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Risk of Gynecological and Breast Cancers in Workers Exposed to Diesel Exhaust: A Systematic Review and Meta-Analysis of Cohort Studies

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ABSTRACT

Background: *This study aimed to explore the association between occupational exposure to diesel exhaust (DE) and gynaecological and breast cancers.* **Methods:** *A systematic review was performed to identify cohort studies reporting results on the association between occupational exposure to DE and risk of gynaecological and breast cancers. STROBE guidelines and PECOS criteria were followed. We identified 6 studies for breast cancer (BC), 4 for cervical cancer (CC), 4 for endometrial cancer (EC) and 7 for ovarian cancer (OC). Random-effects meta-analyses were conducted on the relationship between DE exposure and BC, CC, EC, and OC risk; 95% Confidence Intervals (CI) and prediction intervals (PI) were reported. We investigated between-study heterogeneity and potential publication bias using Egger's test.* **Results:** *No associations were observed between occupational DE exposure and risk of BC [RR=0.93; CI: 0.77-1.13; PI:0.50-1.73, I^2=80.31% (CI: 21.72-95.05%)], EC [RR=0.89; CI: 0.75-1.05; PI:0.61-1.30, I^2=0.78% (CI: 0-85.57%)], and OC [RR=1.08; CI: 0.89-1.32, PI: 0.76-1.56, I^2=11.87% (CI: 0-74.42%)]. A weak association was observed for CC [RR=1.41; CI: 1.17-1.17; PI:0.85-2.30, I^2=6.44% (CI: 0-86.40%)]. No between-study heterogeneity or publication bias was detected.* **Conclusions:** *This study identified an association between DE exposure and CC, which was not adjusted for potential confounders. No evidence of an association was found with BC, EC, and OC.*

1. Introduction

Diesel engines are used in a wide range of industrial applications and, therefore, occupational exposure to diesel exhaust (DE) is common. Exposed workers include mechanics, warehouse workers, professional drivers, shipping, and railroad workers, as well as miners and construction workers and other industries where diesel-powered vehicles and tools are applied [1].

DE is primarily composed of gases (e.g., carbon monoxide and nitrogen oxides), vapours, aerosols, and particulate matter consisting of solid carbonaceous particles which may become chemically active when are adsorbed to metallic particles and polycyclic aromatic hydrocarbons (PAH), in particular nitro-PAH [2]. Exposure to these pollutants may lead to a variety of symptoms and diseases, from acute manifestations (e.g.: eyes, nose, throat and lung irritation, headache, dizziness, coughing, phlegm, and

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nausea) to chronic ones (cardiovascular diseases, respiratory infections, and lung cancer) based on duration and intensity of exposure. However, the relative importance and underlying mechanisms of the different constituents of DE to the observed effects have not yet been fully understood.

According to the International Agency for Research on Cancer (IARC) evaluation in 2012, DE is classified as a Category 1 carcinogen to humans based on evidence in epidemiological studies that occupational exposure is associated with an increased risk for lung cancer [3]. DE is also suspected to be linked to other cancers, including cancers of the bladder, larynx, stomach, liver, pancreas, and ovary [4-8]. However, DE carcinogenicity in humans has not yet been fully investigated [3].

While there are suggestions in the scientific literature that occupational exposure to DE may increase the risk of early-onset estrogen receptor-negative breast cancer (BC) in women [2, 9, 10] and that of ovarian cancer (OC) [11], it is not yet clear if DE exposure can be considered an occupational risk factor for these and other gynecological cancers such as cervical cancer (CC), endometrial cancer (EC), fallopian tube cancer (FTC) and vaginal and vulvar cancer (VVC).

To our knowledge, no meta-analyses have been conducted on occupational DE exposure and female cancers. For this reason, considering the limited information available, we conducted a systematic review and metanalysis aimed at investigating the association between occupational exposure to DE and risk of BC and gynaecological cancers, including CC, EC, OC, FTC and VVC.

2. Methods

2.1 Identification and Selection of Studies

We conducted a systematic review in accordance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12]. A study protocol was registered in the PROSPERO database (Registration No. 352729). The inclusion criteria for study selection followed the PECOS framework (Population; Exposure; Comparators; Outcomes; Study Design) [13].

Our search strategy implied first the inclusion of the publications listed in the most recent IARC Monograph on Diesel Engine Exhaust (DE) [3]. In addition, we searched the PubMed database for studies published subsequent to the IARC report, focusing on research concerning occupational exposure to DE and its association with various types of cancer, excluding lung cancer. The PubMed search was conducted independently by two authors (GC, FT) using the search string *"(diesel OR miner OR garage OR railway OR ((truck OR bus) AND driver) OR (heavy equipment OR docker)) AND (cancer OR neoplasm)"* to identify industry-based studies reporting results on the risk of cancer among workers exposed to DE in sectors such as railway, transportation, construction, and mining. Furthermore, we supplemented our search with reports found in the reference lists of the identified articles. When multiple studies were based on the same population, we included only the most informative one, typically the one reporting the largest number of cases or deaths. An overlap of less than 10% was considered acceptable, and therefore studies with minimal overlap were treated as independent. We excluded studies lacking references to DE exposure, those involving non-occupational exposure, those lacking data on cancers other than lung cancer, and those with a design other than cohort or case-control nested in a cohort (Figure 1).

2.2 Data Extraction

Data were extracted into pre-defined forms. The following information was pulled from the studies:

- Sociodemographic factors;
- Occupation and industry type;
- Person-years of observation;
- Type of cancer – including ICD code with version;
- Measure of association, such as odds ratio (OR), risk ratio, rate ratio, standardized mortality ratio (SMR), or standardized incidence ratio (SIR), collectively referred to as relative risk (RR), with corresponding 95% Confidence Intervals (CI);
- Factors adjusted for in the analysis;

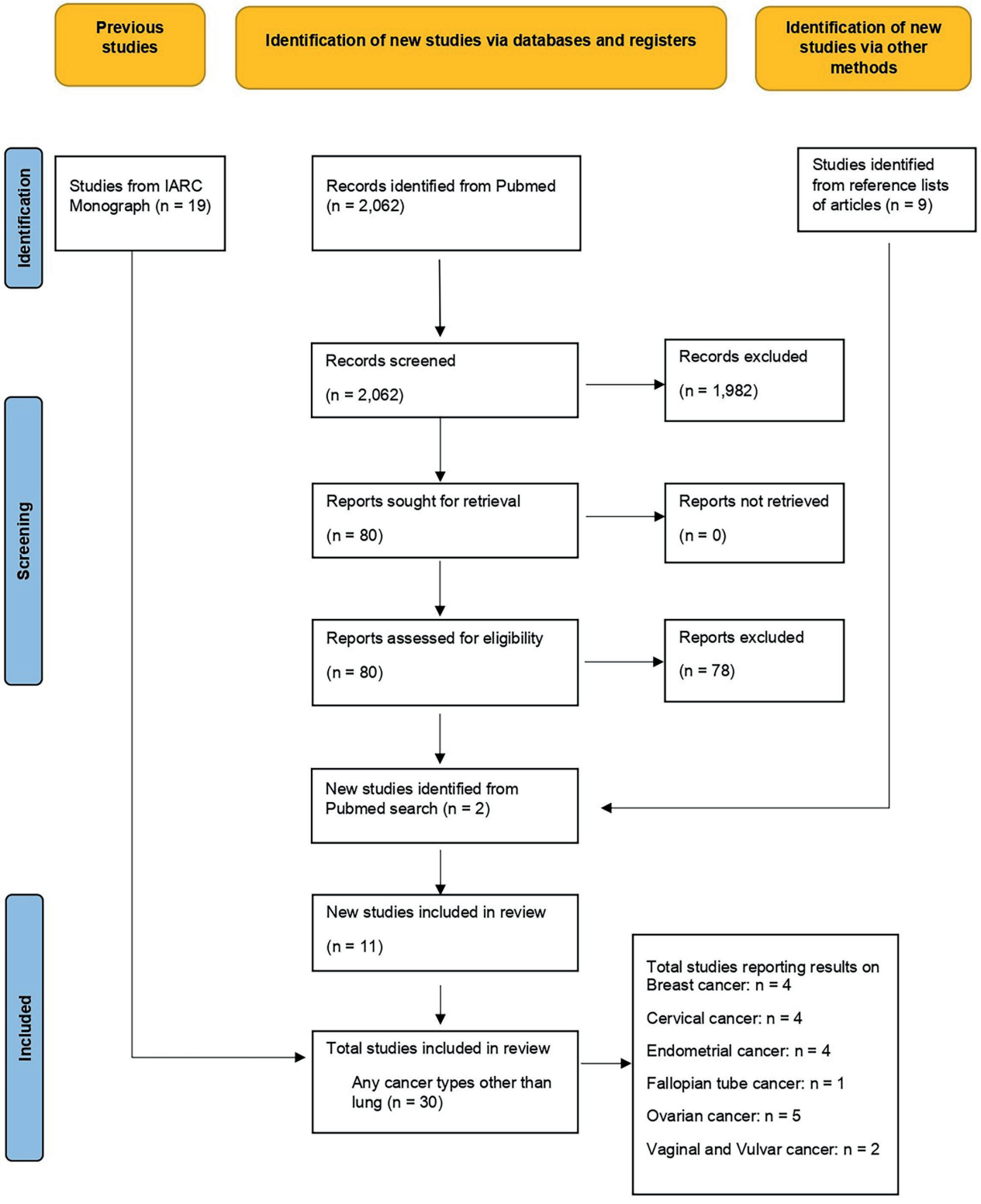

Figure 1. Flow diagram of the study selection process.

- Characteristics of the study population, such as the number of subjects included and the number of cases).

The dataset was then organized by type of cohort study (historical vs. prospective), follow-up period, geographic region, and outcome (incidence vs. mortality). Additionally, when available, we extracted results on dose-response analysis for various indicators of DE exposure.

2.3 Statistical Analysis

We conducted a quality assessment of the included studies using the CASP checklist [14], consisting of 11 items totalling 14 points. The final score was determined by averaging the results obtained independently by two authors (GC and FT). We generated a dichotomous variable, categorizing studies scoring less than 10 as "low quality" and those scoring 10 or higher as "high quality".

While the systematic literature review was performed to identify cohort studies on occupational DE exposure and risk of cancers other than lung, the subset of studies included in this analysis pertains specifically to gynecological and breast cancers. We conducted a series of meta-analyses of non-overlapping studies to calculate pooled estimates with 95% CI for BC, CC, EC, and OC, while FTC and VVC were not analysed due to the small number of studies available (Figure 2). Also, further stratified meta-analyses for any cancer type were not feasible due to the paucity of studies. We utilized the Random-Effects Sidik–Jonkman model for statistical analysis [15], reporting RRs with 95% CI. We considered p-values <0.05 as statistically significant. Moreover, 95% Prediction Intervals (PI) were provided [16]. To assess study heterogeneity, we employed the inconsistency index (I^2 statistic) along with its 95% CI [17], interpreting values as follows: 0-30% for low, 31%-60% for moderate, 61%-75% for substantial, and 76%-100% for considerable heterogeneity [18]. Furthermore, we conducted sensitivity analyses using multiple leave-one-out meta-analyses. Publication bias was evaluated using the Egger test and visual inspection of funnel plots [19] and Galbraith plots [20].

All statistical analyses were performed using STATA, version 17.0 (Stata Corp LLC, College Station, TX, US). Meta-analyses were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. The PRISMA checklist is available in Table S1.

3. Results

3.1 Study Search and Study Characteristics

First, 19 reports were identified in the IARC monograph [3] and included in the systematic review. The PubMed literature search to include studies reported after the publication of the IARC monograph resulted in 2,062 articles, of which 1,982 articles were excluded based on title and abstract, and 78 were excluded after review of the full text. Therefore, 2 new studies were included in the review, together with 9 non-overlapping reports identified from the reference lists of the papers identified in the preceding steps. A final number of 30 articles underwent full review, and 5 of them were included in the final analysis regarding gynecological and breast cancer. Among the 5 studies included for systematic review, 4 reported risk estimates for BC, CC, and EC, 1 for FTC, 5 for OC and 2 for VVC (Figure 1). Four studies were conducted in Europe, specifically in the Nordic countries, and one was conducted in the USA. Selected characteristics of the studies included in the review and meta-analysis are presented in Table 1. Risk of FTC and VVC were not further investigated due to the small number of studies available.

3.2 Breast Cancer

This meta-analysis included 4 studies, which reported 6 risk estimates (4 regarding BC in women and 2 regarding BC in men). The forest plot is shown in Figure 2. Overall, the RR of BC was 0.93 [95% CI: 0.76-1.12, 95% PI: 0.50-1.72]. The leave-one-out meta-analysis indicated that no single study exerted a disproportionately large influence on the estimation of the overall effect size when compared

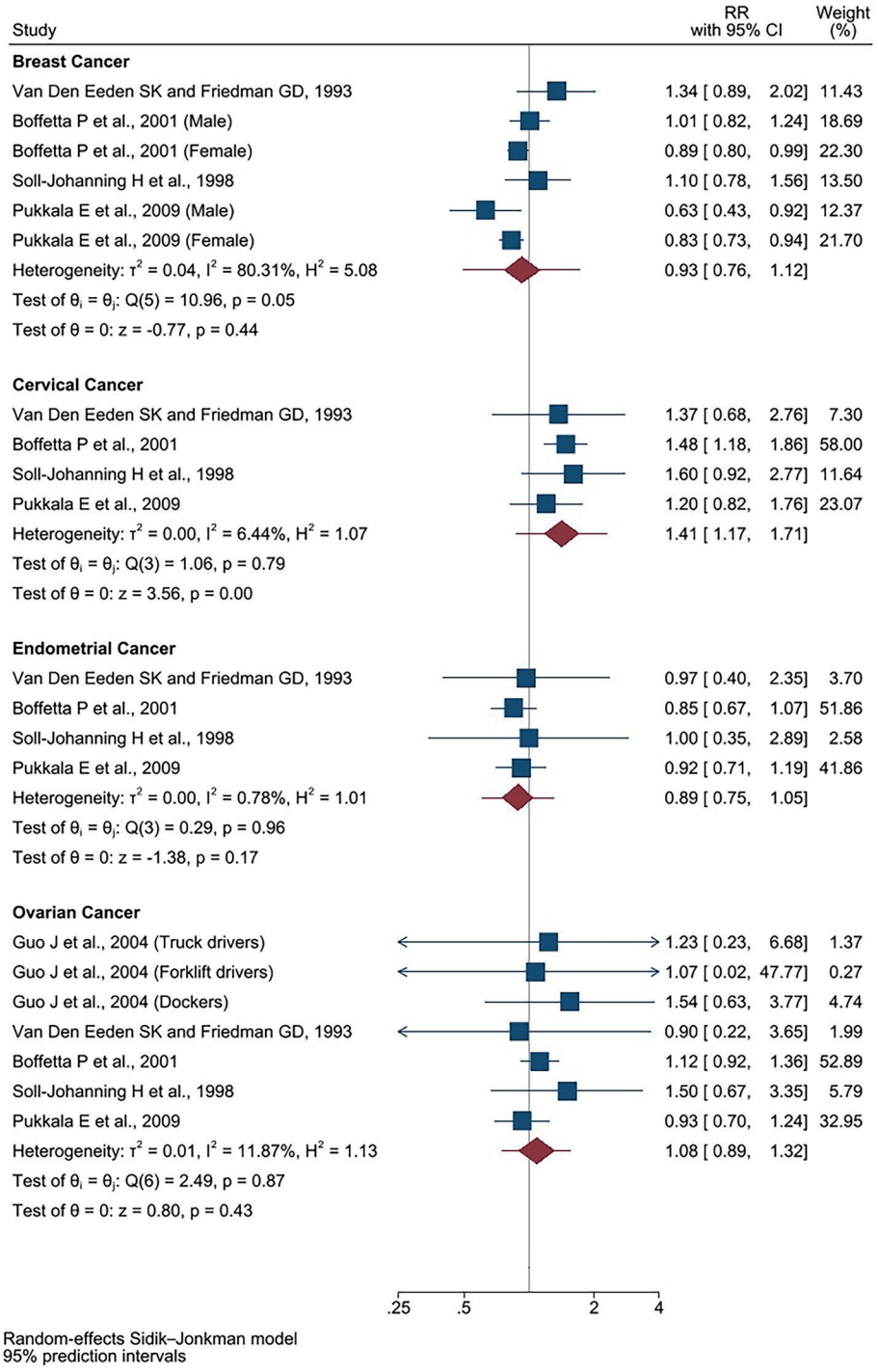

Figure 2. Forest plot of a meta-analysis of cohort studies on occupational exposure to diesel exhaust and breast, cervical, endometrial, and ovarian cancer with a 95% prediction interval.

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

Study	Cancer	Country	Cohort Type	Follow-Up	Population	Person-years	Industry	Number of cases	Adjustments	CASP Assessment
[4]	BC CC EC OC	Denmark	Retrospective Prospective	1943-92	16 023 men 1967 women	386 395	Bus drivers and tramway employers	BC (Female): 29 CC: 14 EC: 4 OC: 7	-	9.5 - Low Quality
[6]	OC	Finland	Retrospective	1971-95	Economically active Finns born between 1906 and 1945	30 million	(1) Miners, quarry workers, no metal ore (2) Engine (locomotive) drivers (3) Road-building vehicle drivers (4) Truck drivers (5) Forklift drivers, NEC (6) Excavation machine operators (7) Road-building machine operators (8) Construction machine operators, NEC (9) Dockers, stevedores	OC (1): 0 OC (2): - OC (3): 0 OC (4): 2 OC (5): 1 OC (6): 0 OC (7): 0 OC (8): 0 OC (9): 6	Socioeconomic status, BMI, number of children, age, and calendar period	12 - High Quality
[21]	BC CC EC OC VVC	USA	Retrospective	1964-88	160 230	-	People of the KPMCP with self-reported exposure, no job or industry titles	BC (Female): 2507 CC: 714 EC: 772 OC: 329 VVC: 125	-	12 - High Quality
[22]	BC CC EC OC	Sweden	Prospective	1971-89	Employed Swedish adult population	Over 7 640 000 (exposed men) Over 240 000 (exposed women)	Different job and industry titles (farmers excluded)	BC (Female): 360 BC (Male): 95 CC: 79 EC: 77 OC: 106	-	11 - High Quality
[23]	BC CC EC FTC OC VVC	Denmark Finland Iceland Norway Sweden	Prospective	1961-2005	15 million (NOCCA cohort)	385 million	Engine operators	BC (Female): 255 BC (Male): 29 CC: 29 EC: 59 FTC: OC: 49 VVC: 10	Age	12.75 - High Quality

BC: breast cancer; CC: cervical cancer; EC: endometrial cancer; FTC: Fallopian tube cancer; OC: ovarian cancer; VVC: vaginal and vulvar cancer; NEC: not elsewhere classified; BMI: body mass index; NOCCA: Nordic Occupational Cancer; KPMCP: Kaiser Permanente Medical Care Program.

with the others (Figure S1). The reported heterogeneity statistic I^2 was 80.31% [95% CI: 21.72-95.05%]. The between-study variance τ^2 is estimated to be 0.04. The Egger test for publication bias was not significant (p=0.61). The corresponding funnel plot and Galbraith plot are reported in Figures S2 and Figure S3. Further stratified meta-analyses could not be performed due to the small number of risk estimates available.

3.3 Cervical Cancer

This meta-analysis included 4 studies, corresponding to 4 risk estimates. The forest plot is shown in Figure 2. Overall, the RR of CC was 1.41 [95% CI: 1.17-1.71, 95% PI: 0.87-2.29]. The leave-one-out meta-analysis indicated that no single study exerted a disproportionately large influence on the estimation of the overall effect size when compared with the others (Figure S4). The reported heterogeneity statistic I^2 was 6.44% [95% CI: 0-86.40%]. The between-study variance τ^2 is estimated to be <0.01. The Egger test for publication bias was not significant (p=0.87). The corresponding funnel plot and Galbraith plot are reported in Figures S5 and Figure S6. Further stratified meta-analyses could not be performed due to the small number of risk estimates available.

3.4 Endometrial Cancer

This meta-analysis included 4 studies, corresponding to 4 risk estimates. The forest plot is shown in Figure 2. Overall, the RR of EC was 0.89 [95% CI: 0.75-1.05, 95% PI: 0.61-1.30]. The leave-one-out meta-analysis indicated that no single study exerted a disproportionately large influence on the estimation of the overall effect size when compared with the others (Figure S7). The reported heterogeneity statistic I^2 was 0.78% [95% CI: 0-85.57%]. The between-study variance τ^2 is estimated to be <0.01. The Egger test for publication bias was not significant (p=0.73). The corresponding funnel plot and Galbraith plot are reported in Figures S8 and Figure S9. Further stratified meta-analyses could not be performed due to the small number of risk estimates available.

3.5 Ovarian Cancer

This meta-analysis included 5 studies, corresponding to 7 risk estimates. The forest plot is shown in Figure 2. Overall, the RR of OC was 1.08 [95% CI: 0.89-1.32, 95% PI: 0.76-1.56]. The leave-one-out meta-analysis indicated that no single study exerted a disproportionately large influence on the estimation of the overall effect size when compared with the others (Figure S10). The reported heterogeneity statistic I^2 was 11.87% [95% CI: 0-74.42%]. The between-study variance τ^2 is estimated to be 0.01. The Egger test for publication bias was not significant (p=0.64). The corresponding funnel plot and Galbraith plot are reported in Figures S11 and Figure S12. Further stratified meta-analyses could not be performed due to the small number of risk estimates available.

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis of cohort studies to assess the association between occupational DE exposure and risk of gynecological and breast cancers. While the meta-analysis suggested a positive association between risk of CC and DE exposure, we found no association between DE exposure and risk of BC, EC, and OC. On the other hand, the results we observed on CC supports the design of occupational interventions aimed at increasing the knowledge of HPV infections, and its vaccination and possibly enhancing access to CC screening programs [24, 25].

BC is causally associated with different reproductive factors, such as age at menarche, age at menopause, parity, number of children, age at first birth, and use of oral contraceptives or hormonal substitutive therapy [26-29]. Previous literature reported that night-shift work may represent an occupational risk associated with BC [30]. Several studies among nurses have indicated that this population has a higher risk of developing BC compared to the general female population [31-33]. The investigation of possible risk factors for BC in large female workers cohorts is showing associations with several chemicals, such as benzene, solvents, and metals [34-37]. Limited evidence has been produced

around DE exposure. A recent study conducted in Denmark (not included in the meta-analysis since published after the end of the systematic review) found no overall association between BC and DE in female workers, despite an increased risk of early-onset estrogen receptor negative BC in the exposed was suggested [9]. Similar results were also obtained from a study investigating exposure to vehicle traffic, which contains diesel exhaust [38]. All in all, studies currently do not allow to establish any causal relationship between occupational risk factors and BC [37].

Obesity is recognized as a risk factor for EC [39], together with hypertension, oral contraceptive use, and parity [40]. Limited evidence is available regarding occupational EC risks, and findings are not conclusive on any possible hazards in specific occupational settings [41, 42].

OC is causally related to hormonal and reproductive factors, with an increased risk related to BMI and usage of hormone replacement therapy (HRT) and a decreased risk related to parity and the number of live births [43-45], while few publications investigated this disease in association to occupational exposures [46-50].

The studies included in this meta-analysis were not designed to investigate female cancers after occupational DE exposure. Report and publication bias are a possibility in these circumstances. Although the test for publication bias was not significant for any cancer, the small number of studies reduced the power of such tests. Moreover, only two studies adjusted for important confounders such as age. The duration of the follow-up period may also have affected the observed results. Latency is indeed a major factor when considering cohort studies on cancer: the longer the follow-up period, the higher the likelihood of observing the occurrence of epithelial cancers in the population [51]. Three out of 5 studies included in this meta-analysis followed up workers for less than 30 years and more cases of female cancer would have been included if the studies had covered longer periods, with the possibility to detect associations that have remained hidden.

As far as the underlying mechanisms involved in DE carcinogenic effects on female organs are scarcely supported by the available literature [2, 3, 9-11], the lack of association found in this analysis is likely reflecting a real lack of effect.

The significant association between DE exposure and CC should nonetheless be pointed out for several reasons. First of all, other studies have reported a significantly increased occupational risk of CC among female workers [22, 37]. This analysis of CC risk was based on 4 risk estimates, limiting the power of the analysis of heterogeneity and publication bias. We used the Sidik–Jonkman method for estimating the between-study variability (τ^2) rather than the most popular DerSimonian–Laird method [52] due to the known tendency of the latter to underestimate τ^2 when the number of studies is small [53]. 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 higher coverage probability than the commonly used interval based on the DerSimonian-Laird method [54], but despite this, the CC risk estimate is still statistically significant. Moreover, 3 out of 4 studies included in this meta-analysis were classified as "high quality", and meta-analysis based on higher-quality studies with robust methodologies tend to provide more reliable evidence while addressing the healthy worker survivor effect as well as potential information bias through appropriate reference selection and lag time analyses. Finally, the consistency among the included studies in terms of the direction and magnitude of the effects adds strength to the conclusions drawn from this meta-analysis, even though, given the small number of studies involved, it was not possible to obtain a precise estimate of the heterogeneity among studies (I^2 = 6.44%, 95% CI: 0-86.40%) [55].

However, the CI addresses only the precision of the mean estimate since it reflects only the error of estimation of the mean. The dispersion of true effect sizes is addressed by the PI, which crossed the no-effect threshold, indicating that there are settings where DE exposure will have no effect or even an effect in the opposite direction on CC [16].

Moreover, the lack of information in all the studies included in the analysis about HPV infection status, and about HPV-related factors such as sexual habits, educational level, and screening participation rates was a major limitation. In fact, HPV is

the most important risk factor in CC development [37]. On turn, occupational risk may explain part of the disparities observed in women of different social classes. In this sense, the fact that women occupationally exposed to DE result in being more likely to develop CC may be the effect of residual confounding as HPV, physical activity, and cigarette smoking [37, 56]. There is also the possibility that participation in the HPV screening programmes varies by occupational category [57]. With this regard, certain working categories might represent special populations to be targeted with interventions aimed at increasing CC screening participation [24, 25, 58]. Also, the workplace might represent a novel setting for screening initiatives [59-60].

Many studies have reported that socioeconomic disparities may be related to a higher HPV prevalence and poor lifestyle habits in less educated, low-income women, as well as to a higher prevalence in low-income countries where HPV is more widespread [61-63]. For this reason, categories of workers exposed to DE – which often include low-income and blue-collar workers – may be at higher risk of developing cancer independently from their occupational exposure, but rather because of other established lifestyle carcinogens. Therefore, studies including adjustments for potential confounders are warranted to explain the relationship we observed in this meta-analysis.

4.1 Strengths and Limitations

This study has several strengths. This is the first systematic review and meta-analysis to investigate the relationship between DE exposure in female workers and the risk of breast and gynecological cancers, providing novel data to better understand the epidemiology of these cancers. Specific workers, such as drivers and engine operators, have generally higher exposure levels than the general population. Most importantly, the exposure assessment among workers is likely to be more valid than that conducted on the general population. For these reasons, we restricted our research specifically to occupational DE exposure, and our data collection focused on working categories who are known to be highly exposed to DE. We also considered only cohort studies since they provide higher-quality data and less opportunity for selection bias compared to case-control or cross-sectional studies [64]. Moreover, the meta-analyses were performed following solid methodological guidelines, and 4 out of 5 studies included were classified as "high quality".

However, the results should be interpreted cautiously, as some limitations should be acknowledged. First, the scarce number of women in working cohorts, next to the low incidence of some of the types of cancers investigated (e.g., OC, VVC, FTC) and the small number of studies included in the analysis, limited the statistical power of the analysis. The small number of studies available for each meta-analysis also resulted in imprecise estimates of the heterogeneity index I^2. Second, differences between the studies in the definition of DE exposure and of the working populations might introduce bias, despite not being differential among cases and non-cases. Also, little information was available on the type of DE exposure and the working activities of the populations included, limiting the possibility of interpreting the results. Third, this meta-analysis is based on only 5 studies, 4 of which were conducted in the Nordic countries, limiting the generalization of the results. Finally, as with all meta-analyses, language bias cannot be ruled out entirely as our analysis is based only on published studies written in English.

5. Conclusions

This study provided no evidence of an increased risk of BC, OC, or EC in workers exposed to DE. We observed a significant increase in the risk of CC. Potential confounding was not controlled for, and other sources of bias cannot be excluded, which preempts conclusions in terms of causality. However, these results suggest that women employed in work settings where they are exposed to DE may benefit from occupational-based CC screening.

Supplementary Materials: The following are available online:

- Table S1: PRISMA checklist
- Figure S1: Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of breast cancer (BC)

- Figure S2: Funnel plot of the analysis on occupational diesel exhaust exposure and risk of breast cancer (BC)
- Figure S3: Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of breast cancer (BC)
- Figure S4: Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of cervical cancer (CC)
- Figure S5: Funnel plot of the analysis on occupational diesel exhaust exposure and risk of cervical cancer (CC)
- Figure S6: Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of cervical cancer (CC)
- Figure S7: Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of endometrial cancer (EC)
- Figure S8: Funnel plot of the analysis on occupational diesel exhaust exposure and risk of endometrial cancer (EC)
- Figure S9: Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of endometrial cancer (EC)
- Figure S10. Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of ovarian cancer (OC)
- Figure S11: Funnel plot of the analysis on occupational diesel exhaust exposure and risk of ovarian cancer (OC)
- Figure S12: Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of ovarian cancer (OC)

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Declaration of Interest: P.B. acted as expert witness in litigation concerning diesel exhaust exposure and gastrointestinal cancers, unrelated to the present work. No conflicts were reported by the other authors.

Author Contribution Statement: PB and GC conceived and designed the study; GC and FT searched the literature, identified relevant articles, and reviewed the full text, with PB assistance; MD conducted the statistical analysis and drafted the manuscript; GC and PB interpreted the data and revised the manuscript.

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La Medicina del Lavoro

Risk of Gynecological and Breast Cancers in Workers Exposed to Diesel Exhaust: A Systematic Review and Meta-Analysis of Cohort Studies

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Supplementary Material

Table S1 – PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pag. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pag. 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pag. 1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pag. 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pag. 2-3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pag. 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Pag. 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pag. 2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pag. 2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pag. 2-4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pag. 2-4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pag. 4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pag. 4

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pag. 2
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pag. 2
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pag. 4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pag. 4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pag. 4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pag. 4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Fig. 1
Study characteristics	17	Cite each included study and present its characteristics.	Tab. 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Tab. 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Fig. 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pag. 4-5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups,	Pag. 4-6

Section and Topic	Item #	Checklist item	Location where item is reported
		describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pag. 4-5
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pag. 4-5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pag. 4-5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pag. 4-5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pag. 9-10
	23b	Discuss any limitations of the evidence included in the review.	Pag. 11
	23c	Discuss any limitations of the review processes used.	Pag. 11
	23d	Discuss implications of the results for practice, policy, and future research.	Pag. 9-10
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pag. 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pag. 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pag. 11
Competing interests	26	Declare any competing interests of review authors.	Pag. 12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Pag. 11

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Figure S1. Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of breast cancer (BC)

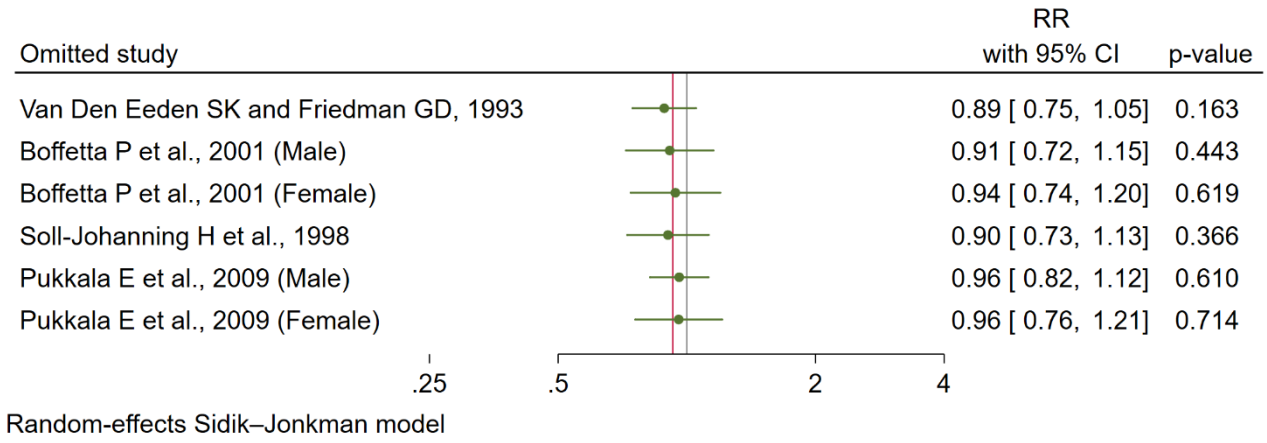

Figure S2. Funnel plot of the analysis on occupational diesel exhaust exposure and risk of breast cancer (BC)

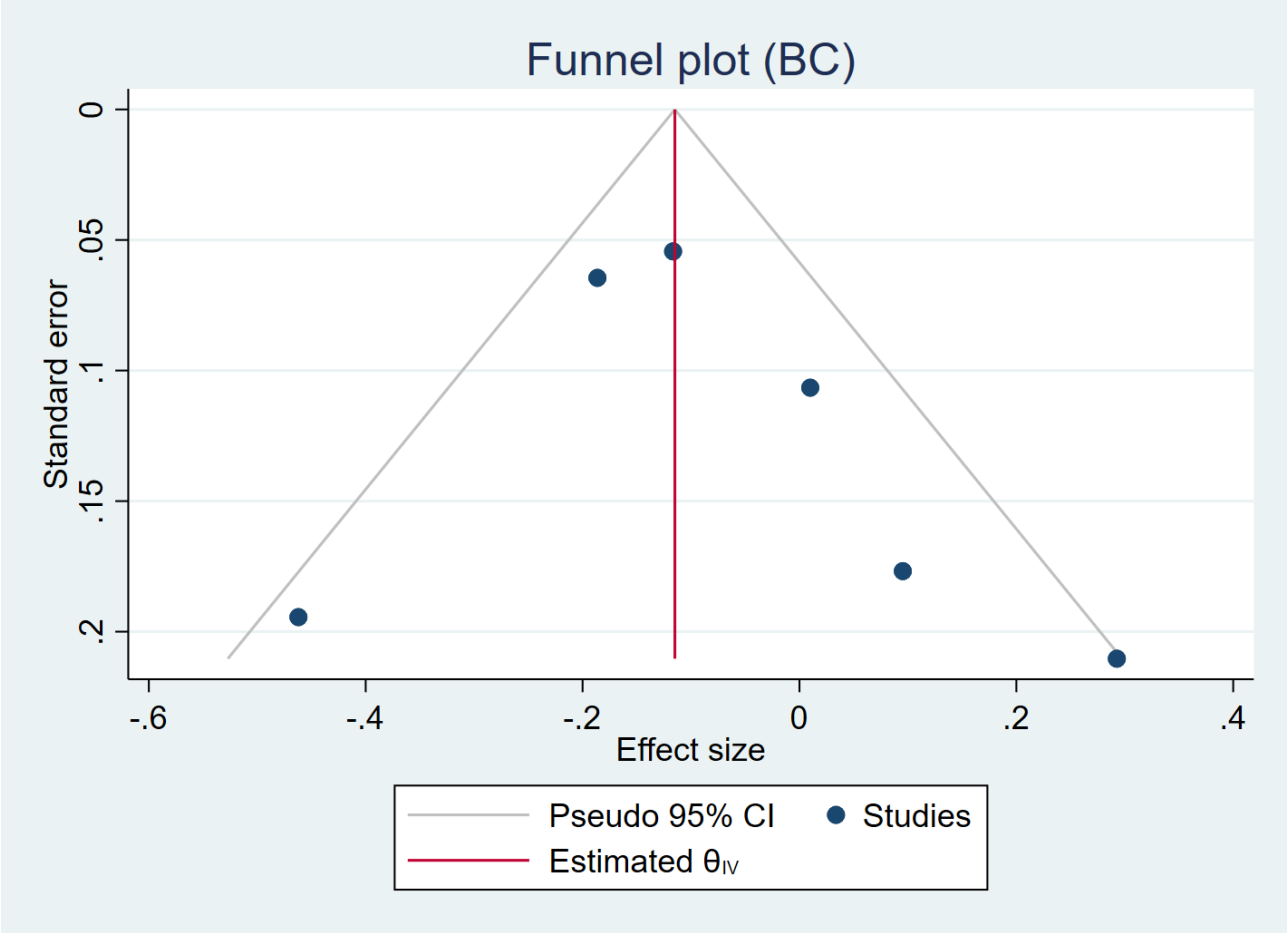

Figure S3. Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of breast cancer (BC)

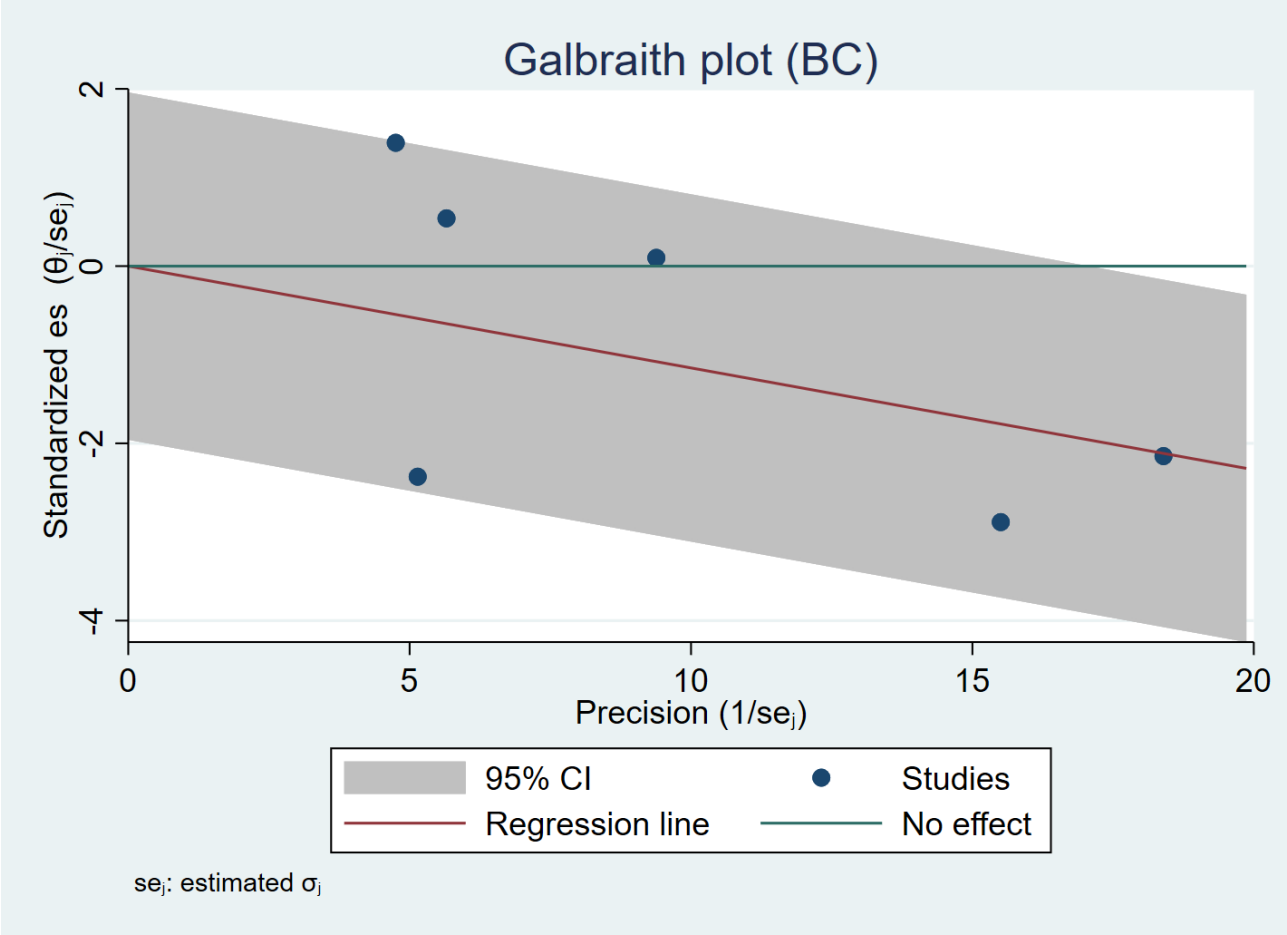

Figure S4. Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of cervical cancer (CC)

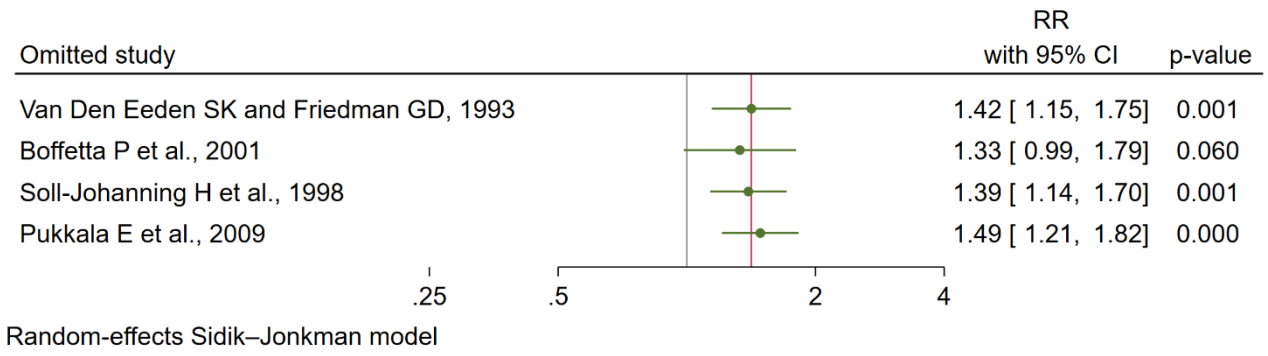

Figure S5. Funnel plot of the analysis on occupational diesel exhaust exposure and risk of cervical cancer (CC)

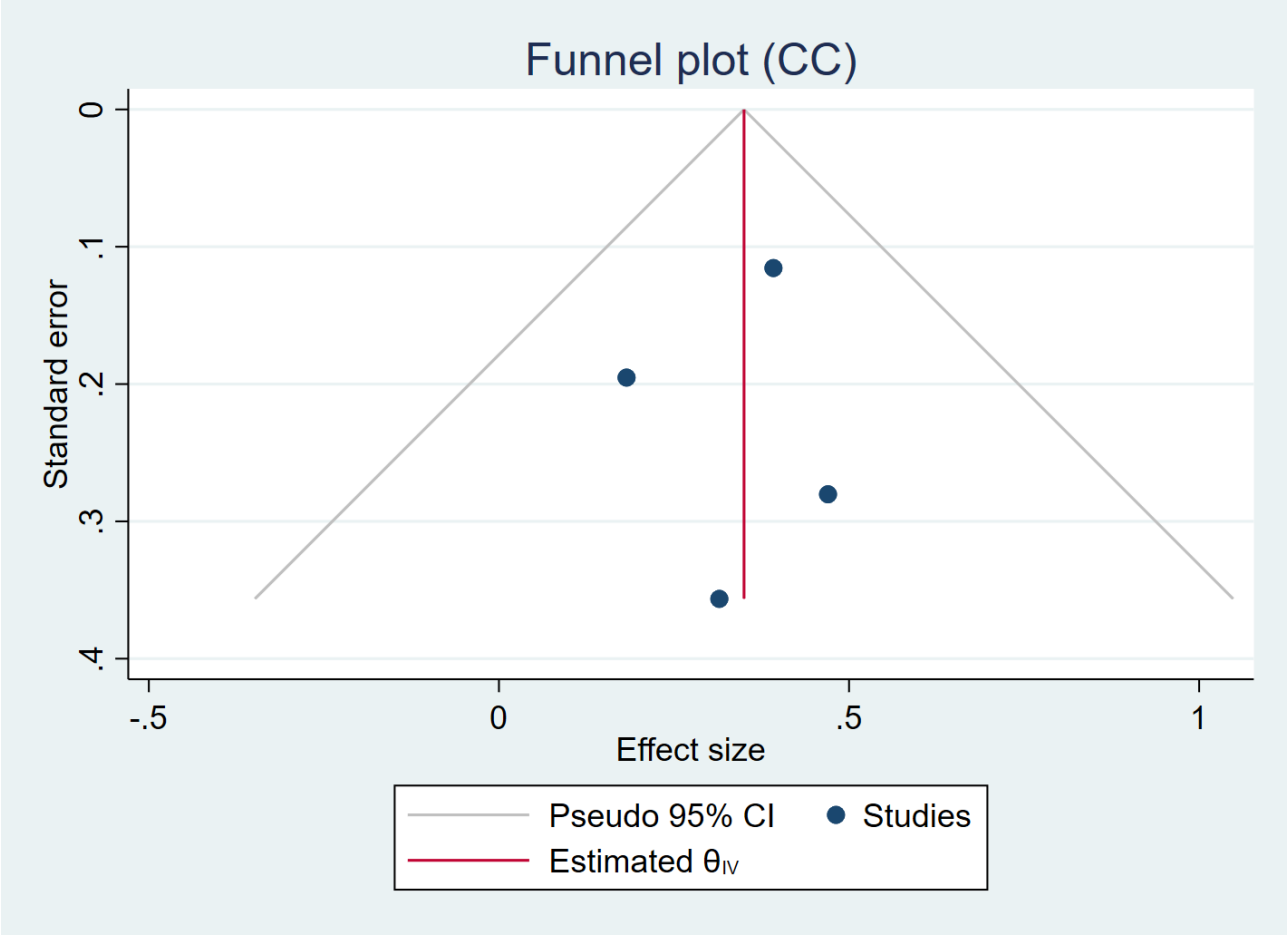

Figure S6. Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of cervical cancer (CC)

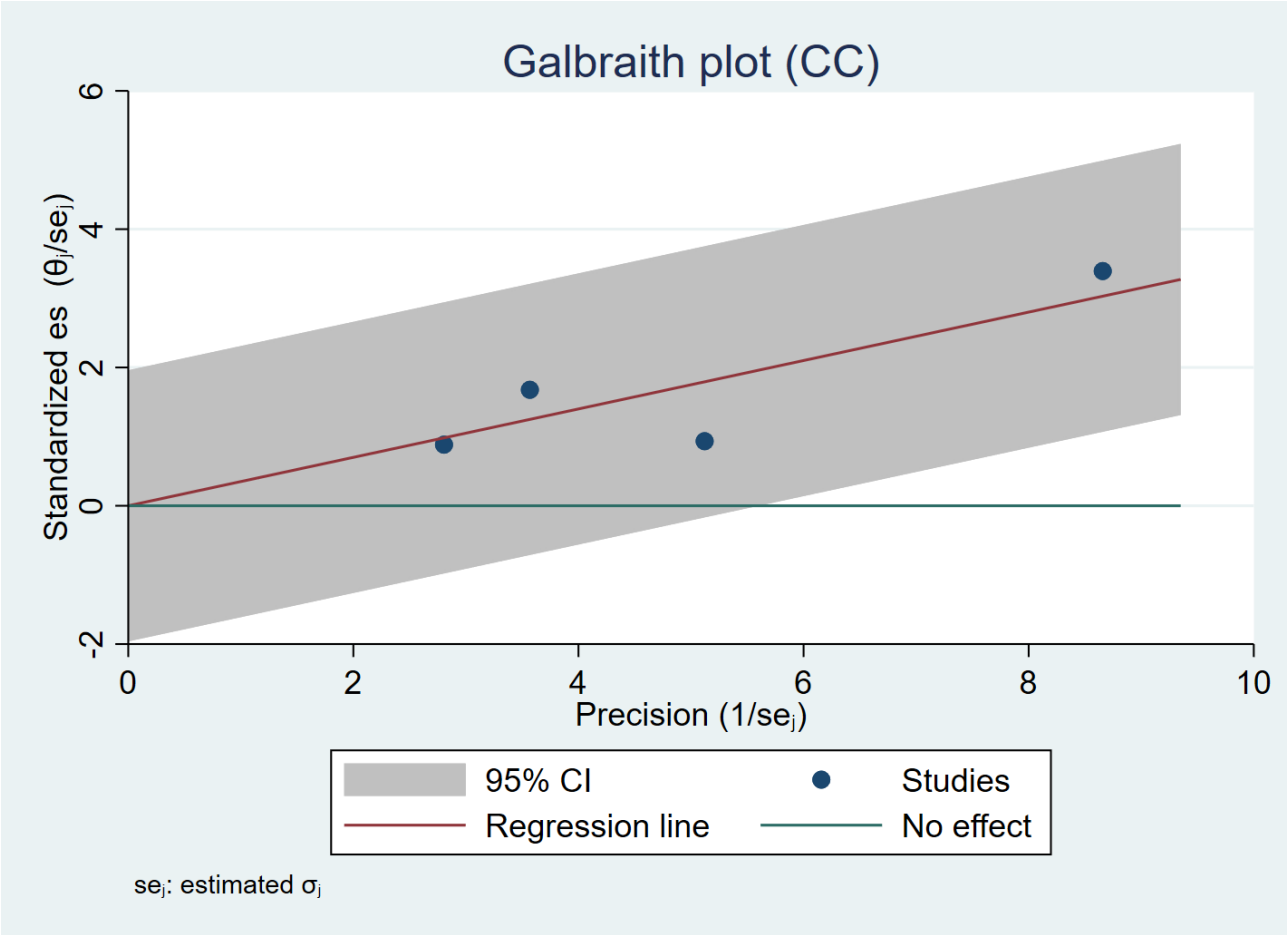

Figure S7. Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of endometrial cancer (EC)

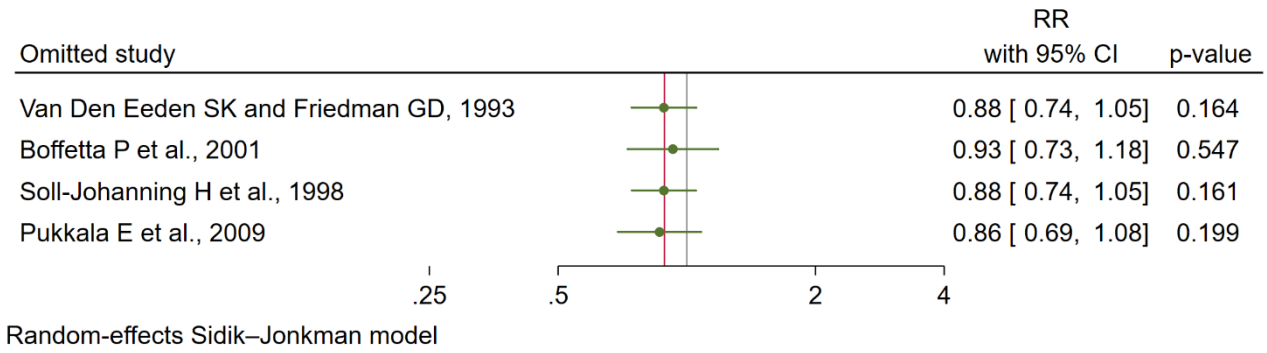

Figure S8. Funnel plot of the analysis on occupational diesel exhaust exposure and risk of endometrial cancer (EC)

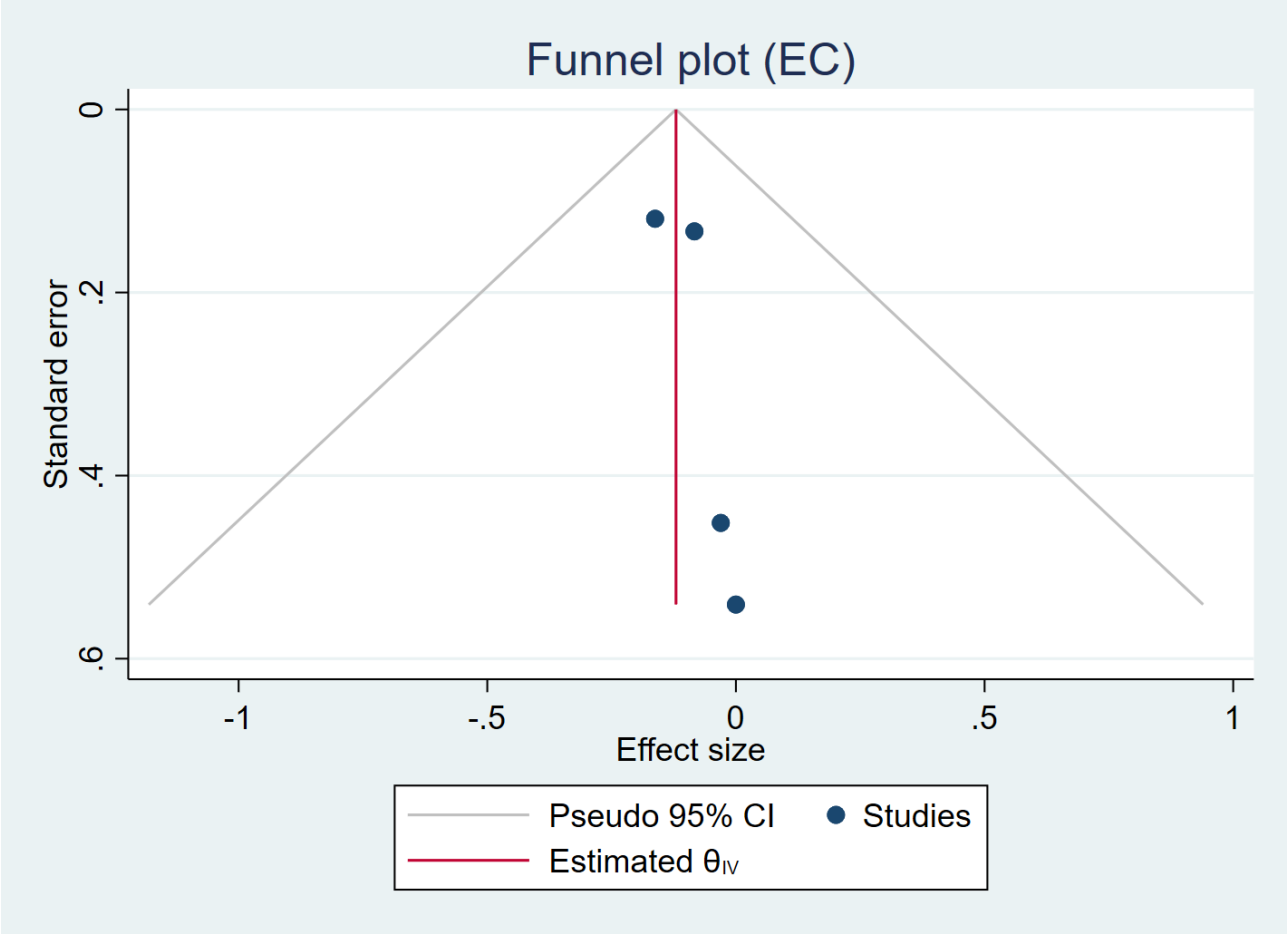

Figure S9. Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of endometrial cancer (EC)

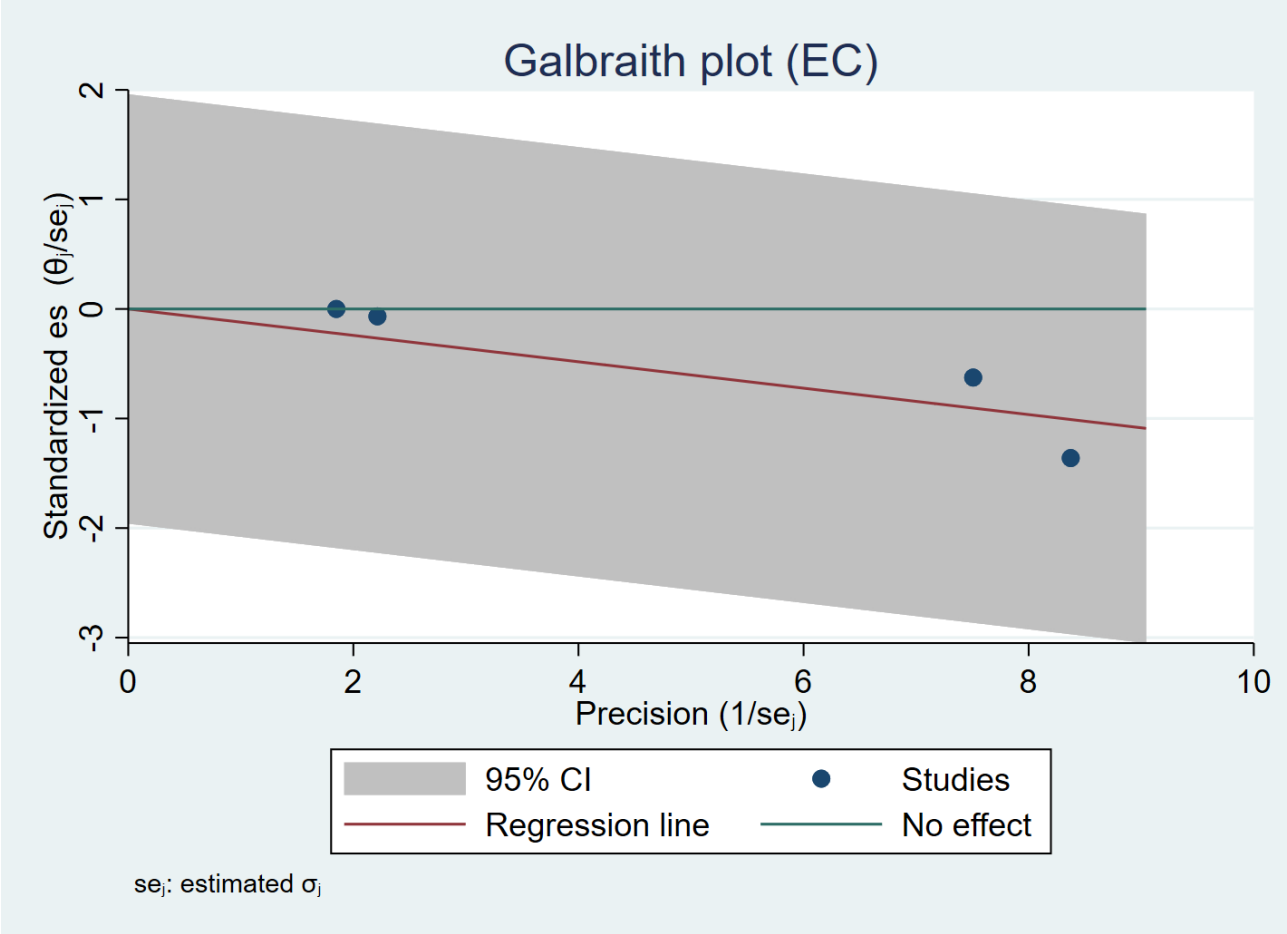

Figure S10. Forest plot of the leave-one-out meta-analysis of cohort studies on occupational diesel exhaust exposure and risk of ovarian cancer (OC)

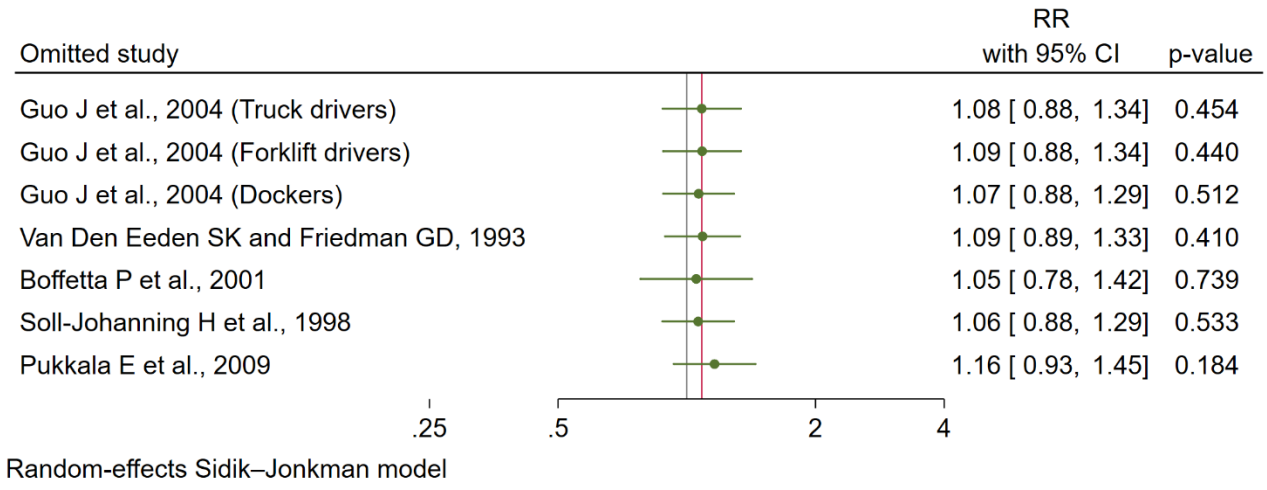

Figure S11. Funnel plot of the analysis on occupational diesel exhaust exposure and risk of ovarian cancer (OC)

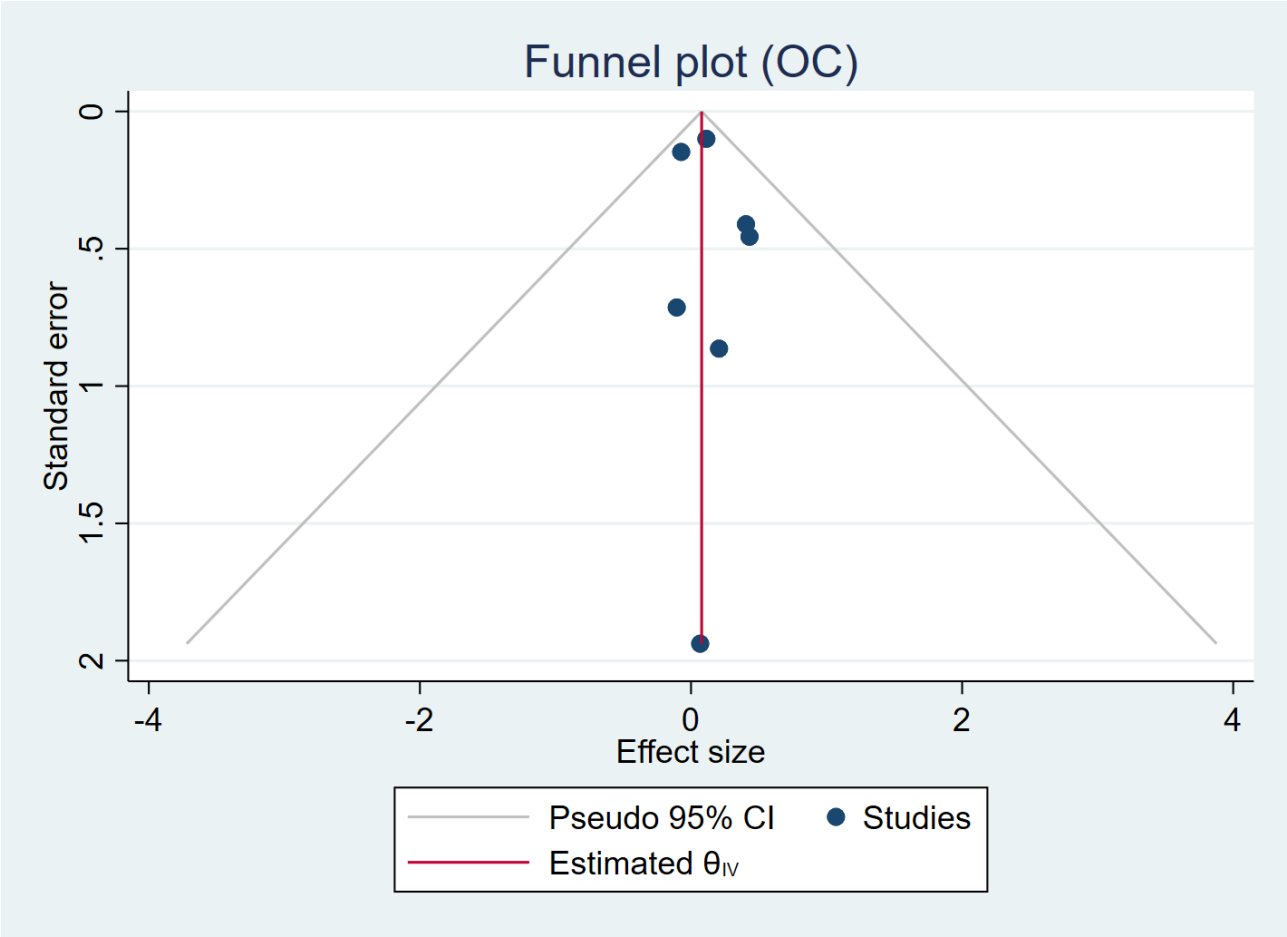

Figure S12. Galbraith plot of the analysis on occupational diesel exhaust exposure and risk of ovarian cancer (OC)