 0.001$), and female studies (RR = 1.77; 95% CI = 1.31–2.39, $P = 0.003$). Our study suggested an association between occupational DE exposure and the risk of HNC, particularly laryngeal cancer. Although residual confounding cannot be ruled out, our results support the importance of controlling occupational DE exposure. *European Journal of Cancer Prevention* 33: 425–432 Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

In 2020, an estimated number of 538 000 individuals developed head and neck cancer (HNC), including the lip, oral cavity, pharynx, and larynx cancer, and 444 000 died from this disease (Sung *et al.*, 2021). Tobacco smoking and use of smokeless tobacco products such as chewing betel quid, opium use, alcohol drinking, consumption of nitrosamine-rich foods, mate drinking, and infection with human papillomavirus (HPV) are the most important risk factors of HNC globally (IARC, 2014; Singh *et al.*, 2021; Heller *et al.*, 2023). Besides them, some occupational exposures may affect HNC incidence risk, including formaldehyde, asbestos, heavy metals, and welding fumes (Shangina *et al.*, 2006; Lin *et al.*, 2022).

Exposure to exhaust fumes from diesel engines and other fossil fuels can cause several severe health issues such

as lung and cardiovascular diseases. In particular, diesel exhaust (DE) has been classified as carcinogen by the International Agency for Research on Cancer (IARC), because of sufficient evidence of an association with lung cancer (IARC, 2014). DE comprises a gaseous and a particulate phase containing many chemicals including carbon dioxide, carbon monoxide (CO), nitric oxide (NO), nitrogen dioxide (NO₂), sulfur oxides (SO₂), organic materials, and hydrocarbons, such as polycyclic aromatic hydrocarbons (PAHs), and in particular nitro-PAHs. For decades, diesel-fueled engines have been used in various industrial settings including mining, public vehicles, sailing, construction, operation of heavy equipment, and farming, in addition to the operation of private vehicles. Therefore, people may be exposed to DE on a daily basis at the workplace, in their environment, and at home (Shangina *et al.*, 2006).

Different metabolites present in DE may cause genotoxic and non-genotoxic effects, acting as a potential carcinogen on human cells (Latifovic *et al.*, 2015; Zhou *et al.*, 2015). Previous research and review studies reported associations between DE exposure and cancer risk

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particularly respiratory tract cancer (Gamble *et al.*, 2012; Boffetta, 2014; Sun *et al.*, 2014; Möhner and Wendt, 2017), but evidence of the effect on HNC remains unclear (Muscat and Wynder, 1995; Boffetta *et al.*, 2001). This systematic review and meta-analysis aimed at investigating the association between occupational exposure to DE and the risk of HNC cancers, including oral cavity, pharyngeal, and laryngeal cancer.

Methods

Search strategy and selection criteria

Our study protocol was registered in the PROSPERO database No. CRD42022352729; we followed the STROBE guidelines to conduct this systematic review and meta-analysis (von Elm *et al.*, 2008).

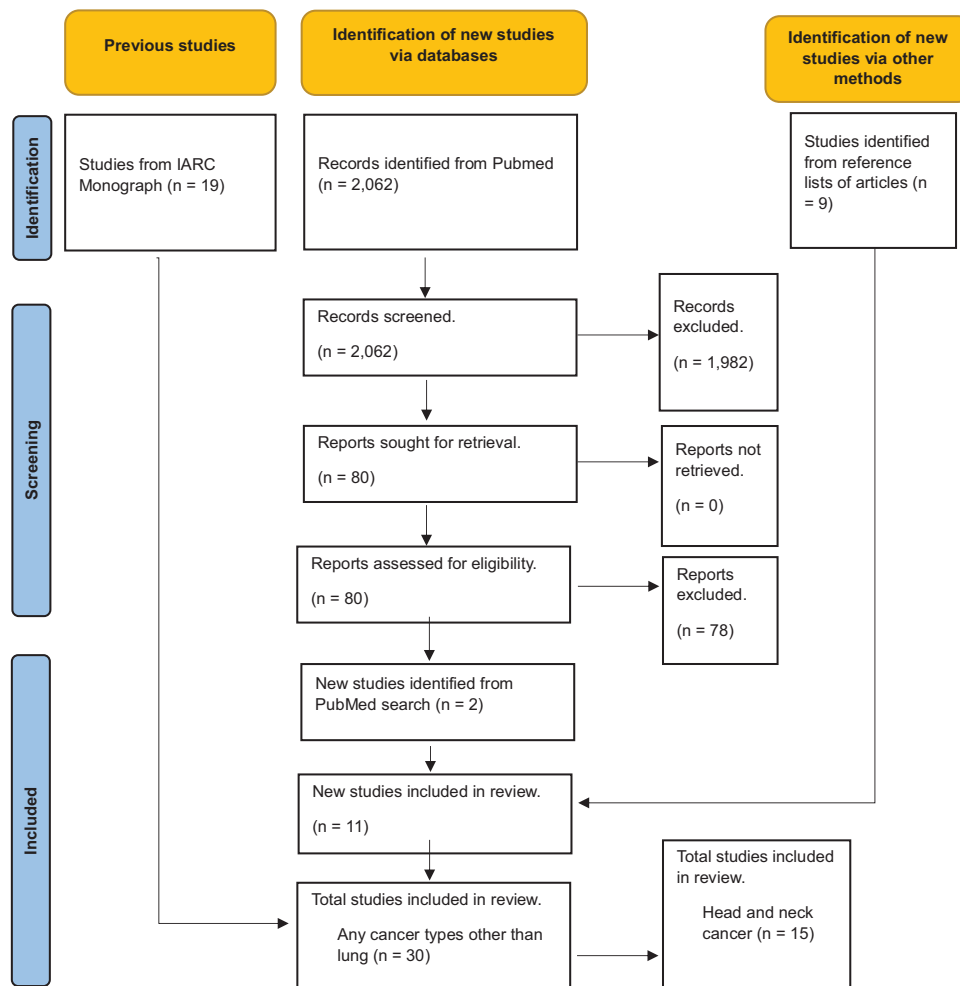
Figure 1 shows the flow diagram of the literature search and study selection process. First, we included all cohort studies which were mentioned in the most recent IARC Monograph on DE published in 2014. Next, we conducted a search in

the PubMed database for studies reported after that publication. Two authors (GC and FT) performed independently the search in online database. Searches were undertaken for English-language peer-reviewed publications published after 2013 on the association of occupational exposure to DE and risk (incidence and mortality) of any type of cancer other than lung. The search strategy was designed using MeSH terms like (diesel OR miner OR garage OR railway OR ((truck OR bus) OR (heavy equipment OR docker)) AND (cancer OR neoplasm). Finally, we reviewed studies included in the list of references of the publications identified in the two preceding steps. In case of multiple reports based on the same population, we included only the most informative one. This strategy led to the identification of 30 independent cohort studies (Fig. 1).

Inclusion criteria and data extraction

We extracted data on type of cohort study (retrospective, prospective), publication year, country, outcome

Fig. 1



Selection of studies for inclusion in the meta-analysis of Head and neck cancer in workers exposed to diesel exhaust.

(mortality, incidence), type of industry of occupation entailing exposure to DE, sample size, number of subjects and person-years, number of cancer cases, type of cancer (ICDO code), effect size measure, including odds ratio, risk ratio, rate ratio, standardized mortality ratio, or standardized incidence ratio, here thereafter referred to as relative risk (RR), and their 95% confidence interval (CI). Results for subgroups of subjects (e.g. by sex, type of job, and level or duration of exposure) were also abstracted.

Exclusion criteria

We excluded studies with no reference to DE, those with exposure other than occupational, those without data on cancers other than lung cancer, and those with a design other than cohort or case-control nested in a cohort.

Quality assessment

Quality assessment of the included articles was performed using the CAPS checklist (CASP, 2018). The quality assessment was conducted by two authors (GC and FT), and we used the mean of the scores and in the event of any major discrepancy, a third author (PB) intervened. We generated a variable for CASP assessment, where studies which scored <10 corresponded to low quality and those which scored ≥ 10 were considered of high quality.

Statistical analysis

We examined the association between DE exposure and HNC cancer based on the effect size measurements and the corresponding 95% CIs of each study. Because of the rare disease assumption, the different risk estimators are assumed to approximate the RRs (Greenland S, 1987). Heterogeneity (het) among studies was evaluated by the Q test, based on the variation across studies rather than within studies, and the I² statistic (the percentage of variance attributable to study heterogeneity) (Higgins JPT and Thompson SG, 2002). Random-effect models were used to account for heterogeneity in design characteristics of the cohorts included in the meta-analysis (DerSimonian R and Laird N, 1986).

We performed a meta-analysis including all non-overlapping studies and then we conducted stratified analysis by site within the HN (oral cavity, pharynx, oral cavity and pharynx combined, larynx) outcome (incidence and mortality), gender (>90% male, >90% female, mixed/unspecified), job or industry type (railroad worker, engine operator, highway maintenance, garage worker, truck driver, docker, workers exposed to DE across multiple jobs and industries), geographic region (Europe and North America) and publication year (before 2000, 2000 and later). In addition, publication bias was examined by creating a funnel plot and regression asymmetry test (Egger *et al.*, 1997). All analyses were completed using the STATA version 14.0 (Stata, College Station, TX, USA).

Results

A total of 30 cohort studies were identified (Fig. 1), of which 15 reported results on HNCs and were included in this review and meta-analysis. Details on these studies were provided in Table 1. These studies included a total of 38 different risk estimates, including seven risk estimates for cancer of the oral cavity, seven for pharyngeal cancer, 10 for oral and pharyngeal cancers combined, 13 for laryngeal cancer, and one for HNC combined (the latter study was not included in the meta-analysis).

The findings of the meta-analysis revealed an association between ever-occupational exposure to DE and overall HNC (RR = 1.08, 95% CI = 1.01–1.17; I² = 54.1%, p-het = <0.001). Stratification analysis according to the sites within the head and neck showed an association for laryngeal cancer (RR = 1.13 95% CI = 1.03–1.24; I² = 21.9%, p-het=0.22) whereas the results for the other sites did not reach the level of statistical significance (Fig. 2). Publication bias was excluded through the asymmetry test ($P = 0.74$) and the examination of the funnel plot (Fig. 3).

Results of stratified analyses for overall HNC according to selected characteristics are reported in Table 2. When restricting the analysis of incidence of HNC (31 risk estimates), the summary RR was 1.13 (95% CI = 1.05–1.22). Mortality results were based on 7 risk estimates (RR = 0.85, 95% CI = 0.73–0.98). The results of these two analyses were different ($P = 0.001$). A difference was also identified in the stratification by gender (RR = 1.77; 95% CI 1.31–2.39 among women vs. RR = 1.05; 95% CI = 0.93–1.13 among both gender vs. RR = 1.19; 95% CI = 0.99–1.43 among men; $P = 0.003$). When stratified by geographical area, the meta-analysis of studies from North America yielded different results than that of European studies (respectively, RR = 0.85, 95% CI = 0.73–0.99; RR = 1.13, 95% CI = 1.05–1.23; $P = 0.001$). There was no difference between industry types ($P = 0.53$), year of publication ($P = 0.72$), or quality score ($P = 0.19$).

Results of the meta-analyses stratified by anatomical subsites and study characteristics are reported in Supplementary Table 1, Supplemental digital content 1, <http://links.lww.com/EJCP/A449>. The risk of oral cavity disease was found to be higher among truck drivers (RR = 1.60, 95% CI = 1.03–2.79), but the test for heterogeneity was NS when compared with other job/industries ($P = 0.06$). Also, we identified a borderline difference between genders in the analysis of laryngeal cancer ($P = 0.049$). Results on level or duration of DE exposure were too sparse to allow a meta-analysis.

Discussion

Our meta-analysis identified an association between occupational DE exposure cancer of the head and

Table 1 Selected characteristics of the studies included in the review and meta-analysis

References	Cancer type	Country	Cohort type	Years of followup	N participants	Persons years	Industry, occupation	N cases	Factors adjusted for other than age, gender, race, calendar period
Howe <i>et al.</i> , 1983	Oral cavity and pharynx, larynx	Canada	Prospective	1965–1977	43 826	290 186	Railroad workers	Oral cavity and pharynx = 71; larynx = 49	
Gubéran <i>et al.</i> , 1992	Oral cavity and pharynx, larynx	Switzerland	Prospective	1949–1970	198 667	N/A	Truck drivers	Oral cavity and pharynx = 27; larynx = 9	
Järholm and Silverman, 2003 ^b	Larynx	Sweden	Prospective	1971–1993	14 364	217 331	Engine operators	Larynx = 9	
					6364	97 930	Truck drivers	Larynx = 7	
Wong <i>et al.</i> , 1985	Oral cavity and pharynx, larynx	USA	Prospective		34 156	372 525.6	Railroad workers	Oral cavity and pharynx = 23; larynx = 10	
Van Den Eeden and Friedman, 1993	Oral cavity, pharynx, larynx	USA	Retrospective	1964–1988	160 230	N/A	DE exposure across jobs	Oral cavity = 107; pharynx = 158; larynx = 144	Education, tobacco smoking
Boffetta <i>et al.</i> , 2001 ^a	Oral cavity and pharynx, larynx	Sweden	Prospective	1971	54 109	Men:7 400 000 Women: 240 000	DE exposure across jobs	Oral cavity and pharynx = 1764; larynx = 735	
Gustavsson <i>et al.</i> , 1990	Larynx	Sweden	Prospective		695	N/A	Garage workers	Larynx = 1	
Merlo <i>et al.</i> , 2010	Larynx	Italy	Prospective	1949	9267	230 009	Garage workers	Larynx = 24	
Soll-Johanning <i>et al.</i> , 1998	Oral cavity, pharynx, larynx	Denmark	Retrospective+prospective	1900	18 174	386 395	Truck drivers	Oral cavity = 16; pharynx = 22; larynx = 39	
Birdsey <i>et al.</i> , 2010	Pharynx	USA	Retrospective	1989	156 241	N/A	Truck drivers	Pharynx = 12	
Purdue <i>et al.</i> , 2006 ^b	Head and neck, oral cavity, pharynx	Sweden	Prospective	1971–1993	307 799	6 471 211	DE exposure across jobs	Head and neck = 91; oral cavity = 29; pharynx = 17	Tobacco smoking
Nokso-Koivisto and Pukkala, 1994	Oral cavity and pharynx	Finland	Retrospective	1953	8391	N/A	Railroad workers	Oral cavity = 17	
Tarvainen <i>et al.</i> , 2008	Oral cavity and pharynx	Finland	Prospective	1971–1995	725 868 males, 825 528 females	46.8 millions	Railroad workers, dockers	Oral cavity = 121	
Bender <i>et al.</i> , 1989	Oral cavity and pharynx	USA	Prospective	1945	4849	N/A	Highway workers	Oral cavity = 7	
Pukkala <i>et al.</i> , 2009 ^a	Tongue, oral cavity, pharynx, larynx	Denmark, Finland, Iceland, Norway, Sweden	Prospective	1961–2006	Men: 7 447 726 women: 7 454 847	Men: 184 934 940 Women: 199 504 026	Engine operators	Tongue = 111; oral cavity = 153; pharynx = 203; larynx = 439	

^aLimited overlap between references 14 and 34.

^bLimited overlap between references 23 and 30.

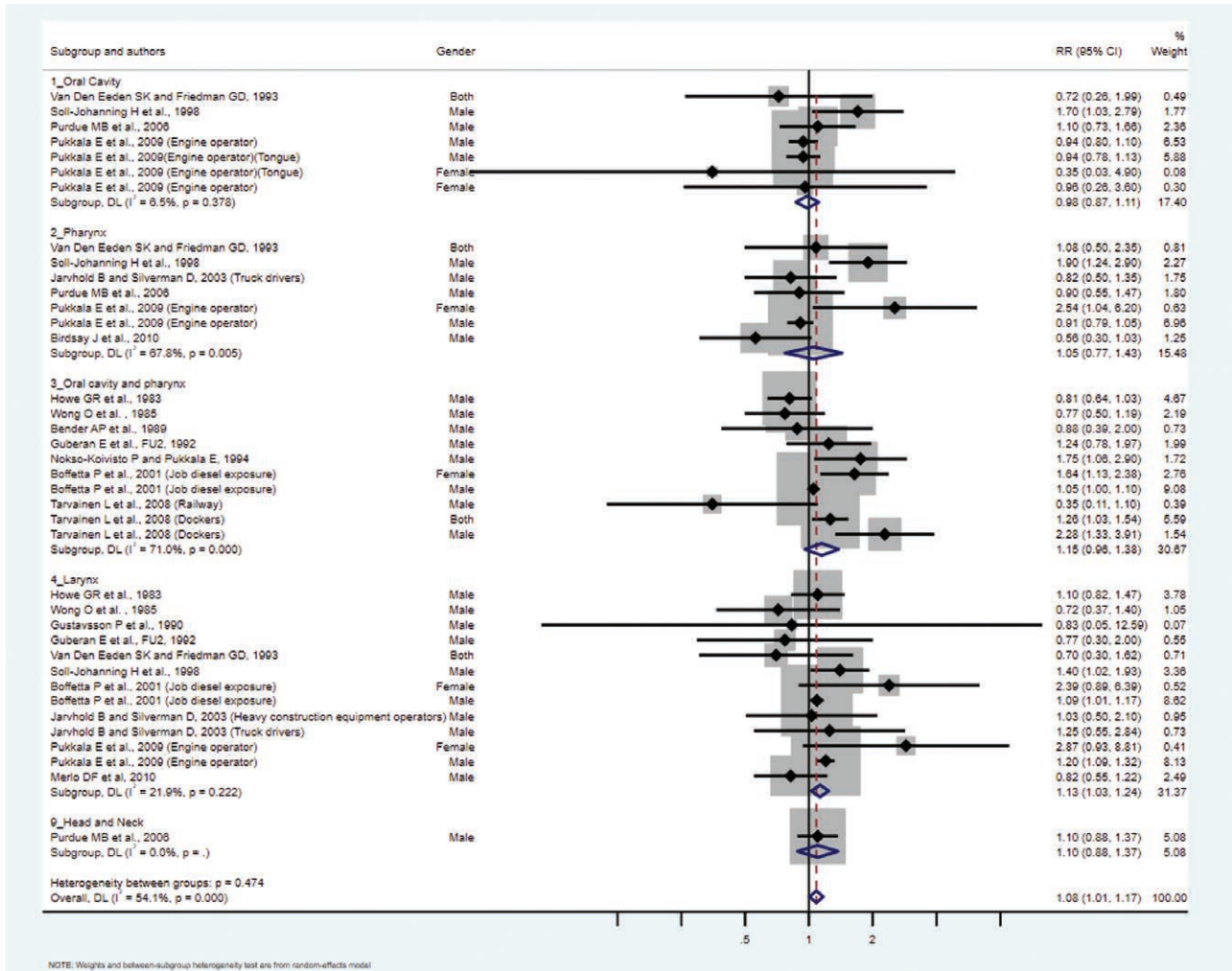
neck, and specifically the larynx, while no such association was identified for oral cavity and pharyngeal cancers.

In stratified analyses, a positive association was detected when considering HNC incidence, but not mortality; among studies from Europe, but not North America; and

in studies including women but not in studies including men.

In 2012, the IARC classified DE as carcinogenic to humans (IARC, 2014; Silverman DT, 2018), based on the evidence on risk of lung cancer. The evidence for other neoplasms, including digestive system cancers, urothelial

Fig. 2



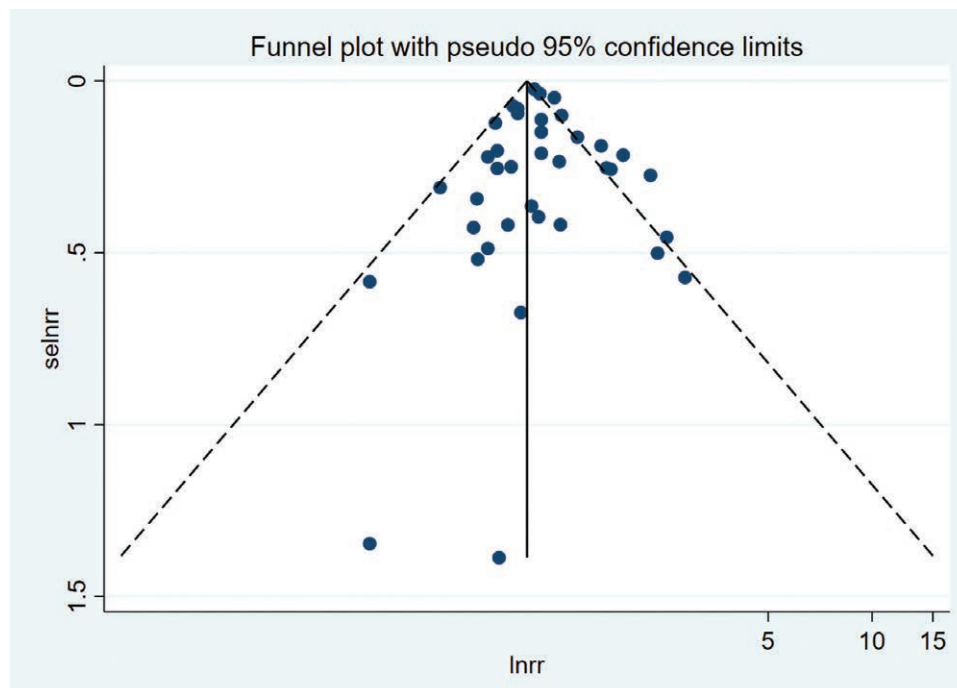
Forest plot (random-effects model) quantifying the association between DE occupational exposure and HNC stratified by anatomical subtypes. List of references included (Howe *et al.*, 1983; Gustavsson *et al.*, 1990, Higgins and Thompson, 2002; Järholm and Silverman, 2003; Merlo *et al.*, 2010; IARC, 2014; Jiang *et al.*, 2014; Latifovic *et al.*, 2015; Mazurek and England, 2016; Haldorsen *et al.*, 2017; Awan *et al.*, 2018; Kwak *et al.*, 2022; Lin *et al.*, 2022; Long and Carlsten, 2022; Heller *et al.*, 2023).

cancer, and HNC in particular laryngeal cancer was considered limited or inadequate (IARC, 2014).

There are relatively few studies and sparse results that specifically focus on DE exposure and risk of HNC, which justified our meta-analysis. Next to the cohort studies, whose results are reported in the present meta-analysis, some case-control studies can be mentioned, such as the one conducted in Turkey, where DE exposure was not associated with larynx cancer (Elci and Akpınar-Elci, 2009). Another case-control study reported no association between jobs that entail exposure to DE, such as automobile mechanics, and the risk of laryngeal cancer; these results may be explained by recall bias or other sources of bias (Muscat and Wynder, 1995).

In light of previous studies and results, it is indeed particularly important to consider other critical confounders relating to HNC, including tobacco smoking and use of smokeless tobacco (snuff and chewing tobacco), alcohol consumption, and HPV infection, the latter mainly for oropharyngeal cancer (Dhull *et al.*, 2018; Gormley *et al.*, 2022). Furthermore, other occupational factors may have introduced confounding, asbestos in particular. It is likely that asbestos was present in many of the workplaces investigated, and in the years when the cohort studies were conducted. In most of the studies included in our review, it was not possible to adjust for potential occupational and non-occupational confounders. Haldorsen *et al.* reported that workplace exposures contributed to cancers related to tobacco and alcohol, such as HNCs, may affect the results in relation to occupational risk factors

Fig. 3



Funnel plot with 95% confidence interval.

(Haldorsen *et al.*, 2017). In addition, unadjusted risk estimates may be more biased than those from studies which included the important cofounders as adjustments (Siemiatycki *et al.*, 1988; Beaumont *et al.*, 1992).

Several elements may support the causal interpretation of the association we found between DE exposure and HNC, particularly laryngeal cancer. Epidemiological and mechanistic studies suggested DE might cause carcinogenesis to operate through mechanisms similar to those of tobacco smoke (Boffetta *et al.*, 2001). According to previous epidemiological and experimental studies, different metals and organic chemicals present in DE such as chromium, nickel, PAHs, and volatile organic chemicals, can contribute to carcinogenesis through various mechanisms, including oxidative stress, chronic systematic inflammation, alteration of gene expression, and direct DNA damage (Pourazar *et al.*, 2005; Xu *et al.*, 2013; Jiang *et al.*, 2014; Douki *et al.*, 2018).

Some heterogeneity was observed between the subsite, with a stronger association for laryngeal cancer and no association for oral cancer. These differences might reflect the amount of DE reaching each organ, which would support a causal interpretation of the results. The established causal relationship with lung cancer also supports our findings on cancer of the larynx, as the organs are proximal and share other risk factors, such as asbestos, for which there is strong evidence for both laryngeal (Peng *et al.*, 2016; Ferster *et al.*, 2017) and lung

cancer (Kwak *et al.*, 2022; Curiel-García *et al.*, 2023) while the evidence for oral and pharyngeal cancer is weaker (Paget-Bailly *et al.*, 2012; Offermans *et al.*, 2014; Awan *et al.*, 2018).

Results of this analysis stratified by quality score showed an association between DE exposure and HNC in high-quality studies, thus supporting the overall findings of the meta-analysis. Previous reports showed that the risk of HNC, particularly laryngeal cancer, is higher in men compared to women (Long and Carlsten, 2022). This is because of the high prevalence of key risk factors like tobacco smoking and alcohol drinking among this group (Freedman *et al.*, 2007). However, in our meta-analysis, we found an association between DE exposure and HNC cancer among women despite the small number of studies. The reasons that can explain these results include: (i) the general prevalence of tobacco smoking and alcohol drinking among women is lower, so these factors may have imperceptible effect on the results, (ii) women working in locations exposed to DE are more likely to be exposed to other serious risk factors related to these cancer types in comparison to women without jobs or in other job groups (Syamlal *et al.*, 2015; Mazurek and England, 2016).

Results of studies from Europe and North America were heterogeneous, with a risk suggested in the first but not in the second group. This may be interpreted as reflecting a temporal trend in DE exposure, as American studies

Table 2 Results of the meta-analyses on head and neck cancer stratified by outcome, region, gender, industry type year of publication and quality score

Characteristic	N risk estimates	RR, 95% CI	Test of heterogeneity across strata, <i>P</i> -value	
Head and neck cancer				
Outcome				
Incidence	31	1.13 (1.05–1.22)	0.001	
Mortality	7	0.85 (0.73–0.98)		
Region				
North America	9	0.85 (0.73–0.99)	0.001	
Europe	29	1.13 (1.05–1.23)		
Gender				
Male	28	1.05 (0.93–1.13)	0.003	
Female	6	1.77 (1.31–2.39)		
Both	4	1.19 (0.99–1.43)		
Industry type				
Railroad worker	4	0.99 (0.67–1.48)	0.525	
Engine operator	11	1.00 (0.86–1.16)		
Highways Job	1	0.88 (0.38–2.00)		
Garage worker	2	0.82 (0.55–1.21)		
Truck driver	8	1.18 (0.89–1.57)		
DE exposure across multiple jobs/industries	11	1.07 (1.01–1.14)		
Dockers	2	1.60 (0.90–2.83)		
Year of publication				
<2000	15	1.11 (0.92–1.34)		0.724
≥2000	23	1.07 (0.99–1.16)		
Quality score				
Low quality	7	1.10 (0.93–1.29)	0.843	
High quality	31	1.08 (1.00–1.17)		

CI, confidence interval; RR, relative risk.

are more recent than European studies, and therefore reflecting different technologies, enhanced protective guidelines to control exposure doses (WHO, 2021), and new healthcare facilities for workers.

Additionally, we found significant differences in outcomes favoring HNC incidence. This may be due to (i) the time difference in exposure to DE before and after diagnosis, (ii) routine checkup and screening programs for workers, and (iii) workers with HNC cancer might have a better prognosis than other patients because of better access to care due to company-based insurance.

Our study has several strengths. To our knowledge, this study is the first systematic review and meta-analysis on the association between occupational DE exposure and risk of HNC, including oral, pharyngeal and laryngeal cancer. We focused on cohort studies, which represent high-quality source of data, and occupational circumstances with high probability and level of DE exposure, in order to enhance the sensitivity and specificity of our results. The systematic review and meta-analysis was conducted according to standardized criteria. We provided several interesting information through stratified analyses, including an assessment of the quality of our data.

An important limitation of our review is the relatively small number of available studies, thus limiting the statistical power of stratified analyses. Moreover, it is important to point out that the lack of adjustment for major risk

factors for HNC – smoking, smokeless tobacco, alcohol drinking, HPV – in the studies included in the meta-analysis prevented us from making conclusions based on the associations we observed. Similarly, despite we focused on studies conducted in the workplace, we could not collect information on occupational risk factors other than DE exposure, which may have caused residual confounding.

In future studies, the influence of occupational DE exposure on HNC should be explored considering the industry type, and gender differences. This is especially true for less studied geographical regions, namely those outside of Europe and North America.

Conclusion

In conclusion, we identified a mild association between occupational DE exposure and risk of HNC, and in particular with laryngeal cancer. no specific association was observed with oral and pharyngeal cancer.

According to that, the implementation of personal protective equipment and guidelines to manage cancer hazards from occupational DE exposure remains an important goal. However, because of the lack of adjustments for important confounders such as smoking, conclusive results were lacking as well and needed a more cautious interpretation.

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The study was conducted with internal resources of the participating institutions.

PB and GC conceived and designed the study; GC and FT selected the studies and extracted the data, with assistance by PB; MSS and PB conducted the statistical analysis; MSS drafted the manuscript; GC and PB provided substantial comments to the manuscript.

Conflicts of interest

PB acted as expert in litigation involving diesel exhaust exposure and risk of head and neck cancer, unrelated to the present work. For the remaining authors, there are no conflicts of interest.

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