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Occupational-Related Exposure to Diesel Exhaust and Kidney Cancer: Systematic Review and Meta-Analysis of Cohort Studies

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Abstract

Background: *The association between diesel exhaust and cancer other than the lung is not well established. We aimed to conduct a systematic review and meta-analysis on the association between diesel exhaust exposure and kidney cancer in workers.* **Methods:** *Two trained researchers conducted a systematic review to identify cohort studies examining the relationship between occupational exposure to diesel exhaust and the risk of cancer other than lung cancer. Of the 43 retained studies, 15 reported information on kidney cancer. We performed random-effects meta-analyses for ever-exposure to diesel exhaust. Summary relative risks (RR) and 95% confidence intervals (CI) were calculated for the association between diesel exhaust exposure and kidney cancer.* **Results:** *Overall, the RR of kidney cancer was 1.08 (95% CI=1.01-1.15, heterogeneity p=0.1, I2=28.6%). The summary RR was 1.08 for incidence (95% CI=1.01-1.16; I2=36.7%) and 1.09 for mortality (95% CI=0.92-1.30, I2=14.5%), p of heterogeneity=0.914. The summary RR of European studies was 1.08 (95% CI=1.00-1.16, I2=37.8 %), that of USA/Canada studies was 1.10 (95% CI=0.94-1.29, I2=8.5%), p of heterogeneity=0.837. Publication bias was not detected.* **Conclusions:** *Workers exposed to diesel exhaust may experience an increased risk of developing kidney cancer, although the evidence is not entirely consistent, and residual confounding cannot be excluded.*

1. Introduction

Diesel exhaust has been investigated as a potential carcinogen for multiple organs [1]. Most of the available studies focus on lung cancer, for which an association has been reported [1]. A carcinogenic effect on the lung is justified by the fact that inhalation represents the main route of exposure. Exposure to diesel exhaust can be occupational as well as environmental, through traffic emissions and machine operation ([2]; Table S1). Workers who are most exposed to diesel exhaust include drivers, heavy equipment operators, and non-metal miners [3].

Among the organs besides the lung for which a carcinogenic effect of diesel exhaust has been reported are the urinary bladder [4-6] and the kidney [6, 7]. The high vascularization of the kidney and its filtering function, combined with the possible

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passage of diesel exhaust particles into the circulatory system, support the hypothesis that the urinary tract may be susceptible to the harmful effects of this agent [8]. The assessment of health effects from diesel exhaust exposure is complicated by various factors, including exposure misclassification and the variable composition of the agent itself. Evidence of an association between diesel exposure and urinary tract cancer remains limited. Cohort studies are the most appropriate research design to describe the effects of exposure to carcinogens [9]. We aimed to conduct a meta-analysis of cohort studies involving workers exposed to diesel exhaust and the risk of cancers other than the lungs. The present paper focuses on the association with kidney cancer.

2. METHODS

2.1. The Preferred Reporting Items for Systematic reviews and Meta-Analyses

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was followed to conduct this meta-analysis [10]; the checklist is available in Table S2. A study protocol was built and registered in the PROSPERO database (Registration No. 352729).

The systematic review was based on the Patients, Exposure, Comparator, Outcomes, Study design (PECOS) criteria [11], with the following structure:

- Population (P): workers in multiple industrial settings;
- Exposure (E): occupational diesel exhaust exposure;
- Comparator (C): individuals not exposed to diesel exhaust;
- Outcomes (O): incidence or mortality of cancer types other than lung cancer;
- Study design (S): industry-based or population-based studies reporting information on the exposure (including nested case-control studies).

We reviewed all publications included in the IARC Monograph on diesel exhaust [1] and conducted a PubMed search in May 2024 for studies reported after that publication. This search aimed to identify studies reporting results on occupational exposure to diesel exhaust and the risk of any cancer type except lung cancer. The search was performed independently by two authors (GC and FT) and focused on studies of cancer among workers exposed to diesel exhaust in industries such as railway, transportation, and mining. We created a search string using the terms (diesel OR miner OR garage OR railway OR ((truck OR bus) AND driver) OR (heavy equipment OR docker)) AND (cancer OR neoplasm). Additionally, we included reports from the personal archives of one of the authors (PB), adding nine non-overlapping studies. If multiple reports were published on the same population, we only included the most informative one, usually the one with the largest number of cases or deaths. Studies with minor overlap (less than 10%) were considered independent.

We abstracted data using a standardized form on (i) sociodemographic factors, (ii) occupation and industry type, (iii) person-years of observation, (iv) type of cancer and ICD code with version, (v) measure of association (odds ratio (OR), risk ratio, rate ratio, standardized mortality ratio [SMR], or standardized incidence ratio [SIR], henceforth referred to as relative risk [RR]) and 95% confidence intervals (CI), (vi) factors adjusted for in the analysis and (vii) characteristics of the study population (eg., number of subjects included, number of cancer cases). The dataset was organized by type of cohort study (historical vs prospective), design of the study (industry-based vs population-based), follow-up period, geographic area (USA/Canada vs Europe), and outcome (incidence vs mortality). Composition of the population by sex was reported when data were reported, as well as sex-specific results. When available, we abstracted results on dose-response analysis for different indicators of diesel exhaust exposure.

Next, we excluded studies with no reference to diesel exhaust, those with exposure other than occupational, those without data on cancer other than lung cancer, and those with a design other than cohort. We assessed the quality of the included studies based on the CASP scale [12]. We considered 11 questions for a total score of 14 points. We used the mean of the scores assessed separately by two authors (GC and FT). Studies which scored <8 were considered of low quality, 8-9.5 of medium-low quality, >9.5 & <11.25 of medium-high, and >=11.25 of high quality. Additional information is available on Supplementary Tables S3 and S4.

Data were collected for different types of cancers, excluding the lungs. We conducted analyses by cancer type. This paper focuses on the association between occupational diesel exhaust exposure and kidney cancer. We conducted a random-effects meta-analysis based on the Sidik-Jonkman method [13]. In the primary analysis, we included results on both kidney cancer incidence and mortality. Next, we stratified the meta-analyses by outcome (incidence and mortality), geographic area (USA/Canada and Europe), design of the study (industry-based and population-based), and quality score (low or low-medium and medium-high or high score). Data for women were too limited to allow a separate analysis.

We tested the heterogeneity among studies using the I-square test [14]. We assessed publication bias by the visual inspection of the funnel plot and the Egger test [15]. To address the plausibility of results on kidney cancer, we compared them to the corresponding results on lung cancer when reported. All the statistical analyses were performed on STATA, version 16.1 (Stata Corp., College Station, TX, US) [16].

3. Results

The flow chart showing the selection of studies is included in Supplementary Figure S1. Out of 2,867 potentially relevant publications, we retained a total of 3 publications reporting results on kidney cancer. An additional 19 publications were abstracted from the IARC Monograph [1], of which one study of U.S. non-metal miners was excluded because a more recent report from the same study was available, and 16 studies were retrieved from the reference lists of the studies identified earlier; among these, 9 were non-overlapping. Of the 30 non-overlapping studies meeting the inclusion criteria, 15 reported results on kidney cancer [3, 6, 7, 17-28].

The 15 studies retained in the review comprised 23 estimates of the association between diesel exhaust exposure and risk of kidney cancer, including eight studies (16 risk estimates) based on incidence and seven studies (seven risk estimates) based on mortality. They are illustrated in Table 1.

Figure 1 shows the main results of our meta-analysis. Overall, the RR of kidney cancer was 1.08 (95% CI=1.01-1.15, p-value of test for heterogeneity [p-het] =0.1, I2=28.6%). The p-value of the test for publication bias was 1.00.

Table 2 summarizes the results of the stratified analyses. When focusing on results on cancer incidence, the summary RR was 1.08 (95% CI=1.01-1.16, p-het=0.036, I2=36.7%), while the summary RR from mortality studies was 1.09 (95% CI=0.92-1.30, p-het=0.324, I2=14.5%). Results by outcome were not statistically heterogeneous (p=0.914). Publication bias was excluded for both study types (p=0.912 for incidence studies and p=0.884 for mortality studies). The summary RR of studies conducted in the USA/Canada was 1.10 (95% CI=0.94-1.29, p-het =0.248, I2=8.5%), whereas that of European studies was 1.08 (95% CI=1.00-1.16, p-het 0.042, I2=37.8%). These results were not heterogeneous (p-het=0.837). When considering study design, no significant difference was observed between industry-based (RR=1.07, 95% CI=0.93-1.24, p-het=0.284, I2=17.3%) and population-based studies (OR=1.08, 95% CI=1.01-1.17, p-het=0.07, I2=39.7%), with p for heterogeneity among the two categories equal to 0.910.

The summary RR for low- and medium-quality studies was 1.22 (95% CI=1.01-1.47, p-het=0.039, I2=41.4%), that for medium-high- and high-quality studies was 1.06 (95% CI=1.03-1.09, p-het<0.001, I2=0.0%); this difference was not statistically significant (p-het=0.147). Results on dose-response were too sparse to justify a meta-analysis, as well as those by sex.

Finally, we identified 16 cohorts with results reported for both lung and kidney cancers; the unweighted correlation coefficient was 0.23 (p=0.40). Supplementary Figure 2 shows the scatter plot of the results of the individual studies. Supplementary Table S4 provides information on the main characteristics of some common occupational exposures to diesel exhaust, based on IARC 2012 [1].

Table 1. Characteristics of the included studies.

Study	Country	Design (P, population-based; I, industry-based)	Years of FU	N participants	Persons years	Industry type	Exposure data	N cases kidney cancer	Adjustments	RR/SMR/SIR kidney cancer	RR/SMR/SIR lung cancer
Koutros et al., 2023 (17)	USA	I	1960-2015	12,315 people, both sexes	422,343 (miners) 282,840 (ever-underground miners)	Miners	Data collected from 8 non-metal miners US facilities. Historical measurements and surrogate exposure data were used to estimate exposure to diesel exhaust for each worker. Work history record were abstracted from employer personnel files. For six facilities, this information was available through end 1999; one facility only through 1997, and another facility through 1993.	34 (23 among ever underground miners)	Race and ethnicity	SMR=1.02, 0.71-1.43	SMR=1.24, 1.13, 1.37
Guo J et al., 2004 (7)	Finland	P	1971-94	Men and women	30 million person-years	Non-metal miners Truck drivers Forklift drivers Dockers	Occupations from the population census in 1970 were converted to exposures to diesel exhausts with a job-exposure matrix (FINJEM).	13 in men (non-metal miners) 131 in men, 2 in women (truck drivers) 15 in men (forklift drivers) 24 in men, 3 in women (dockers)	SES, smoking, BMI	Non-metal miners men: RR=0.88, 0.47-1.50 Truck drivers men: RR=1.00, 0.84-1.19; women: 2.50, 0.30-9.02) Forklift drivers men: RR=0.92, 0.0.53-1.58 Dockers men: RR=0.98, 0.63-1.45; women: RR=1.52, 0.31-4.43	no result reported for lung cancer

Jarvholm B and Silverman D, 2003 (18)	Sweden	I	1971-92	14364 men (heavy construction equipment operators) 6364 men (truck drivers)	217331 (heavy construction equipment operators) 97930 (truck drivers)	Heavy construction equipment operators Truck drivers	A computerised register of Swedish construction workers participating in health examinations between 1971 and 1992 was used. the referent group was carpenters/ electricians and general population for lung cancer, while for other cancers the referent group was only general population.	24 in heavy construction equipment operators 23 in truck drivers		SIR=0.74, 0.47-1.10 heavy construction equipment operators SIR=1.12, 0.71-1.68 in truck drivers	SMR=0.70 (95% CI=0.51-0.92) for heavy construction equipment operators SMR= 1.18 (95% CI=0.89-1.53) for truck drivers SIR= 1.14 (95% CI=0.87-1.46) for truck drivers and SIR= 0.76 (95% CI=0.58-0.97) for heavy construction equipment operators
Wong O et al., 1985 (19)	USA	I	1964-78	34156 men	372525.6	Construction equipment operators	Data derived from records maintained at Operating Engineers Local Union N3, San Francisco. No historical environmental measurements, but partial work histories were available for some cohort members through the union dispatch computer tapes. An attempt was made to relate mortality experience to the union members' dispatch histories.	17		SMR=0.74, 0.43-1.18	SMR= 0.99 (95% CI=0.88-1.10)
Van Den Eeden SK and Friedman GD, 1993 (20)	USA	P	1964-72	160230, both sexes (overall results reported)		Diesel exhaust exposure assessed across multiple jobs and industries	Diesel exhaust exposure reported in questionnaire interview during routine health examination, among members of the Northern California Kaiser Permanente Medical Care Program. Questions referred to exposure in the past year.	268	Race, education, smoking status (and smoking duration and smoking amount)	RR=1.38, 0.80-1.38, 0.80-2,41	RR=1.02 (95% CI=0.81-1.29)

Table 1 (*Continued*)

Study	Country	Design (P, population-based; I, industry-based)	Years of FU	N participants	Persons years	Industry type	Exposure data	N cases kidney cancer	Adjustments	RR/SMR/SIR kidney cancer	RR/SMR/SIR lung cancer
Boffetta P et al., 2001 (6)	Sweden	P	1971-89	All Swedish adult population	7 400 000 for men exposed and 240 000 for women exposed	Diesel exhaust exposure assessed across multiple jobs and industries	After excluding farmers, job and industry titles were classified according to estimated probability and intensity of exposure to diesel emissions (based on Swedish Cancer Environment Register III).	2243 in men 33 in women		SIR =1.06, 1.02-1.11 in men; SIR=0.82, 0.57-1.16 in women	SIR=1,09 (95% CI=1.06-1.12) in men, SIR=1.09 (95% CI=0.83-1.42) in women
Gustavsson P et al., 1990 (21)	Sweden	P	1952-86 for mortality 1958-84 for incidence	695 men	21317.5 16695	Bus garage workers	The intensity of the exposure to diesel exhaust was assessed by industrial hygienists and structured in a job-exposure matrix.	2 1		SMR=0.72, 0.09-2.59 SIR=0.70, 0.14-2.04	SMR= 1.15 (95% CI=0.67- 1.84) SIR=1.61 (95% CI=0.94- 2.57)
Soll-Johanning H et al., 1998 (22)	Denmark	P	1943-92	15249 men	386395 total person-years	Bus drivers and tramway employers	Computerised, highly-reliable individual data on employment.	83 in male workers employed at least 3 months		SIR=1.60, 1.30-2.00 (men employed for at least 3 months)	SIR= 1.6 (95% CI=1.5-1.8) for men SIR=2.6 (95% CI=1.5-4.3) for women
Rafnsson V and Gunnarsdottir h, 1991 (23)	Iceland	I	1951-88	28788 (truck drivers) 19284 (taxi drivers)	868 (truck drivers) 726 (taxi drivers)	Truck drivers Taxi drivers	Data obtained from the membership registers and files of truck and bus drivers (length of time, period of employment etc.)	6 8		SMR=1.77, 0.65-3.85 for truck drivers SMR=1.97, 0.54-5.05 for taxi drivers	SMR= 2.14 (95% CI=1.37-3.18) for truck drivers; SMR=1.39 (95% CI=0.72-2.43) for taxi drivers
Birdsay J et al., 2010 (24)	USA	I	1989-2004	156241 people, both sexes; 146,261 men		Truck drivers	Occupational data from electronic membership files of a trade association providing services to truck drivers.	55 (no sex distinction)	Smoking status	SMR=1.08, 0.82-1.41	SMR=1.00 (95% CI=0.92-1.09)

Schenker MB et al., 1984 (25)	USA	I		1967-79	2519 men	284000	Railway workers	Diesel exhaust exposure estimated for about 150 railway job classifications. Exposure determined based on previous reviews on railways and based on data from industrial hygiene measurements.	6		SMR=1.66, 0.61-3.62	SMR=0.82 (95% CI=0.59- 1.11)
Nokso-Koivisto P and Pukkala E, 1994 (26)	Finland	I		1953-90	8391 men	212 800	Locomotive drivers	Reconstruction of usual working conditions and standard hygienic operations, with the help of older workers; air sample collection; measurement of diesel exhaust exposure.	38		SIR=1.25, 0.88-1.70	SIR= 0.86 (95% CI=0.75-0.97)
Pukkala E et al., 2009 (3)	Denmark, Finland, Iceland, Norway, Sweden	P		1961-2006	15 million people, both sexes 385 000 000	385 000 000	Machine operators	Original national occupation codes converted to a common classification with 53 categories + one category of economically inactive persons.	1142 in men, 23 in women		SIR=1.08, 1.02-1.14 in men; SIR=0.93, 0.59-1.40 in women	SIR =1.20 (955 CI=1.17- 1.23) in men; SIR=2.61 (95% CI=2.19- 3.11) in women
Bender AP et al., 1989 (27)	USA	I		1945-84	4849 men	96 567	Highway workers	Employment data on highway maintenance workers.	6		SMR=0.63, 0.23-1.37	SMR=0.69
Howe GR et al., 1983 (28)	USA	I		1965-77	43 826 men, 17838 ascertained cause of death	290 186	Pensioners of the Canadian National Railway Company	Experts classified occupations based on specific exposures, including diesel exhaust	58		RR=1.26, 0.97-1.64	SMR=1.06

FU= follow-up.
N= number.
BMI= body max index.
SES= socioeconomic status.
SMR/SIR= standardized mortality ratio/standardized incidence ratio.
CI=confidence interval.

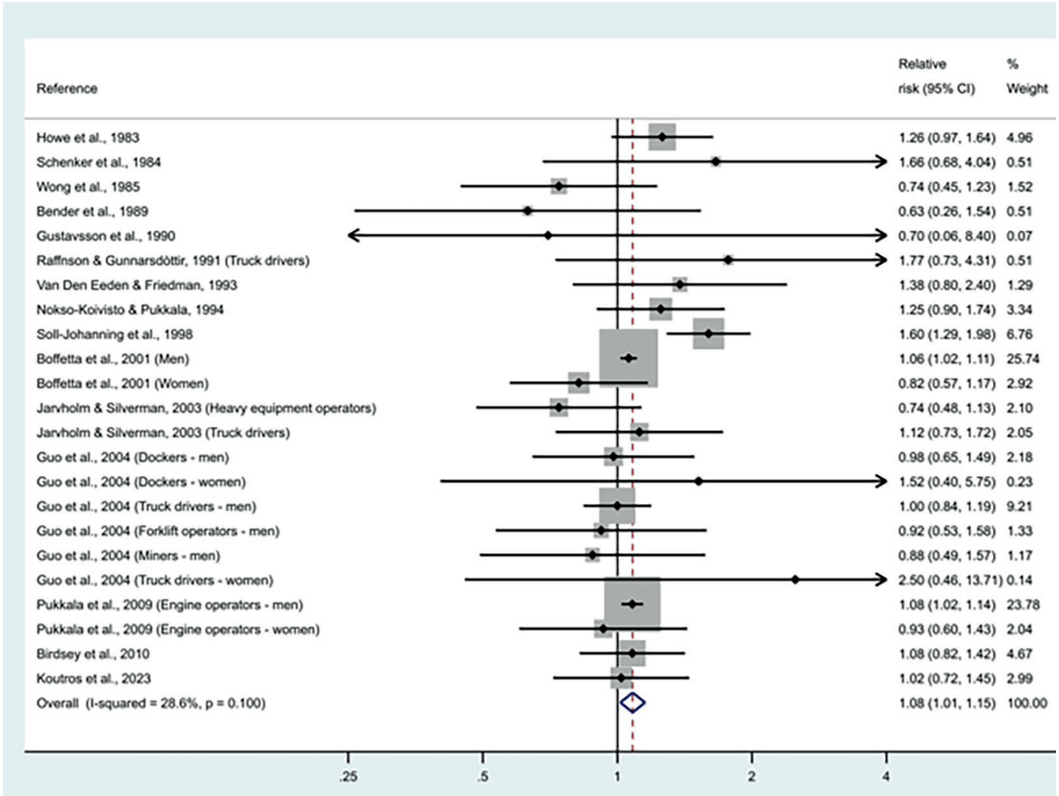

Figure 1. Results of the overall meta-analyses of studies on occupational exposure to diesel exhaust and risk of kidney cancer.

Note: confidence intervals do not match with those reported in Table 1 and in the original publications because of Stata approximations.

4. Discussion

We identified a weak association between occupational exposure to diesel exhaust and the risk of kidney cancer. The association did not vary according to outcome (incidence vs. mortality from kidney cancer) and geographic regions (Europe vs. North America).

We focused this meta-analysis on cohort studies because this design allows for a better definition of exposure. Industry-based and population-based studies, such as census-based ones, were included and analyzed separately, with no statistical difference observed. Census-based studies, like those by Boffetta et al. [6] and Pukkala et al. [3], as well as most cohort studies based on industry or occupation, essentially include all individuals employed in specific occupations but lack detailed data on diesel exhaust exposure. In fact, these studies estimate exposure based on occupation type rather than questionnaires or measurements. Additionally, census-based studies usually provide job title information at a single point in time. These factors make industry-based studies more appropriate for investigating occupational epidemiology. Conversely, the study by Koutros et al. [17], conducted among non-metal miners in the US, provided detailed diesel exhaust exposure data based on historical measurements and surrogate indicators, including hygiene levels. Exposure estimates were made independently of outcomes, and cumulative and intensity exposures over time were calculated.

Additionally, exposure to other major occupational confounders was also estimated. These

Table 2. Results of the meta-analysis by main characteristics.

Characteristic	N risk estimates	RR, 95% CI; I2; p-het	Test heterogeneity between strata (p value)
Outcome			
Incidence	16	1.08, 1.01-1.16; 36.7%; 0.036	0.914
Mortality	7	1.09, 0.92-1.30; 14.5%; 0.324	
Country			
USA/Canada	7	1.10, 0.94-1.29, 8.5%; 0.248	0.837
Europe	16	1.08, 1.00-1.16, 37.8%; 0.042	
Design of the study			
Industry-based	10	1.07, 0.93-1.24, 17.3%; 0.284	0.910
Population-based	16	1.08, 1.01-1.17, 39.7%; 0.07	
Quality score			
Low or low-medium	9	1.22, 1.01-1.47, 41.4%; 0.039	0.147
Medium-high or high	14	1.06, 1.03-1.09, 0.0%; <0.001	

Notes: N, number; RR, relative risk; 95% CI= 95% confidence interval; p-het, p for heterogeneity within the studies.

strengths make the study by Koutros et al. [17] the most rigorous in quality. Notably, their analysis found no relationship between diesel exhaust and kidney cancer (SMR 1.02, 0.72-1.45) [17]. Given the significant effort to account for various confounders and the well-documented diesel exhaust exposure within the cohort, the absence of an association with kidney cancer questions the validity of findings from other studies. In particular, the increased risk reported elsewhere may be due to exposure misclassification and residual confounding. Further insight is gained by comparing these results with those for lung cancer, which showed a significant increase, supporting the hypothesis that diesel exhaust does not have an actual causal role in kidney cancer [17].

The study by Pukkala et al. [3] presents some potential overlap with other census-based studies. They analyzed 53 job categories based on 1961-1981 censuses from five Nordic countries, and we selected engine operator as the category with the highest probability of exposure to diesel exhaust [3]. For example, the study by Boffetta et al. [6] included different types of machine operators, including engine operators, based on the 1971 census from Sweden, with the possibility of overlap of some data reported by Pukkala et al. [3]. We combined results on incidence and mortality from kidney cancer under the assumption that exposure to diesel exhaust is not associated with kidney cancer survival, i.e., that the association, if any, would be comparable for the two outcomes. We tested this assumption in the meta-analysis stratified by outcome, which resulted in no heterogeneity between studies based on incidence and studies based on mortality. For this reason, we maintained that including both outcomes was our primary analysis.

There was no evidence of a different risk of kidney cancer in studies from Europe or USA/Canada, despite some difference including: (i) different diesel technologies reducing emission levels [29]; (ii) different working conditions [30]; (iii) differences in lifestyle habits [31, 32]; (iv) higher prevalence of other occupational risk factors in Europe, including asbestos [33-35]; (v) time of exposure, where European studies were based on older exposure.

The lack of sufficient data impaired the analyses by sex. In particular, most studies were conducted on men, and studies involving both sexes included a small proportion of women (eg, <10%) or did not report results separate by sex [20, 24]. As a consequence, our results refer to both sexes, but apply mainly to the male population, based on available data.

The identification of the role of diesel exhaust in cancer causation must take into account the latency between exposure and cancer occurrence. Our choice of focusing on cohort studies is based on the assumption that several decades are needed to observe the carcinogenic effect of diesel exhaust; in fact, a prospective design allows the detection of differences between exposed and non-exposed. According to the IARC [1], latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity. While many included studies covered a period shorter than 20 years, others followed up the workers for several decades, including the extensive census-based study by Pukkala et al. [3], which covered between 1961 and 2006. Therefore, we cannot exclude that more extended observation of the study populations would have led to the identification of an increased risk of kidney cancer. Findings from long-follow-up studies should be considered more reliable and help in interpreting our results.

A few community-based studies reported results on occupational exposure to diesel exhaust and the risk of kidney cancer. Although they were not included in the meta-analysis, these studies can provide supporting evidence, since the results of some of these studies were adjusted for potential confounders such as tobacco smoking and overweight/obesity. In particular, Peters and coauthors reported an OR of 1.23 (95% CI = 0.99-1.53) for kidney cancer in Canadian men exposed to diesel exhaust at the workplace [36]. Also, the risk of kidney cancer in association with outdoor air pollution, including diesel exhaust, was investigated in a meta-analysis of 14 European cohort studies, where an increased likelihood of cancer occurrence was suggested (HR = 1.57, 95%CI: 0.81-3.01 per 5 $\mu g/m^3$ $PM_{2.5}$ and HR = 1.36, 95%CI: 0.84-2.19 per 10^{-5} m^{-1} $PM_{2.5}$ absorbance) [37].

Established risk factors for kidney cancer include cigarette smoking, obesity, and hypertension [38], as well as some medications (e.g., antihypertensive drugs) [39]. IARC lists trichloroethylene and X- and gamma-radiation among the carcinogens with sufficient evidence for kidney cancer in humans. In contrast, the kidney is not listed among known or suspected target organs for carcinogenicity of diesel exhaust [40].

The potential carcinogenic effects of diesel exhaust on the kidney include direct genotoxicity, oxidative stress, and inflammation. A hypothesis suggests an effect mediated by ultrafine particles that can be filtered by the kidney [8]. The role of diesel exhaust in the development of kidney disease is also supported by findings from studies conducted in rats [41, 42]. To our knowledge, this is the first meta-analysis on the association between occupational exposure to diesel exhaust and kidney cancer and provides new evidence on the carcinogenicity of diesel exhaust. The systematic review was conducted according to established guidelines. We focused on cohort studies, thus considering studies of the same design, and the most reliable in the literature in providing evidence on the presence or absence of an association, as information on the exposure is independent from the occurrence of the outcome. Restriction on studies reporting results on occupational exposure was imposed to focus on the population with the highest exposure to diesel exhaust. Also, a large number of publications could be included in this meta-analysis, allowing us to obtain precise results, even though kidney cancer is a relatively uncommon disease, which may be challenging to investigate in individual studies.

4.1. Limitations of the Study

This study suffers from some limitations, which suggest caution in the interpretation of our results. There was a high degree of heterogeneity between the results included in the meta-analysis. Exposure misclassification may have impaired the analysis because the subjects classified as unexposed may have been to some extent exposed to diesel exhaust in the general environment or in other occupations. Also, exposed workers could have been in contact with additional occupational carcinogens, which might be confounders that we could not account for because of missing information. This could lead to an underestimate of the investigated association; however, other sources of bias could have operated. To date, only the DEMS study [17] has adopted a detailed quantitative approach to the assessment of diesel exhaust exposure, using detailed exposure measurements. It should be noted that no excess of kidney cancer was reported in this study. Indeed, diesel exhaust exposure could vary between cohorts investigating the same job or industry, or within the single cohort, because of the different composition, intensity, frequency, and probability of exposure [43]. Moreover, only a few of the included studies accounted for confounders [7, 20, 24], like cigarette smoking and additional occupational factors.

We checked and compared the association observed with lung cancer in the same studies, to (i) understand if exposure misclassification might have impaired both kidney and lung cancer findings, and (ii) verify if a study which failed to assess an association with kidney cancer due to paucity of observed cases was able to identify an association for lung cancer. By doing this, we corroborated that some studies [19, 20, 24-26] could not find an increased risk of lung cancer in workers exposed to diesel exhaust, and that this unexpected finding was attributed to a lack of adjustment for important confounders, short monitoring period, or healthy worker effect. However, exposure misclassification, which receives considerable attention in occupational epidemiology, is an even more important limitation to consider. In addition, it is more challenging to evaluate the impact of exposure misclassification on relative risks in occupational studies than for confounding because of the absence of information on the level of misclassification present, and because exposure misclassification probably occurs in all studies.

An additional potential limitation is the fact that we focused on cohort studies. We made this choice since exposure assessment in case-control studies is less reliable, and selection bias is a potential limitation of this type of study. However, evidence from case-control studies is broadly consistent with our results [1, 36].

A few studies (e.g., [7]) reported results for multiple occupational groups exposed to diesel exhaust, using the same (or a largely overlapping) unexposed population. These risk estimates are therefore not independent, inflating the contribution of the overlapping populations to the results of the meta-analysis. Also, while the number of studies was relevant, it was insufficient to exclude publication bias with enough statistical power. We used the Sidik–Jonkman method for estimating the between-study variability (τ2) rather than the most popular DerSimonian–Laird method [44] due to the known tendency of the latter to underestimate τ^2 when the number of studies is small [45]. This offered a better picture of the inner uncertainties behind the results. We also wanted to relax the assumption that the distribution of random effects is normal. Using the Random-Effects Sidik–Jonkman model, the confidence interval has a higher coverage probability than the commonly used interval based on the DerSimonian-Laird method [46].

5. Conclusion

In conclusion, this meta-analysis suggests a weak positive association between occupational exposure to diesel exhaust and kidney cancer. This finds support in previous literature [36, 37]. Anyway, this positive evidence is not exempt from limitations and potential bias, and is balanced by several arguments, including (i) lack of association reported in the DEMS study [17], which had the highest quality; (ii) lack of adjustments for important potential confounders. Thus, the causal nature of the association cannot be conclusively determined. Additional high-quality prospective studies are needed to elucidate better the relationship between diesel exhaust exposure and kidney cancer. Cohort studies similar to the DEMS study [17], with information on the level of diesel exhaust exposure, and accounting for potential confounders, would provide high-quality data. New studies would gain additional value when conducted on selected industry types (e.g., mechanics, highway workers, engine operators, and handlers) and geographical areas (e.g., Latin America, Asia, and Australia) from which few data have been reported. Moreover, studies including a considerable proportion of women are needed to provide evidence on a possible modification of the association by sex.

Despite these limitations, the hypothesis of a carcinogenic effect of diesel exhaust exposure on the kidney remains. Workers should be aware of this potential hazard, which is mainly due to the risk of lung cancer but may also affect other sites, and should be provided with adequate personal protection equipment.

Supplementary Materials: The following are available online: Table S1. Characteristics of common occupational diesel exposures; Table S2. PRISMA checklist; Table S3. Modified version of the Critical Appraisal Skills Programme (CASP) checklist for cohort studies adopted for quality assessment; Table S4. Quality assessment of the included studies according to the Critical Appraisal Skills Programme (CASP) score; Figure S1. Flow diagram of the study selection process; Figure S2. Scatter plot of unweighted correlation coefficients between risk of lung and kidney cancers of the 16 studies reporting them.

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Author Contribution Statement: PB and GC conceived and designed the study; GC and FT performed the literature research; GC and PB performed the data analysis; GC wrote the manuscript; PB supervised the work; PB revised the manuscript; all authors approved the final version of this manuscript.

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