La Medicina del Lavoro

Reviews, Commentaries, Perspectives

Med. Lav. 2025; 116 (1): 16357
DOI: 10.23749/mdl.v116i1.16357

Occupational Diesel Exposure and Brain Tumors: A Systematic Review and Meta-Analysis

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Keywords: Occupation; Diesel; Brain Tumor; Central Nervous System Cancers; Meta-Analysis

Summary

Diesel exhaust (DE) is recognized as a carcinogen for the lungs, although evidence linking it to adult brain tumors is limited. We aimed to systematically review the evidence regarding the association between occupational DE exposure and adult brain and other central nervous system (CNS) tumors. A systematic literature review was conducted to identify cohort studies on occupational DE exposure and the risk of adult cancers other than lung cancer. We meta-analyzed relative risks (RRs) and 95% confidence intervals (CIs) for brain or CNS tumors using the DerSimonian and Laird random-effects model. Fourteen studies were included in the meta-analysis. The results showed no increased risk of brain or CNS tumors among workers exposed to DE (RR: 0.99; 95% CI: 0.91, 1.07). Findings were consistent when analyzing studies based on incidence (RR: 0.96; 95% CI: 0.90, 1.03; six studies) and mortality (RR: 1.09; 95% CI: 0.87, 1.37; nine studies) separately, as well as in subgroup analyses based on sex, publication year, geographic region, and study quality score. No evidence of publication bias was found (p=0.244). The findings of our meta-analysis suggest that occupational DE exposure is not associated with adult brain or CNS tumors. Given the limitations of the included studies, these results should be interpreted with caution.

1. Introduction

Brain and other central nervous system (CNS) tumors in adults currently rank as the nineteenth and twelfth most common types of cancer and causes of cancer death worldwide, respectively. It has been suggested that their impact on the global population, both in terms of incidence and mortality, has been increasing in recent decades and is exceptionally high in high-income countries [2].

Various potentially relevant environmental and occupational risk factors for brain and CNS tumors, including diesel exhaust (DE), have been investigated over time. Indeed, among suspected or confirmed carcinogens that can be found in DE, polycyclic aromatic hydrocarbons, nitroarenes, and 3-nitrobenzathrone are also found [3–5]. DE is also categorized as a Group 1 carcinogen, according to the International Agency for Research on Cancer (IARC), based on sufficient human evidence for lung cancer [5]. Parental occupational DE exposure might increase the risk of childhood brain and other CNS cancers, [6–8] possibly through key pollutants such as polycyclic aromatic hydrocarbons (PAHs) [6, 9]. PAHs, in particular, have also been associated with brain cortical thinning among adults, [10]

Received 17.09.2024 – Accepted 10.01.2025
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which would suggest that they can cross the blood-brain barrier among adults too. Furthermore, DE exposure has been shown to impair functional brain connectivity in adults acutely, [11] similarly confirming the ability of DE particles and their compounds to reach brain cells through the bloodstream in this population group. Also, DE exposure may be correlated with chronic nervous inflammation and oxidative stress [12, 13]. Hence, if the association between parental occupational DE exposure and childhood brain cancer risk is causal, a similar association could be expected between exposure to DE and brain tumors among adults. However, no previous systematic review evaluated the risk of brain and CNS tumors among adult workers exposed to DE, hence hampering the interpretation of available literature. Thus, we aimed to summarize the evidence from cohort studies on this potential association.

2. Methods

We conducted a systematic review according to Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) guidelines [14] and reported it in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. The protocol of the review was registered in PROSPERO (CRD42022352729).

We retained cohort and nested case-control studies from last IARC Monograph on DE. [5] Additionally, we searched reference lists of the studies included in IARC Monograph, and conducted a search in Pubmed for studies on the association between occupational DE exposure and cancer, published after IARC Monograph (from 2012 onwards). We developed the search strategy according to the Patients, Exposure, Comparator, Outcomes, Study design (PECOS) framework, [14] as follows:

- Population (P): workers in multiple industrial settings;
- Exposure (E): occupational DE exposure;
- Comparator (C): individuals not exposed or with the lowest exposure level to diesel;
- Outcomes (O): incidence or mortality of cancer types other than lung cancer;
- Study design (S): industry-based cohort and nested case-control analysis.

Hence, we conducted the search using the following string: *(diesel OR miner OR garage OR railway OR ((truck OR bus) AND driver) OR (heavy equipment OR docker)) AND (cancer OR neoplasm)*. The search was first conducted in June 2021 and then updated in November 2024.

Two researchers independently evaluated titles, abstracts, and, subsequently, full texts of identified articles. Reference lists of included articles were also screened to identify additional studies. Disagreements were solved by discussion.

The present systematic review is part of a larger project that includes all cancer types other than lung cancer [16]. Thus, during the phases of the study selection process, inclusion criteria were as follows: (i) peer-reviewed studies evaluating the association between occupational DE exposure and incidence or mortality of any cancer types other than lung, (ii) cohort (including nested case-control) design, (iii) studies reporting relative measures of association, such as relative risk (RR), hazard ratio, standardized mortality ratio, and standardized incidence ratio, or reporting sufficient data for their computation.

Exclusion criteria were: (i) case-control studies not nested within a cohort, (ii) cross-sectional and descriptive studies, (iii) systematic reviews or meta-analyses, (iv) conference abstracts, theses, letters, commentaries, book chapters, (v) studies not focused on occupational exposures, (vi) studies not mentioning DE exposure, (vii) studies not in English. Whenever multiple articles referred to the same study population, we included the most recent update or the one with the highest number of cases in the review. If study populations overlapped by less than 10% across different studies, we considered them independent.

The following information was independently extracted by two researchers from included studies: author details, publication year, country, study period, type of cohort (retrospective, prospective), type of reference (internal, external), type of workers, person-years of observation time, sample size,

participants' sex, outcome (incidence, mortality), type of cancer and International Classification of Diseases (ICD) code, number of cases, and main results, including adjustment factors.

Hence, the present meta-analysis retained studies on adult brain and other CNS tumors, which are the focus of this report. Studies on childhood brain tumors were excluded because of the differences in molecular and clinical characteristics between the two groups of neoplasms.

Two researchers independently evaluated study quality using a modified Critical Appraisal Skills Programme (CASP) checklist for cohort studies [17]. The modified scale includes three sections: 'Are the study's results valid?' (6 items), 'What are the results?' (2 items), and 'Will the results help locally?' (3 items). The scale has 11 items, and the total score ranged between 0 and 14 (Table S1).

We considered all relative measures of association described above as approximations of RRs. Hence, we estimated pooled RRs and 95% Confidence Intervals (CIs) using the DerSimonian-Laird random-effects model [18] and evaluated statistical heterogeneity using the I^2 statistic. [19, 20]. We performed the analysis by combining data on both incidence and mortality (including incidence for studies reporting both outcomes), and then separately for each outcome. Where needed, stratified estimates from a single study were combined using an inverse variance fixed-effects model before being pooled with those from other studies. Whenever possible, we included in the analysis estimates specifically for brain and other CNS tumors only and for nervous system cancers without further specification if the former were not available.

We performed sensitivity analyses by excluding studies that required computation of 95% CIs, omitting one study at a time, and limiting the analysis to studies that used an external reference population. Furthermore, we carried out subgroup analyses according to publication year (< 2000, ≥ 2000), participants' sex (≥ 90% male, ≥ 90% female), study region (North America, Europe), and CASP score (≤ median, > median).

The occurrence of publication bias was assessed by visual inspection of a contour-enhanced funnel plot and through Egger's test [21–23].

Analyses were performed using STATA software version 17.0 (StataCorp LLC, College Station, Texas, USA).

3. Results

The study selection process is reported in Figure 1. We initially identified 19 studies from the IARC Monograph [5]. Furthermore, the search of studies published after 2012 allowed the identification of 2,988 records, 2,902 of which were excluded from the screening phase according to title and abstract. Subsequently, 81 studies were excluded after evaluating their full text for the reasons reported in Figure 1. Hence, we eventually identified 33 studies on DE exposure and cancer types other than lung. Fourteen of them reported estimates on brain and other CNS tumors, which were included in the meta-analysis [24–37].

The main characteristics of the included studies are summarized in Table 1. They were published between 1983 and 2012, with half of them (n=7) conducted in North America [24, 26–28, 31, 36, 37], and the other half (n=7) in Europe [25, 29, 30, 32–35]. Most studies were conducted in retrospective cohorts (n=12, 86%) [24–26, 28–36], and they utilized an external population as a reference (n=12 86%) [24–26, 28–30, 32–37].

The median CASP score of the studies included was 9.63 (interquartile range: 9, 11). Overall, 5 of the studies (36%) reported estimates solely on the incidence of brain and other CNS tumors [31–35], while 8 of them (57%) reported estimates on mortality only [24–28, 30, 36, 37]. One study provided results on both incidence and mortality instead [29].

When analyzing results for combined incidence and mortality, no association was found between occupational DE exposure and brain or other CNS tumors (Figure 2, RR: 0.99; 95% CI: 0.91, 1.07). Estimates remained consistent across subgroups based on participants' sex, study country, and CASP score, as well as when excluding studies that required the computation of the 95% CI or when limiting the analysis to studies that used an external reference population (Table 2 and Figure S1).

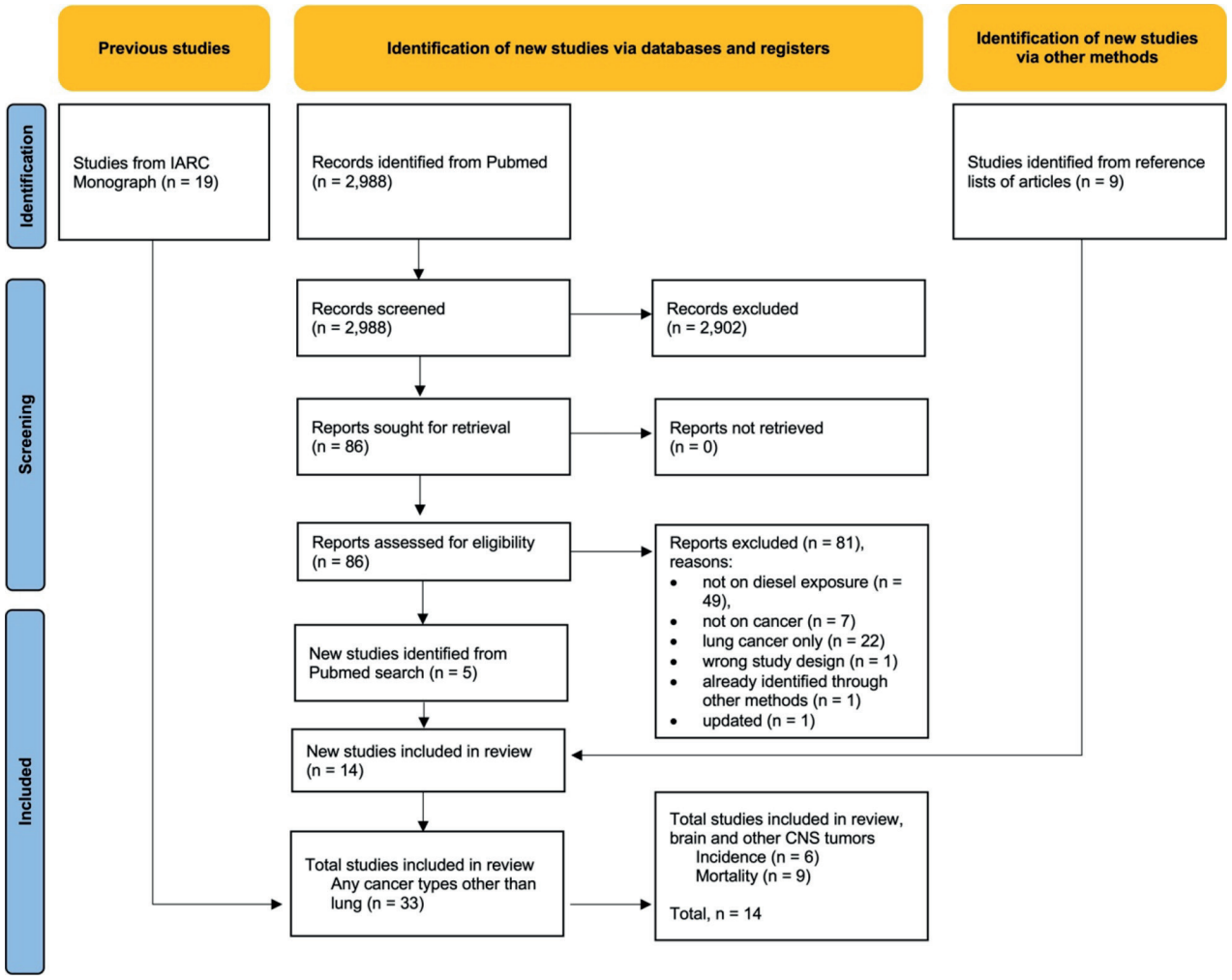

Figure 1. Flow diagram of the study selection process.

The results on incidence were similar (RR: 0.96; 95% CI: 0.90, 1.03). In line with the results on incidence and mortality combined, no substantial variations occurred in subgroup analyses (Table 2).

Similarly, the analysis of mortality revealed no association, both overall (RR: 1.09; 95% CI: 0.87, 1.37) and across the considered subgroups (Table 2). The results generally demonstrated a low degree of heterogeneity (Table 2). Furthermore, the results mostly remained similar when one study was omitted at a time, although estimates occasionally tended to move towards an inverse association (Figure S2).

As for publication bias, no substantial asymmetry in the contour-enhanced funnel plot was evident (Figure 3), and Egger's test result (p=0.244) paralleled this.

4. Discussion

The findings of our study do not support the hypothesis of an association between occupational DE exposure and the incidence or mortality of adult brain or CNS tumors. Inhalation of pollutants from DE could enter the bloodstream, potentially reaching various organs where they might exert carcinogenic effects. Exposure to PAHs, which are also found in DE, has been reported to be associated with neurodegeneration in adults [38], and DE exposure has been shown to impair functional brain connectivity in humans [11], suggesting that these pollutants could cross the blood-brain barrier. In fact, DE exposure may alter the blood-brain barrier itself, making it easier for pollutants to cross pollutants [39].

Table 1. Main characteristics of the studies included in the meta-analysis

First author, year [ref]	Country	Study period	Type of cohort	Reference	Type of workers	Person-years	Sample size	Sex, male (%)	Outcome	ICD code	Number of cases	Results, estimate (95% C.I.)	Variables controlled for	CASP score
Howe GR, 1983 [24]	Canada	1965-1977	Retrospective	External	Railway workers	290,186	43,826	100	M	ICD-7: 193; ICD-8: 191, 192	38	SMR: 1.15	Age (standardization)	9
Rushton L, 1983 [25]	United Kingdom	1968-1975	Retrospective	External	Bus garage workers	50,008		100	M		7	SMR: 1.21	Age (standardization)	7
Schenker MB, 1984 [26]	USA	1967-1979	Retrospective	External	Railway workers	28,400	2,519	100	M	ICD-8: 191, 192	5	SMR: 1.32 (0.43, 3.08)	Age (standardization)	7
Boffetta P, 1988 [27]	USA	1982-1984	Prospective	Internal	Mixed	939,817	476,648	100	M	ICD-9: 191	Exposed: 12	RR: 0.90	Age, smoking, other occupational exposures (standardization)	10
Bender AP, 1989 [28]	USA	1945-1984	Retrospective	External	Highway maintenance workers		4,849	100	M	ICD-9: 191.0-192.9	6	SMR: 0.66 (0.24, 1.44)	(standardization)	10
Gustavsson P, 1990 [29]	Sweden	1952-1986	Retrospective	External	Bus garage workers		695	100	M	ICD-8: 191	4	SMR: 2.20 (0.60, 5.63)	Age, sex (standardization)	10
		1958-1984							I	ICD-7: 193	6	SIR: 1.90 (0.70, 4.15)		
Rafnsson V, 1991 [30]	Iceland	1951-1988	Retrospective	External	Truck drivers	28,788	868	100	M	ICD-7: 193	3	SMR: 1.40 (0.29, 4.10)	Age (standardization)	9
Van Den Eeden SK, 1993 [31]	USA	1964-1988	Retrospective	Internal	Mixed		160,230	46	I		130	HR: 1.38 (0.79, 2.41)	Age, gender, education, race/ethnicity, smoking status, duration, amount	12
Soll-Johanning H, 1998 [32]	Denmark	1943-1992	Retrospective	External	Bus drivers and tramway employees	386,395	18,120	100	I		36	SIR: 0.70 (0.50, 1.00)	Age, sex (standardization)	10
								0			5	SIR: 1.60 (0.50, 3.80)		

Table 1 (*Continued*)

First author, year [ref]	Country	Study period	Type of cohort	Reference	Type of workers	Person-years	Sample size	Sex, male (%)	Outcome	ICD code	Number of cases	Results, estimate (95% C.I.)	Variables controlled for	CASP score
Boffetta P, 2001 [33]	Sweden	1971-1989	Retrospective	External	Mixed	5,305,895		100	I	ICD-7: 193	1318	SIR: 0.94 (0.89, 0.99)	Age (standardization)	11
						240,586		0			40	SIR: 0.90 (0.65, 1.23)		
Järvholm B, 2003 [34]	Sweden	1971-1995	Retrospective	External	Heavy construction equipment operators		14,364	100	I	ICD-7: 193	32	SIR: 0.97	Age (standardization)	11
					Drivers		6,364				16	SIR: 0.92		
Pukkala E, 2009 [35]	Denmark, Finland, Iceland, Norway, Sweden	1960-2005	Retrospective	External	Engine operators		~14.9 million (entire cohort)	100	I		804	SIR: 0.98 (0.91, 1.05)	Age (standardization)	13
								0			44	SIR: 1.19 (0.86, 1.60)		
Birdsey J, 2010 [36]	USA	1989-2004	Retrospective	External	Truck drivers		156,241	94	M		45	SMR: 0.76 (0.56, 1.02)	Age, race/ ethnicity, and sex (standardization)	9
Koutros S, 2023 [37]	USA	1960-2015	Prospective	External	Non-metal miners	422,343	12,315	96	M		45	SMR: 1.41 (1.03, 1.88)	Age, calendar-time, race, and sex (standardization)	10

I: incidence, M: mortality, HR: hazard ratio, SMR: standardized mortality ratio, SIR: standardized incidence ratio, RR: relative risk, ICD: International Classification of Diseases, CASP: Critical Appraisal Skills Programme.

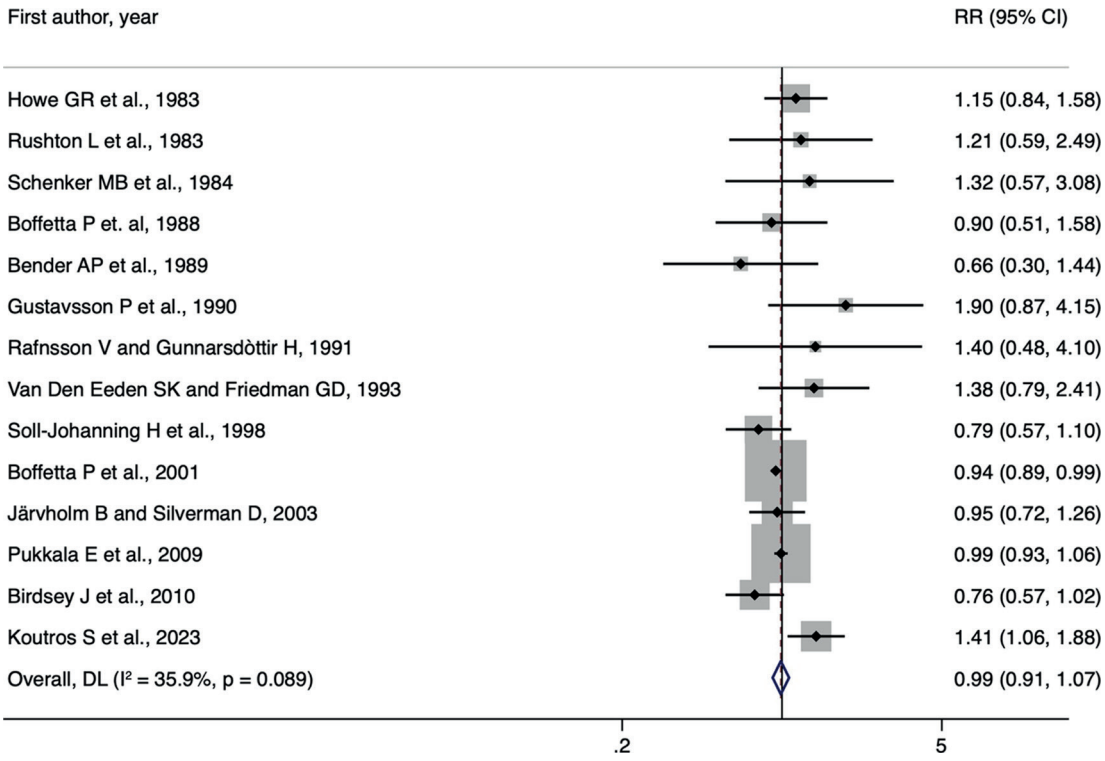

Figure 2. Results of the meta-analysis on the association between occupational exposure to diesel exhausts and brain and CNS tumors incidence and mortality combined.

Previous meta-analyses explored the link between occupational DE exposure and various cancer types, but evidence suggests an increased risk only for lung and bladder cancers [40-42]. While associations have been reported between parental occupational DE and PAH exposures and childhood brain and other CNS cancers [6-9], the estimates from individual studies in adults included in our review consistently indicate a lack of association. The combination of these findings may imply an increased susceptibility during early childhood, potentially due to the incompletely developed blood-brain barrier. Indeed, these earlier studies highlight the adverse effects of exposures occurring before birth [6, 9]. Germline mutations or epigenetic modifications of germ cells have also been proposed as mechanisms of childhood carcinogenesis, particularly for exposures happening before conception and for paternal exposure [9], and these mechanisms would not apply to cancer development in adults.

Among the limitations of our study is the lack of a detailed environmental assessment of exposure in the included studies, which were primarily based on occupations involving DE exposure. While we included only studies on likely exposed cohorts of workers in the meta-analysis, this approach does not account for variations in intensity, frequency, and duration of exposure among study participants, assuming exposure is the same for all individuals within a specific occupation. Additionally, due to insufficient data, we could not evaluate the effects of varying doses and durations of exposure, nor the time since cessation of exposure. In this context, a certain degree of exposure heterogeneity can be anticipated across different cohorts, as individuals in various occupations may experience different levels of exposure, and even among participants within the same cohort due to differing tasks performed.

Overall, a non-differential misclassification of the exposure might be expected, potentially biasing our

Table 2. Meta-analysis on the association between occupational exposure to diesel exhausts and brain and CNS tumors.

Outcome	Stratum	n of studies	RR	95% CI	I^2, p-value
Incidence and mortality	Sex				
	Male	13	0.98	0.90, 1.06	39.4%, 0.071
	Female	3	1.08	0.84, 1.38	20.2%, 0.286
	Publication year				
	Before 2000	9	1.05	0.87, 1.27	7.7%, 0.371
	2000 or later	5	0.98	0.89, 1.07	63.0%, 0.029
	Region				
	North America	7	1.06	0.84, 1.34	49.1%, 0.067
	Europe	7	0.96	0.91, 1.01	10.0%, 0.353
	CASP score				
	≤ median	7	0.91	0.76, 1.10	12.3%, 0.335
	> median	7	1.01	0.92, 1.12	53.3%, 0.045
	Without computed CIs	10	0.99	0.89, 1.09	51.7%, 0.029
Incidence	Overall	6	0.96	0.90, 1.03	32.7%, 0.191
	Sex				
	Male	5	0.95	0.88, 1.03	40.9%, 0.149
	Female	3	1.08	0.84, 1.38	20.2%, 0.286
	Publication year				
	Before 2000	3	1.17	0.69, 1.99	65.8%, 0.054
	2000 or later	3	0.96	0.92, 0.997	0.0%, 0.471
	Region				
	North America	1	1.38	0.79, 2.41	na
	Europe	5	0.96	0.90, 1.02	30.7%, 0.217
	CASP score				
	≤ median	1	0.79	0.57, 1.10	na
	> median	5	0.97	0.91, 1.04	34.3%, 0.193
	Without computed CIs	5	0.97	0.89, 1.05	46.2%, 0.115
Mortality	Overall	9	1.09	0.87, 1.37	41.2%, 0.093
	Sex				
	Male	9	1.09	0.87, 1.37	41.2%, 0.093
	Female	0	nc		
	Publication year				
	Before 2000	7	1.12	0.90, 1.40	0.0%, 0.582
	2000 or later	2	1.04	0.57, 1.90	88.5%, 0.003
	Region				
	North America	6	1.02	0.79, 1.33	54.2%, 0.053
	Europe	3	1.49	0.90, 2.46	0.0%, 0.609

Outcome	Stratum	n of studies	RR	95% CI	I^2, p-value
	CASP score				
	≤ median	6	0.96	0.77, 1.21	15.9%, 0.311
	> median	3	1.31	0.90, 1.91	35.7%, 0.211
	Without computed CIs	6	1.12	0.77, 1.62	61.4%, 0.024

RR: relative risk, CI: confidence interval, nc: not computable, na: not applicable.

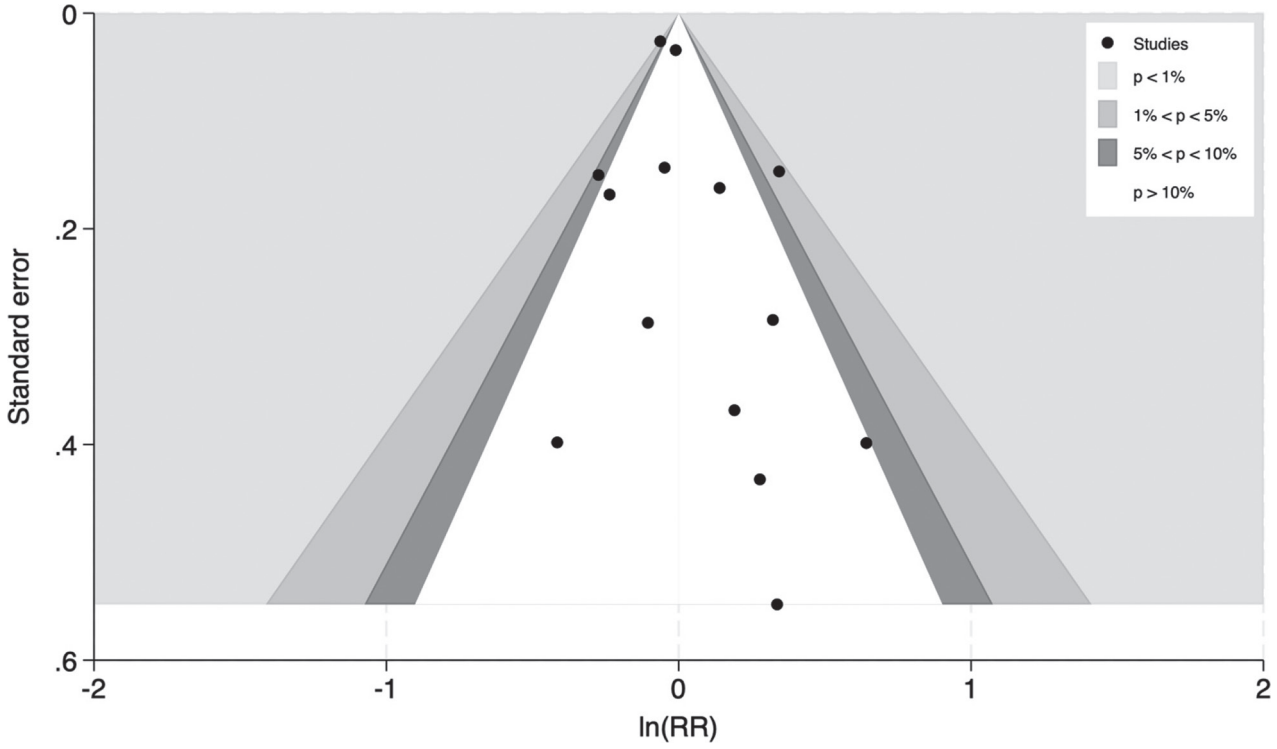

Figure 3. Contour-enhanced funnel plot to explore small-study effect for brain and CNS tumors incidence and mortality combined.

estimates towards the null. Additionally, the included studies did not report whether measures to prevent exposure were implemented in the workplaces. Furthermore, most studies did not consider other occupational exposures occurring concurrently with DE exposure or prior to it, even though these could bias the results towards a positive association. Most studies utilized an external population as a comparator, which might introduce the healthy worker effect and bias the results towards the null [43, 44]. Moreover, we excluded case-control studies not nested within cohorts due to a higher potential for exposure misclassification, particularly if community-based [45]; however, this may have resulted in the exclusion of other potentially relevant studies. Grouping various types of cancers of the nervous system in primary studies might also have caused outcome misclassification, likely in a non-differential manner. Ultimately, relying solely on PubMed as the database for searching scientific papers published after the IARC

Monograph may have limited the comprehensiveness of our search, potentially causing us to miss additional studies on the topic.

5. Conclusion

In summary, our meta-analysis's results indicate that occupational DE exposure does not increase the risk of adult brain or CNS tumors. However, these findings should be interpreted with caution due to limitations in the studies' exposure assessments, including the reliance on an external population as a reference in most cases and the potential oversight of co-exposures. Therefore, further high-quality studies with detailed and quantitative exposure assessments using an internal reference population could help to completely rule out this possible association.

Supplementary Materials: The following are available online: Table S1. A modified version of the Critical Appraisal Skills Programme (CASP) checklist for cohort studies adopted for quality assessment. Figure S1. Results of the meta-analysis on the association between occupational exposure to diesel exhausts and brain and CNS tumors incidence and mortality combined, including only studies that used an external reference population. Figure S2. Leave-one-out meta-analysis for the association between occupational exposure to diesel exhausts and brain and CNS tumors incidence and mortality combined.

Funding: None.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Declaration of Interest: P.B. acted as an expert witness in litigation concerning diesel exhaust exposure and cancer, unrelated to the present work. The other authors reported no conflicts of interest.

Author contribution statement: All authors contributed to the study's conception and design. G.C. and F.T. carried out study selection and quality assessment; M.S. performed the statistical analysis and wrote the first draft of the manuscript; P.B. supervised the study. All authors reviewed the manuscript and read and approved its final version.

Declaration on the use of AI: None.

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Supplementary Material

Table S1. Modified version of the Critical Appraisal Skills Programme (CASP) checklist for cohort studies adopted for quality assessment.

Items	Possible scores
Section A: Are the results of the study valid?	
1. Did the study address a clearly focused issue?	- 1.5 - 1.0 - 0.0
2. Was the cohort recruited in an acceptable way?	- 1.5 - 1.0 - 0.0
3. Was the exposure accurately measured to minimise bias?	- 1.0 - 0.5 - 0.0
4. Was the outcome accurately measured to minimise bias?	- 1.0 - 0.5 - 0.0
5. (a) Have the authors identified all important confounding factors?	- 1.0 - 0.5 - 0.0
5. (b) Have they taken account of the confounding factors in the design and/or analysis?	- 1.0 - 0.5 - 0.0
6. (a) Was the follow up of subjects complete enough?	- 1.0 - 0.5 - 0.0
6. (b) Was the follow up of subjects long enough?	- 1.0 - 0.5 - 0.0
Section B: What are the results?	
7. What are the results of this study?	Excluded
8. How precise are the results?	- 1.0 - 0.5 - 0.0
9. Do you believe the results?	- 1.0 - 0.5 - 0.0
Section C: Will the results help locally?	
10. Can the results be applied to the local population?	- 1.0 - 0.5 - 0.0
11. Do the results of this study fit with other available evidence?	- 1.0 - 0.5 - 0.0
12. What are the implications of this study for practice?	- 1.0 - 0.5 - 0.0

For each item, scores were assigned according to researchers' consideration of the quality of the content (higher score means higher quality).

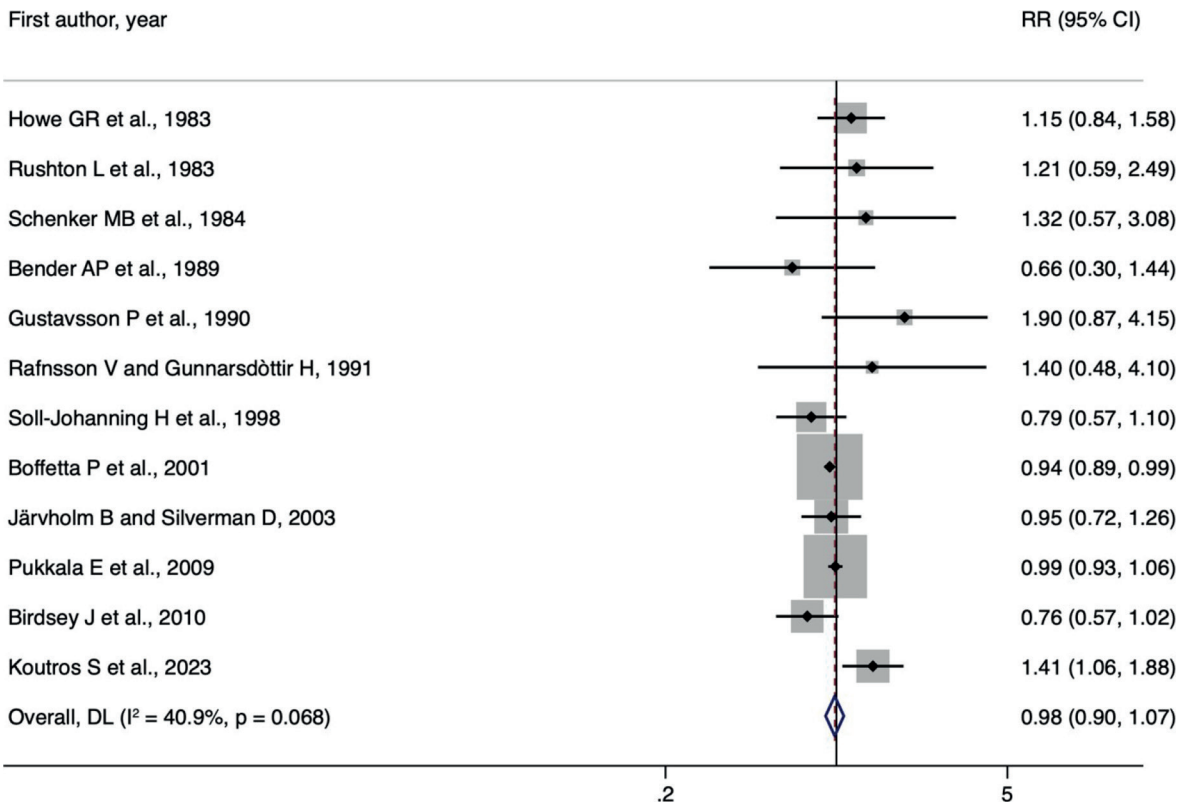

Figure S1. Results of the meta-analysis on the association between occupational exposure to diesel exhausts and brain and CNS tumors incidence and mortality combined, including only studies which used an external reference population.

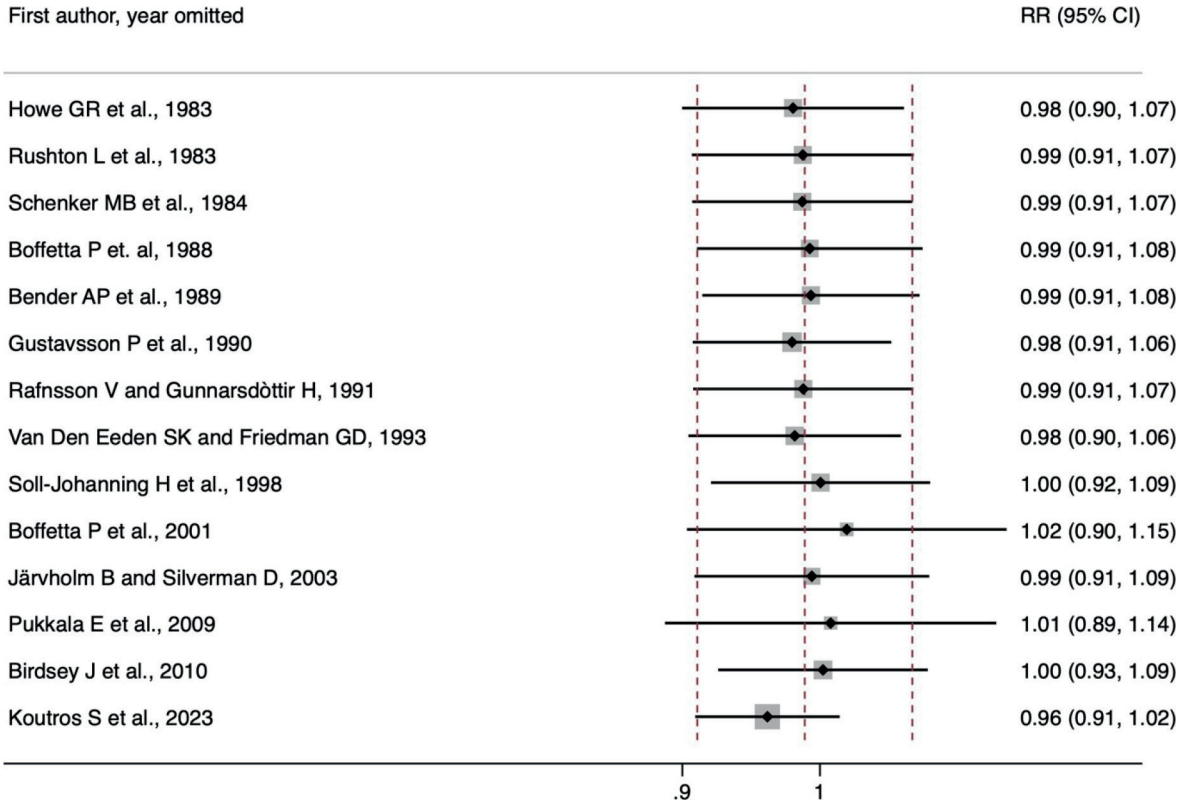

Figure S2. Leave-one-out meta-analysis for the association between occupational exposure to diesel exhausts and brain and CNS tumors incidence and mortality combined.