STATENS BEREDNING FÖR MEDICINSK OCH SOCIAL UTVÄRDERING

Appendix 8 Analyses: Occupational Exposures and COPD

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This appendix contains the statistical analyses carried out within this systematic review. For each of the five exposure categories (presented in the following order: inorganic dust, organic dust, unspecified dust, gases, vapors and fumes, and pesticides), the following information is provided:

1. *Main analyses*. Meta-analyses of odds ratios to gauge the overall relationship between occupational exposure and COPD, across the included studies.

2. *Sensitivity analyses.* To explore if the overall result was significantly affected if one study at a time was removed from the analyses.

3. *Moderator analyses*. We compared the estimates of the association for two groups of studies: those with or without an initial fixed effect weighing.

4. *Additional studies.* These are studies that belong to the exposure category but had not reported odds ratios. Presented in table form.

5. *Publication bias*. To investigate the effect of possible publication bias, we present both funnel plots (with log odds ratios) and statistical analyses using the trim-and-fill method.

6. Description of identified *subgroups* (quartz dust, metal dust, welding particles and fumes, wood dust, and exhausts). The studies that could be attributed to these subgroups are summarized in table form. Only those that contained five or more studies are presented.

Inorganic dust

The meta-analysis included 27 studies with odds ratio (OR) data. In addition, 8 relevant studies did not report ORs.

Main analysis

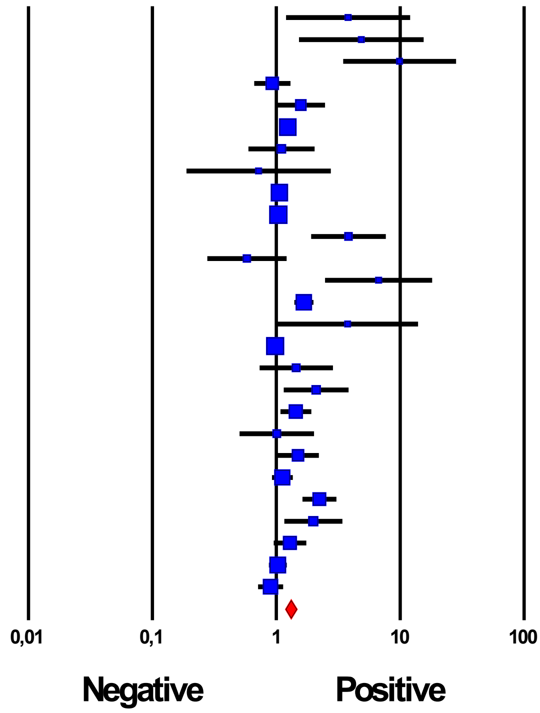
The overall weighted relationship (random effects-analysis) for inorganic dusts was OR=1.31 (95% CI, 1.19 to 1.45), z=5.34, p <.001. Heterogeneity: Q(26)=159.62, p <.001. I^2=84%, τ^2=0.03. See Fig 1.

Figure 1 Meta-analysis for 27 studies examining the relationship between inorganic dust and COPD.

Inorganic dust

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
	Statistics for each study					
Mastrangelo 2003	3,800	1,210	11,934	2,286	0,022	0,69
Stepniewski 2003	4,860	1,540	15,337	2,696	0,007	0,68
Mwaiselage 2004	9,900	3,500	28,003	4,321	0,000	0,82
Matheson 2005	0,930	0,670	1,291	-0,434	0,664	4,34
Weinmann 2008	1,580	1,020	2,447	2,049	0,040	3,16
Eduard 2009	1,240	1,120	1,373	4,142	0,000	7,60
Govender 2011	1,100	0,600	2,017	0,308	0,758	2,02
Lamprecht 2011	0,720	0,190	2,728	-0,483	0,629	0,52
Nordby 2011	1,060	0,950	1,183	1,042	0,297	7,50
Soyseth 2011	1,040	1,010	1,071	2,626	0,009	8,20
Möhner 2013	3,830	1,930	7,600	3,840	0,000	1,67
Hansell 2014	0,580	0,280	1,201	-1,466	0,143	1,51
Cui 2015	6,700	2,500	17,956	3,782	0,000	0,90
Dement 2015	1,670	1,410	1,978	5,939	0,000	6,65
Koh 2015	3,770	1,030	13,799	2,005	0,045	0,55
Taeger 2016	0,980	0,930	1,033	-0,756	0,450	8,07
Tagiyeva 2017	1,450	0,740	2,841	1,083	0,279	1,72
Vinnikov 2017	2,100	1,160	3,802	2,450	0,014	2,09
Doney 2019	1,440	1,090	1,902	2,567	0,010	5,00
Henneberger 2020	1,010	0,510	2,000	0,029	0,977	1,68
Ma 2022	1,500	1,030	2,184	2,114	0,035	3,77
Rous 2023	1,120	0,930	1,349	1,195	0,232	6,40
Wang 2023a	2,230	1,640	3,032	5,115	0,000	4,60
Wang 2023b	1,990	1,170	3,385	2,539	0,011	2,45
Wardyn 2023	1,290	0,960	1,733	1,689	0,091	4,76
Guseva Canu 2024	1,030	0,880	1,206	0,368	0,713	6,83
Loeb 2024	0,900	0,720	1,125	-0,925	0,355	5,82
Pooled	1,310	1,186	1,446	5,336	0,000	

Odds ratio and 95% CI



Random effects Meta-analysis

Sensitivity analyses

Sensitivity analyses were performed using the one-study-removed principle. Removing any of the included 27 studies did not affect the point estimate, confidence interval or p-value significantly. In other words, if any one study were to be removed from the meta-analysis the result would not change. The range for ORs was 1.26 to 1.40.

Moderator analyses

Six studies in the meta-analysis (Eduard [1], Dement [2], Rous [3], Soyseth [4], Loeb [5], and Weinmann [6]) used an internal fixed-effect OR-value. To find out if the data provided by these studies would give a different overall estimate we conducted a moderator analysis with separate groups for studies with and without an initial fixed effect weighing.

- REM within the FEM-group (k=6): OR=1.20 (95% CI, 1.02 to 1.41), p <.05.
- REM for the rest of the studies (k=21): OR=1.49 (95% CI, 1.26 to 1.76), p <.001.

Conclusion: both types of input data generate significant positive relationships.

Additional studies

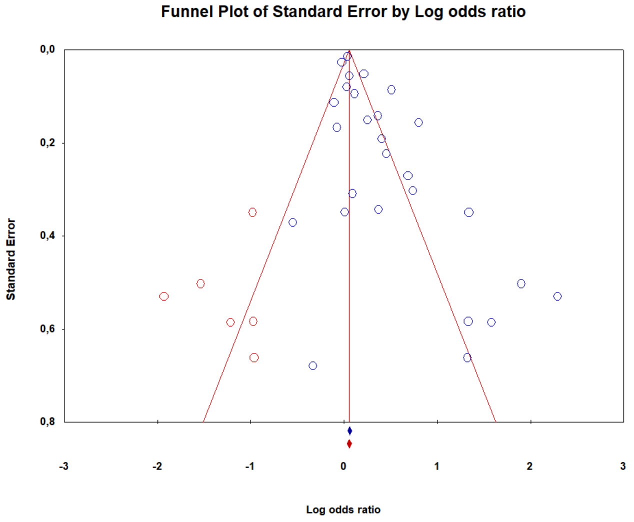
Study Reference	Point estimate (95% CI)	Comment
Bala 2010 [7]	RR=5.11 (3.30 to 6.50)	Positive relationship (sig)
Mehta 2012 [8]	IRR=1.10 (1.01 to 1.20)	Positive relationship (sig)
Alif 2017 [9]	RR=1.03 (0.97 to 1.10)	Positive relationship (non sig)
Lytras 2018 [10]	RR=1.07 (0.73 to 1.56)	Positive relationship (non sig)
Moitra 2020 [11]	PR=0.96 (0.84 to 1.09)	Negative relationship (non sig)
Grahn 2021 [12]	HR=1.28 (1.16 to 1.40)	Positive relationship (sig)
DeMatteis 2022 [13]	PR=0.92 (0.87 to 0.97)	Negative relationship (sig)
Darby 2012 [14]	OR=2.50	Neither CI, SE nor exact p-value reported

A more varied result emanates: three significant and positive, two non-significant positive, one study reporting a non-significant negative relationship, and one study a significant negative relationship. Overall, however, the other studies point towards a positive relationship between exposure for inorganic dust and COPD.

Publication bias

A trim-and-fill analysis results in the imputation of six studies. The re-analysis still shows a significant overall OR: 1.22 (95% CI, 1.10 to 1.35). See Figure 2.

Figure 2 Funnel plot for studies examining exposure to inorganic dust



Subgroups

Quartz dust

Study Reference	Point estimate (95% CI)	Effect size measure	Comment
Eduard 2009 [1]	1.30 (0.96 to 1.80)	OR	Positive relationship (non sig)
Möhner 2013 [15]	3.83 (1.93 to 7.57)	OR	Positive relationship (sig)
Hansell 2014 [16]	0.82 (0.26 to 2.59)	OR	Negative relationship (non sig)
Dement 2015 [2]	2.13 (1.50 to 3.03)	OR	Positive relationship (sig)
Wardyn 2023 [17]	1.29 (0.96 to 1.72)	OR	Positive relationship (non sig)
Loeb 2024 [5]	0.73 (0.39 to 1.36)	OR	Negative relationship (non sig)
Grahn 2021 [12]	1.46 (1.13 to 1.90)	HR	Positive relationship (sig) men only

In the quartz dust subgroup, we found mixed results: five positive (whereof three significant) and two negative relationships (both non-significant). In general, there is some support for occupational exposure to quartz dust having a statistical relationship with COPD.

Metal dust

Study Reference	Point estimate (95% CI)	Effect size measure	Comment
Weinmann 2008 [6]	1.50 (0.98 to 2.30)	OR	Positive relationship (non sig)
Soyseth 2011 [4]	1.04 (1.01 to 1.08)	OR	Positive relationship (sig)
Ma 2022 [18]	1.50 (1.06 to 2.18)	OR	Positive relationship (sig)
Rous 2023 [3]	1.14 (0.93 to 1.40)	OR	Positive relationship (non sig)
Bala 2010 [7]	5.11 (3.30 to 6.50)	RR	Positive relationship (sig)
Alif 2017 [19]	1.71 (1.03 to 2.88)	RR	Positive relationship (sig)
Lytras 2018 [10]	1.00 (0.50 to 1.60)	RR	Zero relationship
Grahn 2021 [12]	1.24 (0.97 to 1.60)	HR	Positive relationship (non sig)
DeMatteis 2022 [13]	0.89 (0.82 to 0.97)	PR	Negative relationship (sig)

In the metal dust subgroup, we found a positive relationship between the occupational exposure to metal dust and COPD for seven out of nine studies.

Welding particles and fumes

Study Reference	Point estimate (95% CI)	Effect size measure	Comment
Koh 2015 **[20]**	3.77 (1.03 to 16.21)	OR	Positive relationship (sig)
Hansell 2014 [16]	0.95 (0.39 to 2.30)	OR	Negative relationship (non sig)
Dement 2015 [2]	1.50 (1.05 to 2.14)	OR	Positive relationship (sig)
Stepniewski 2023 **[21]**	4.86 (1.54 to 15.30)	OR	Positive relationship (sig)
Grahn 2021 [12]	1.25 (0.97 to 1.60)	HR	Positive relationship (non sig)

For welding particles and fumes, the general finding was a positive relationship between occupational exposure to welding particles and fumes and COPD. Three of five studies are both positive and significant, and a fourth study contributes a non-significant but positive finding.

Organic dust

The meta-analysis included 19 studies with odds ratio (OR) data. In addition, 7 relevant studies did not report ORs.

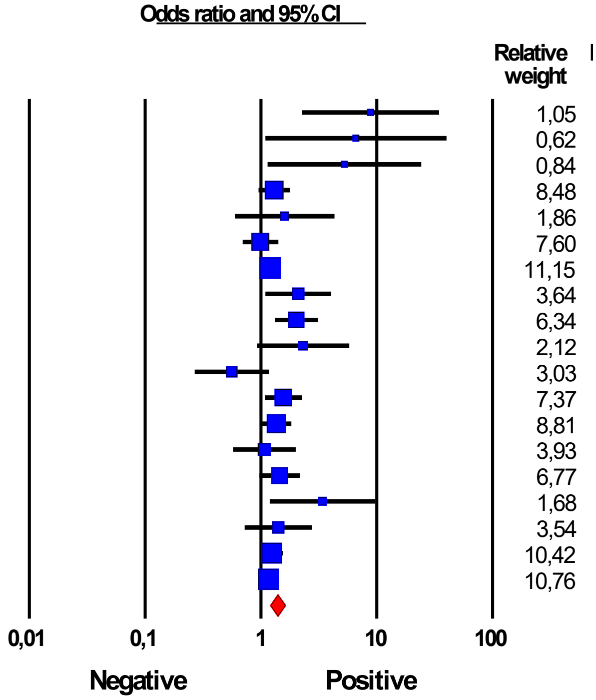
Main analyses

The overall weighted relationship (random effects-analysis) for inorganic dusts was OR=1.39 (95% CI, 1.20 to 1.61), z=4.48, p <.001. Heterogeneity: Q(18)=37.00, p <.001. I^2=51%, τ^2=0.04. See Fig 3.

Figure 3 Meta-analysis for 19 studies examining the relationship between organic dust and COPD.

Organic dust

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Mastrangelo 2003	8,860	2,290	34,279	3,160	0,002	1,05
Monso 2004	6,600	1,100	39,600	2,064	0,039	0,62
Ijadunola 2005	5,250	1,150	23,967	2,140	0,032	0,84
Matheson 2005	1,300	0,960	1,760	1,696	0,090	8,48
Jacobsen 2008	1,600	0,600	4,267	0,939	0,348	1,86
Weinmann 2008	0,990	0,700	1,400	-0,057	0,955	7,60
Eduard 2009	1,200	1,000	1,440	1,960	0,050	11,15
Govender 2011	2,100	1,100	4,009	2,249	0,025	3,64
Lamprecht 2011	2,020	1,330	3,068	3,297	0,001	6,34
Doney 2014	2,310	0,930	5,738	1,804	0,071	2,12
Hansell 2014	0,560	0,270	1,161	-1,558	0,119	3,03
Würtz 2015b	1,560	1,090	2,233	2,431	0,015	7,37
Dement 2015	1,360	1,020	1,813	2,095	0,036	8,81
Tagiyeva 2016	1,070	0,580	1,974	0,217	0,829	3,93
Doney 2019	1,450	0,980	2,145	1,859	0,063	6,77
Andersson 2020	3,400	1,200	9,633	2,303	0,021	1,68
Henneberger 2020	1,410	0,730	2,723	1,023	0,306	3,54
Rous 2023	1,240	1,000	1,538	1,960	0,050	10,42
Loeb 2024	1,160	0,950	1,416	1,457	0,145	10,76
Pooled	1,390	1,204	1,606	4,482	0,000	



Random effects Meta-analysis

Sensitivity analyses

Sensitivity analyses were performed using the one-study-removed principle. Removing any of the included 19 studies did not affect the point estimate, confidence interval or p-value significantly. In other words, if a study were to be removed from the meta-analysis the result would not change. The range for ORs was 1.35 to 1.43.

Moderator analyses

Seven studies in the meta-analysis (Eduard [1], Jacobsen [22], Lamprecht [23], Dement [2], Tagiyeva [24], Loeb [5], and Rous [3]) used an internal fixed-effect OR-value. To find out if these data provided a different estimate of the overall estimation, we conducted a moderator analysis with separate groups for studies with and without an initial fixed effect weighing.

- REM within the FEM-group (k=7): OR=1.26 (95% CI, 1.13 to 1.41), p <.001.
- REM for the rest of the studies (k=12): OR=1.61 (95% CI, 1.21 to 2.15), p <.001.

Conclusion: both types of input data generate significant positive relationships.

Additional studies

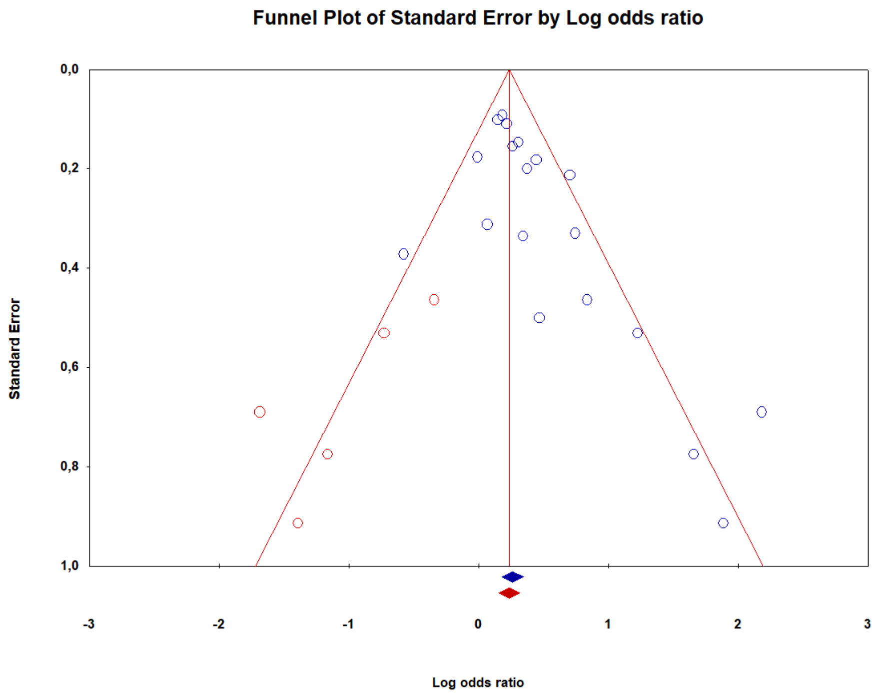
Study Reference	Point estimate (95% CI)	Comment
Mehta 2012 [8]	IRR=1.15 (1.04 to 1.26)	Positive relationship (sig)
VanKampen 2016 **[25]**	RR=1.18 (0.99 to 1.42)	Positive relationship (non sig)
Alif 2017 [9]	RR=1.05 (0.97 to 1.13)	Positive relationship (non sig)
Lytras 2018 [10]	RR=1.60 (1.10 to 2.30)	Positive relationship (sig)
Grahn 2021 [12]	HR=1.33 (1.12 to 1.51)	Positive relationship (sig)
DeMatteis 2022 [13]	PR=1.00 (0.95 to 1.21)	Zero relationship
Darby 2012 [14]	OR=2.0	Neither CI, SE nor exact p-value reported

Studies not included in the meta-analysis provide positive, and most often, significant, relationship estimates between occupational exposure to organic dust and COPD.

Publication bias

A trim-and-fill analysis results in the imputation of five studies. The re-analysis still shows a significant overall OR: 1.30 (95% CI, 1.11 to 1.53). See Fig 4.

Figure 4 Funnel plot examining studies of organic dust exposure



Subgroups

Wood dust

Study Reference	Point estimate (95% CI)	Effect size measure	Comment
Jacobsen 2008 **[22]**	1.60 (0.60 to 4.27)	OR	Positive relationship (sig)
Hansell 2014 [16]	0.78 (0.35 to 1.74)	OR	Negative relationship (non sig)
Dement 2015 [2]	1.17 (0.80 to 1.69)	OR	Positive relationship (non sig)
Tagiyeva 2016 **[24]**	2.46 (1.19 to 5.09)	OR	Positive relationship (sig)
Loeb 2024 [5]	1.24 (0.88 to 1.70)	OR	Positive relationship (non sig)
Grahn 2021 [12]	1.09 (0.78 to 1.51)	HR	Positive relationship (non sig)

The wood dust subgroup suggests a modest positive relationship between occupational exposure to wood dust and COPD.

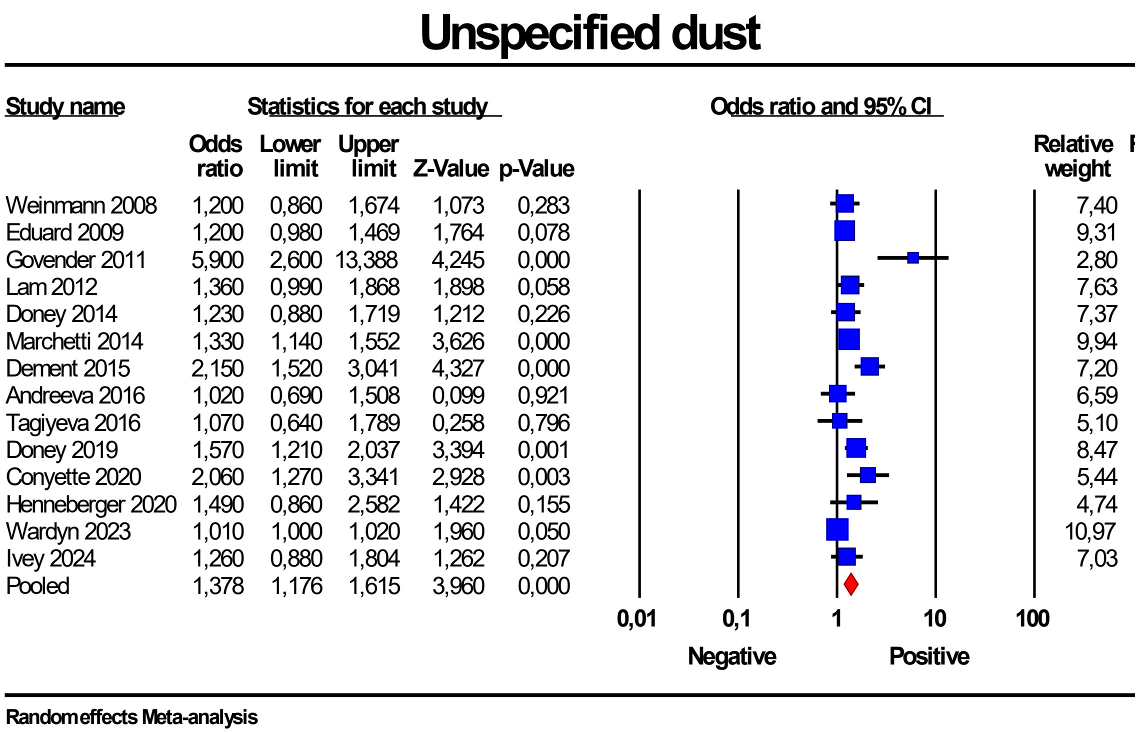
Unspecified dust

The meta-analysis included 14 studies with odds ratios, and one study using a different relationship statistic.

Main analyses

The overall weighted relationship (random effects-analysis) for inorganic dusts was OR=1.38 (95% CI, 1.18 to 1.62), z=3.96, p <.001. Heterogeneity: Q(13)=78.89, p <.001. I^2=84%, τ^2=0.06. See Fig 5.

Figure 5 Meta-analysis for 14 studies examining the relationship between unspecified dust and COPD.



Sensitivity analyses

Sensitivity analyses were performed using the one-study removed principle. Removing any of the included 14 studies did not affect the point estimate, confidence interval or p-value significantly. In other words, if a study were to be removed from the meta-analysis the result would not change. The range for ORs was 1.32 to 1.42.

Moderator analyses

One study in the meta-analysis (Tagiyeva) used an internal fixed effect OR-value. That study reports a non-significant, positive relationship (see Figure 5). Odds ratio for the other 13 studies: 1.40 (95% CI, 1.17 to 1.60).

Additional studies

In this category of exposures, we included one study not reporting odds ratios. Sahdra (2020) [26] gives a prevalence ratio 1.07 (0.99 to 1.16). A non-significant, positive relationship.

Publication bias

A trim-and-fill-analysis show that no studies are missing. Hence, a re-analysis provides the same estimate as the main analysis.

Vapors, gases, and fumes

The meta-analysis included 23 studies with odds ratio (OR) data. In addition, 9 relevant studies did not report ORs.

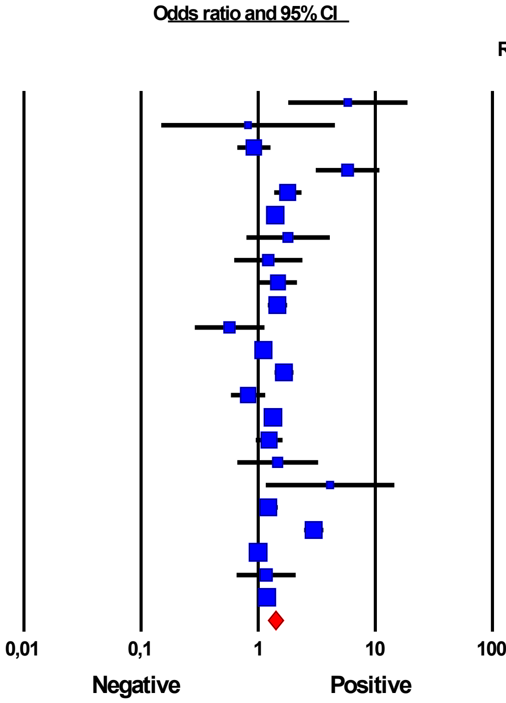
Main analysis

The overall weighted relationship (random effects-analysis) for gases, vapors and fumes was OR=1.41 (95% CI, 1.21 to 1.62), z=4.63, p <.001. Heterogeneity: Q(22)=371.05, p <.001. I^2=94%, τ^2=0.08. See Fig 6.

Figure 6 Meta-analysis for 23 studies examining the relationship between gases, vapors and fumes, and COPD.

Vapors, gases and fumes

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Mastrangelo 2003	5,830	1,820	18,675	2,968	0,003	1,24
Monso 2004	0,820	0,150	4,483	-0,229	0,819	0,65
Matheson 2005	0,920	0,670	1,263	-0,515	0,606	4,98
Hu 2006	5,800	3,130	10,748	5,586	0,000	2,98
Weinmann 2008	1,790	1,380	2,322	4,387	0,000	5,41
Eduard 2009	1,400	1,270	1,543	6,767	0,000	6,39
Govender 2011	1,800	0,800	4,050	1,421	0,155	2,13
Lamprecht 2011	1,220	0,630	2,363	0,590	0,555	2,75
Lam 2012	1,480	1,030	2,127	2,120	0,034	4,64
Doney 2014	1,460	1,220	1,747	4,130	0,000	5,97
Hansell 2014	0,570	0,290	1,120	-1,630	0,103	2,68
Marchetti 2014	1,110	0,950	1,297	1,314	0,189	6,11
Dement 2015	1,660	1,390	1,982	5,596	0,000	5,98
Tagiyeva 2017	0,820	0,590	1,140	-1,182	0,237	4,89
Doney 2019	1,340	1,240	1,448	7,396	0,000	6,46
Dumas 2019	1,240	0,960	1,602	1,647	0,099	5,44
Henneberger 2020	1,470	0,670	3,225	0,961	0,337	2,22
Chen 2021	4,110	1,170	14,438	2,205	0,027	1,09
Rous 2023	1,220	1,020	1,459	2,177	0,030	5,97
Wang 2023a	2,980	2,490	3,566	11,913	0,000	5,97
Wardyn 2023	1,000	0,990	1,010	0,000	1,000	6,58
Ivey 2024	1,170	0,660	2,074	0,537	0,591	3,22
Loeb 2024	1,190	1,050	1,349	2,724	0,006	6,27
Pooled	1,405	1,217	1,622	4,633	0,000	



Random effects Meta-analysis

Sensitivity analyses

Sensitivity analyses were performed using the one-study-removed principle. Removing any of the included 23 studies did not affect the point estimate, confidence interval or p-value significantly. In other words, if a study were to be removed from the meta-analysis the result would not change. The range for ORs was 1.32 to 1.44.

Moderator analyses

Ten studies in the meta-analysis (Eduard [1], Dement [2], Doney 2014 [27], Doney 2019 [28], Govender [29], Lamprecht [23], Monso [30], Tagiyeva [24], Loeb [5], and Wardyn [17]) used an internal fixed-effect OR-value. To find out if these data provided a different estimate of the overall estimation, we conducted a moderator analysis with separate groups for studies with and without an initial fixed effect weighing.

- REM within the FEM-group (k=10): OR=1.26 (95% CI, 1.07 to 1.49), p <.001.
- REM for the rest of the studies (k=13): OR=1.61 (95% CI, 1.20 to 2.15), p <.001.

Conclusion: both types of input data generate significant positive relationships.

Additional studies

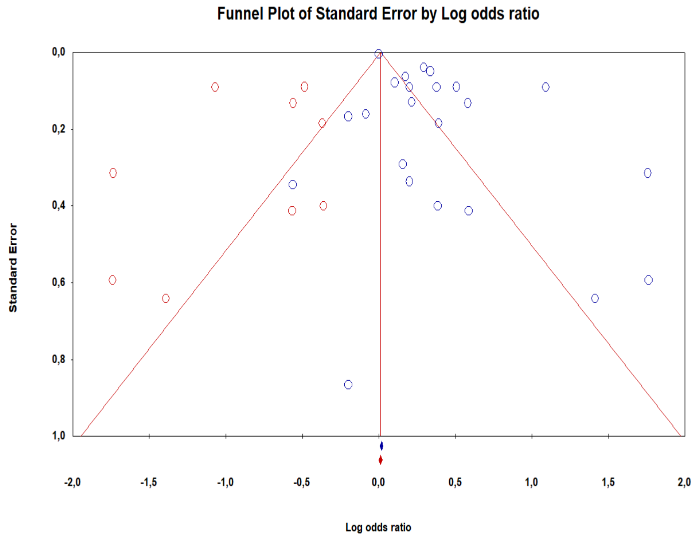
Study Reference	Point estimate (95% CI)	Comment
Mehta 2005 **[31]**	PR=4.30 (1.20 to 15.70)	Positive relationship (sig)
Pronk 2009 **[32]**	PR=2.40 (1.10 to 6.80)	Positive relationship (sig)
Mehta 2012 **[31]**	IRR=1.10 (1.02 to 1.19)	Positive relationship (sig)
Andreeva 2016 **[33]**	HR=1.40 (0.90 to 2.18)	Positive relationship (non sig)
Alif 2017 [9]	RR=1.02 (0.96 to 1.09)	Positive relationship (non sig)
Lytras 2018 [10]	RR=1.50 (1.00 to 2.20)	Positive relationship (sig)
Grahn 2021 [12]	HR=1.11 (0.97 to 1.26)	Positive relationship (non sig)
DeMatteis 2022 [13]	PR=0.97 (0.92 to 1.02)	Negative relationship (non sig)
Darby 2012 [14]	OR=1.4	Neither CI, SE nor exact p-value reported

There was one study reporting a non-significant negative relationship. However, the rest all reported either significant or non-significant positive relationship between exposure to gases, vapors and fumes, and COPD. Hence, the general finding is in line with the finding from the meta-analysis.

Publication bias

A trim-and-fill analysis results in the imputation of nine studies. The re-analysis still shows a significant overall OR: 1.40 (CI, 1.22 to 1.62) Trim-and-fill-analyses show that the relationship would still have been positive (and significant) even after not accounting for nine missing studies (ORs from 1.22 to 1.62). See Fig 7.

Figure 7 Funnel plot for studies examining exposure to vapors, gases and fumes



Subgroups

Exhausts

Study Reference	Point estimate (95% CI)	Effect size measure	Comment
Weinmann 2008 [6]	1.90 (1.30 to 3.00)	OR	Positive relationship (sig)
Dement 2015 [2]	1.76 (1.23 to 2.52)	OR	Positive relationship (sig)
Doney 2019 **[28]**	1.44 (1.12 to 1.85)	OR	Positive relationship (sig)
Grahn 2011 [12]	1.18 (0.99 to 1.39)	HR	Positive relationship (non sig)
Sadhra 2020 **[26]**	1.02 (0.87 to 1.20)	PR	Positive relationship (non sig)

For engine exhausts, the general finding was a positive relationship between exposure and COPD. Three of five studies are both positive and significant, and the two other studies contribute non-significant but positive findings.

Pesticides

The meta-analysis included 4 studies with odds ratio (OR) data. In addition, we included 3 relevant studies that did not report ORs.

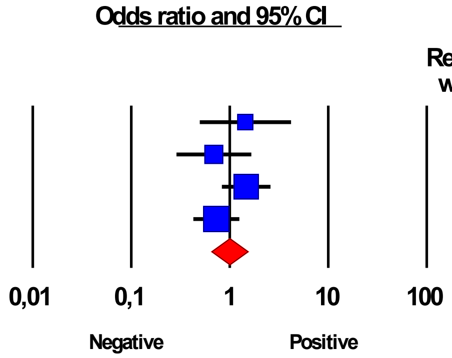
Main analysis

The overall weighted relationship (random effects-analysis) for pesticides was OR=0.997 (95% CI, 0.66 to 1.52), z= –0.01, p=.99. Heterogeneity: Q(3)=4.34, p=.23. I^2=31%, τ^2=0.06. See Fig 8.

Figure 8 Meta-analysis for 4 studies examining the relationship between pesticides and COPD.

Pesticides

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Cha 2012	1,440	0,500	4,147	0,676	0,499	13,19
Hansell 2014	0,690	0,290	1,642	-0,839	0,401	18,19
Tagiyeva 2016	1,470	0,840	2,573	1,349	0,177	33,21
Plombon 2022	0,730	0,430	1,239	-1,165	0,244	35,41
Pooled	0,997	0,655	1,517	-0,014	0,989	



Random effects Meta-analysis

Sensitivity analyses

Sensitivity analyses were performed using the one-study-removed principle. Removing any of the included 4 studies did not affect the point estimate, confidence interval or p-value significantly. In other words, if a study were to be removed from the meta-analysis the result would not change. The range for ORs was 0.94 to 1.20.

Moderator analyses

One study in the meta-analysis (Plombon [34]) used an internal fixed effect OR-value. To find out if these data provided a different estimate of the overall estimation, we conducted a moderator analysis with separate groups for studies with and without an initial fixed effect weighing.

- REM using internal FEM (k=1): OR=0.73 (95% CI, 0.43 to 1.24), p=.24.
- REM for the rest of the studies (k=3): OR=1.20 (95% CI, 0.76 to 1.90), p=.43.

Conclusion: both types of input data generate non-significant estimates of the relationship between pesticides and COPD.

Additional studies

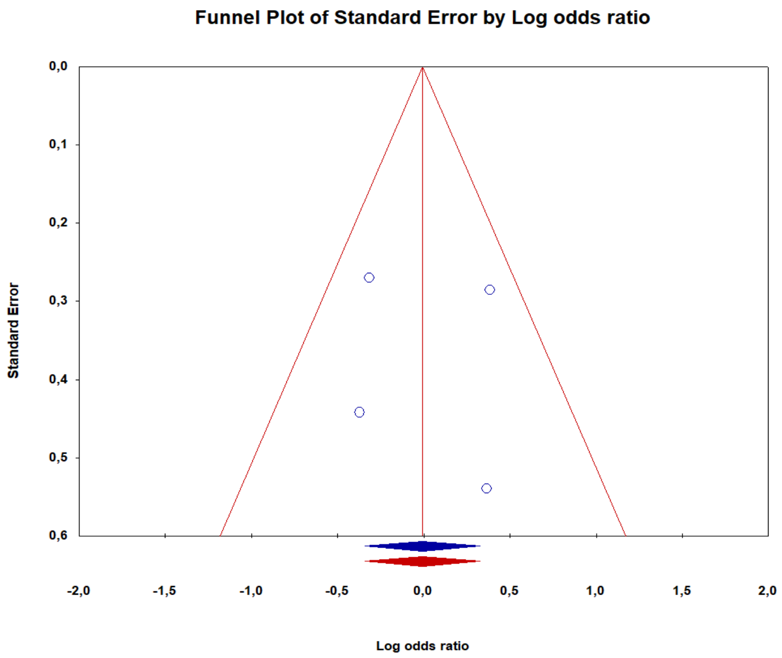
Study Reference	Point estimate (95% CI)	Comment
Alif 2017 [9]	RR=1.12 (1.00 to 1.25)	Positive relationship (sig)
Lytras 2018 [10]	RR=2.20 (1.10 to 3.80)	Positive relationship (sig)
DeMatteis 2022 [13]	PR=1.11 (0.99 to 1.25)	Positive relationship (non-significant according to the CI)

All three additional studies report positive (most often significant) relationship between occupational exposure to pesticides and COPD.

Publication bias

A trim-and-fill-analysis show that no studies are missing. Hence, a re-analysis provides the same estimate as the main analysis. See Fig 9.

Figure 9. Funnel plot for studies examining exposure to pesticides



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