

Supplemental Materials

Major Air Pollutants and Acute Risk of COPD: A Systematic Review and Meta-analysis

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S1 Detailed search strategy

1). MEDLINE and EMBASE

1. exp chronic obstructive pulmonary disease.mp. or COPD. mp. or Chronic Obstructive Pulmonary Disease.mp./
2. exp chronic obstructive airway disease. mp. or chronic obstructive lung disease.mp. or chronic airflow obstruction.mp. or pulmonary emphysema.mp. /
3. 1 or 2
4. [(air or atmosphere or atmospheric) adj (pollutant* or polluted or contamination or contaminated)].mp.(mp=ti, ab, sh, tn, hw, ot, dm, mf, ps, rs, ps, nm, ui, tx, ct, kw)/
5. exp ambience particulate matter.mp. or PM_{2.5}.mp or PM₁₀. mp./
6. exp ozone.mp. or Ozone.mp. or O₃.mp./
7. exp carbon monoxide.mp. or Carbon Monoxide .mp. or CO.mp./
8. exp sulphur dioxide.mp. or Sulphur Dioxide.mp. or SO₂. mp./
9. exp nitrogen dioxide.mp. or Nitrogen Dioxide.mp. or NO₂. mp./
10. 4 or 5 or 6 or 7 or 8 or 9
11. 3 and 10

2). Global Health, Web of Science, CINAHL, EBSCO, Cochrane Library

“chronic obstructive pulmonary disease” OR “COPD” OR “chronic obstructive airway disease” OR “Chronic Airflow obstructive” OR “Pulmonary Emphysema”

AND

“Air pollution” OR “ambient particular matter” OR “PM_{2.5}” OR “PM₁₀” OR “Ozone” OR “O₃” OR “carbon monoxide” OR “CO” OR “sulfur dioxide” OR “SO₂” OR “nitrogen dioxide” OR “NO₂” OR “Nitrogen oxides” OR “NO_x”)

S2 Eligibility criteria

Inclusion Criteria

1. No language limitation
2. Full-length peer-reviewed studies with original data
3. Time-series studies and case-crossover studies
4. Had adequate sample sizes
5. Focus on the short-time air pollution exposure to the acute effects of COPD exacerbation, including mortality and hospitalization admission

Exclusion Criteria

1. Studies about case report/series, commentaries, letters, editorials, summaries, reviews
2. Focus on vivo or vitro or toxicological or mechanisms studies
3. Duplicate publications
4. Just conduct the long-term air pollution researches
5. The duration of study less than one year
6. No interested endpoints reported

Table S1 Contextual details of included studies

Study(year)	Lag exposure	Species	average concentration	lag-pattern	Model	Air pollutant concentration	Pollutant measurement quality score	Outcome measurements	Adjustments	Generalizability
Kloog <i>et al</i> 2014¹	Lag01	PM _{2.5}	10.8±5.7	single-day	mono	mean	1	1	0	1
Meng <i>et al</i> 2013²	Lag01	BJ PM ₁₀	138.9±87.0	single-day	both	mean	1	1	1	1
	Lag0-1	BJ SO ₂	41.4±43.8							
	Lag0-2	BJ NO ₂	57.6±24.7							
	Lag0-3	SH PM ₁₀	102±64.8							
		SH SO ₂	44.7±24.2							
		SH NO ₂	66.6±25.0							
		GZ PM ₁₀	73.8±40.2							
		GZ SO ₂	50.1±33.0							
		GZ NO ₂	65.9±31.7							
		HK PM ₁₀	51.6±22.3							
		HK SO ₂	17.8±12.1							
		HK NO ₂	58.7±20.1							
Tellez-Rojo <i>et al</i> 2000³	Lag1	PM ₁₀	75.1±23.7	single-day	multi	both	1	1	1	1
	Lag2	O ₃	134.5±33.4							
	Lag3	SO ₂	0.02±0.005							
	Lag4	NO ₂	0.038±0.01							
	Lag5									
Wordley <i>et al</i> 1997⁴	Lag1	PM ₁₀	70.0	single-day	both	mean	1	1	1	1
	Lag2									
	Lag3									
Neuberger <i>et al</i> 2007⁵	Lag0-1	NO ₂	31.0	mean days	mono	mean	1	1	1	0
	Lag0-7	SO ₂	5.0							
		O ₃	46.0							
		TSP	31.0							
		PM ₁₀	30.0							

Arbex et al 2009¹²	Lag0	CO	2.7±1.2	both	mono	both	1	1	1	1
	Lag1	O ₃	95.8±44.2							
	Lag2	NO ₂	120.3±49.9							
	Lag3	SO ₂	14.0±6.2							
	Lag4	PM ₁₀	48.7±21.9							
	Lag5									
	Lag6									
Forastiere et al 2008¹³	Lag0-1	PM ₁₀	40.0	mean days	mono	mean	1	1	1	1
Ko et al 2007¹⁴	Lag0	NO ₂	51.2±21.8	both	both	mean	0	1	1	1
	Lag1	PM ₁₀	50.1±23.9							
	Lag2	O ₃	31.0±16.2							
	Lag3	SO ₂	15.0±11.6							
	Lag4	PM _{2.5}	35.7±20.6							
	Lag5									
	Lag0-1									
	Lag0-2									
	Lag0-3									
	Lag0-4									
	Lag0-5									
Zanobetti et al 2000¹⁵	Lag0	PM ₁₀	<50.0	single-day	both	mean	1	1	0	1
	Lag1									
	Lag2									
	Lag3									
	Lag4									
Morgan et al 1998¹⁶	Lag0	Particulates	0.3±0.2	both	both	both	1	1	1	1
	Lag1	O ₃	25.0±13.0							
	Lag2	NO ₂	15.0±6.0							
	Lag0-2									
Anderson et al 1997¹⁷	Lag1	SO ₂	33.3			mean	0	1	1	1

	Lag1-3	NO ₂	52.8	both	mono					
	Lag1-5	BS	21.6							
		TSP	85.5							
		O ₃	46.8							
Peel et al 2005¹⁸	Lag0	PM ₁₀	27.9±12.3	both	both	mean	1	1	1	1
	Lag1	NO ₂	45.9±17.3							
	Lag2	CO	1.8±1.2							
		SO ₂	16.5±17.1							
		O ₃	55.6±23.8							
		PM _{2.5}	19.2±8.9							
Chen et al 2003¹⁹	Lag0	PM ₁₀	13.3±6.1	both	both	mean	0	1	1	1
	Lag1	PM _{10-2.5}	5.6±3.6							
	Lag2	PM _{2.5}	7.7±3.7							
	Lag3	COH	0.3±0.1							
	Lag4	CO	0.7±0.3							
	Lag5	O ₃	14.3±6.7							
	Lag6	NO ₂	16.8±4.3							
	Lag7	SO ₂	3.5±1.8							
	Lag0-3									
Wong et al 2002²⁰	Lag0	NO ₂	56.4±19.2	both	both	mean	0	1	1	1
	Lag1	PM ₁₀	51.5±24.8							
	Lag2	O ₃	33.9±23.2							
	Lag3	SO ₂	16.7±11.6							
	Lag4									
	Lag5									
	Lag0-5									
	Lag0-3									
Tenias et al 2002²¹	Lag0	BS	38.8		both	both	0	0	1	1
	Lag1	NO ₂	57.7							
	Lag2	O ₃	62.8							
	Lag3	SO ₂	26.6							

Lin et al 2012³¹	Lag0	NO ₂	33.0±43.9	mean days	both	both	1	1	1	1
	Lag1	O _x	48.8±21.8							
	Lag2	O ₃	25.5±24.3							
	Lag3	PM ₁₀	48.4±121.2							
	Lag4									
	Lag5									
Bateson et al 2004³²	Lag1	PM ₁₀	37.6±15.5	single-day	mono	both	0	1	1	1
Sunyer et al 2001³³	Lag2	PM ₁₀	13.5	mean days	mono	mean	0	0	1	0
		NO ₂	8.5							
		O ₃	10.5							
		CO	2.3							
Kan et al 2003³⁴	Lag0-5	NO ₂	91.14±15.3	mean days	mono	mean	0	1	0	1
		SO ₂	42.49±6.1							
		PM ₁₀	32.46±3.6							
Braga et al 2001³⁵	Lag0	PM ₁₀	33.1	both	mono	mean	0	1	1	1
	Lag0-1									
Schwartz et al 1992³⁶	Lag2	TSP	77.2±22.4	mean	both	mean	0	1	1	1
		SO ₂	21±3.8							
Fischer et al 2003³⁷	Lag1 O3	PM ₁₀	34±68.4	both	mono	mean	0	1	1	1
	Lag0-6	BS	10±30.4							
		O ₃	47±57.4							
		NO ₂	32±50.0							
		SO ₂	10±62.7							
Wong et al 2009³⁸	Lag0-1	CO	406±624.0							
		NO ₂	58.7±20.0	mean		mean	0	1	1	1
		SO ₂	17.8±12.1							
		PM ₁₀	51.6±25.3							
Xu et al 2009³⁹	Lag0-3	O ₃	36.9±23.0							
		TSP	430.4±67.9	mean		mean	0	1	1	1
		SO ₂	196.9±12.3							
Janssen et al 2002⁴⁰	Lag1/2	PM ₁₀	NA	mean	mono	mean	0	1	1	1

Dominici et al 2006⁴¹	Lag0	PM _{2.5}	13.4±0.5	both	mono						
	Lag1										
	Lag2										
Yang et al 2000⁴²	Lag1	PM ₁₀	36.6±27.9	single-day	mono	mean	0	1	1	1	
Schwartz et al 1994⁴³	Lag1	PM ₁₀	24±3.3	single-day	mono	both	0	1	1	1	
		O ₃	41±7.6								
Schwartz(s) et al 1994	Lag0-2	PM ₁₀	25±4.3	both	mono	both	0	1	1	1	
Schwartz(t) et al 1994	Lag0-2	PM ₁₀	48±8.2	mean	mono	both	0	1	1	1	
		O ₃	21±4.1								
Sunyer et al 1993⁴⁶	Lag1	SO ₂	49±7.9	both	multi	mean	1	1	1	1	
	Lag0-2	BS	29±5.1								
Lippmann et al 2000⁴⁷	Lag1	TSP	68.7±9.4		multi	mean	1	1	1	1	
	Lag2	PM ₁₀	45.4±7.9								
	Lag0-1	SO ₂	9.8±1.7								
	Lag0-2	NO ₂	23.3±3.1								
	Lag0-3	O ₃	20.9±4.0								
Dab et al 1996⁴⁸	Lag0	CO	0.9±0.1								
		SO ₂	29.7	both	both	both	1	1	1	1	
		BS	31.9								
		PM ₁₃	50.8								
		NO ₂	45.0								
Leitte et al 2009⁴⁹	Lag0-7	O ₃	27.7								
		SO ₂	11.8±3.8	both	multi	both	1	1	1	1	
		NO ₂	4.7±1.6								
Pande et al 2002⁵⁰	Lag1	TSP	123.5±44.1								
		TSP	417.5±151.0	mean	both	mean	1	1	1	1	
		CO	5138.0±2651.0								
		NOx	65.0±25.0								
		SO ₂	23.0±11.5								

Table S2 Sensitivity analysis of included studies (Before & after removing studies with increased risk of bias)

Pollutants	RR	LL	UL
Nitrogen dioxide			
Overall estimate	1.04	1.02	1.06
Estimate excluding studies at risk of bias	1.03	1.02	1.04
Carbon monoxide			
Overall estimate	1.01	1.00	1.01
Estimate excluding studies at risk of bias	1.00	1.00	1.01
Sulphur dioxide			
Overall estimate	1.01	1.00	1.01
Estimate excluding studies at risk of bias	1.01	1.00	1.01
Ozone			
Overall estimate	1.01	1.01	1.02
Estimate excluding studies at risk of bias	1.02	1.01	1.03
PM_{2.5}			
Overall estimate	1.01	1.00	1.01
Estimate excluding studies at risk of bias	1.02	1.02	1.03
PM₁₀			
Overall estimate	1.01	1.01	1.01
Estimate excluding studies at risk of bias	1.02	1.02	1.02

Table S3 Results of subgroup analysis

Subgroup Characteristics	Gaseous Pollutants				Particulate Pollutants	
	SO ₂ (10 µg/m ³)	NO ₂ (10 µg/m ³)	O ₃ (10 µg/m ³)	CO (100µg/m ³)	PM _{2.5} (10 µg/m ³)	PM ₁₀ (10 µg/m ³)
Lag Subgroup						
Study number	5	8	6	6	4	7
Lag exposure, d	0	0	3	1	0	3
Heterogeneity, I ² (%)	91.5	94.9	5.9	61.4	76.8	55.8
RR (95%CI)	1.007 (1.003,1.011)	1.030 (1.026,1.033)	1.013 (1.010,1.016)	1.000 (0.987,1.003)	1.002 (1.001,1.005)	1.009 (1.006,1.011)
Egger's test, <i>P</i>	0.312	0.780	0.351	0.410	0.362	0.127
Quality Subgroup						
*Study number	28	27	28	13	15	34
Heterogeneity, I ²	76.5	98.1	63.0	92.9	91.1	83.8
RR (95%CI)	1.000 (1.000,1.000)	1.017 (1.015,1.019)	0.958 (0.958,0.958)	1.006 (1.002,1.011)	1.007 (1.005,1.009)	1.008 (1.007,1.009)
Egger's test, <i>P</i>	0.007	0.147	0.001	0.163	0.447	0.001
Property Subgroup						
^Category (number)	Age≥65(10)	Mortality(7)	Age≥65(12)	Mortality(2)	Mortality(2)	Non-Asian(10)
Heterogeneity, I ²	62.4	21.9	27.1	2.7	47.2	66.3
RR (95%CI)	1.004 (0.999,1.008)	1.017 (1.012,1.021)	1.009 (1.006,1.011)	1.012 (0.999,1.026)	1.025 (1.007,1.043)	1.006 (1.005,1.007)
Egger's test, <i>P</i>	0.129	0.881	0.315	NA	NA	0.001

● Include good quality and intermediate quality

^ The category that reduced the heterogeneities most significantly

Table S4 Meta-regression analyses of the studies

A: Carbon Monoxide

Stratified study	No. of studies	Meta-regression			Heterogeneity	
		Coef.	Adj R ² (%)	<i>p</i> -value	I ² (%)	<i>p</i> -value
Study design		-0.166	14.52	0.178		
Time-series	8				75.5	0.001
Case crossover	7				98.5	0.001
Location		-0.271	38.49	0.056		
Asia	5				90.6	0.001
Non-Asia	10				70.8	0.001
COPD Subtype		0.066	-10.90	0.729		
Mortality	2				2.70	0.311
Hospital Admission	13				78.5	0.001
Age		-0.125	-13.83	0.502		
≥65	12				81.2	0.005
All	3				77.4	0.001

B: Sulfur dioxide

Stratified study	No. of studies	Meta-regression			Heterogeneity	
		Coef.	Adj R ² (%)	<i>p</i> -value	I ² (%)	<i>p</i> -value
Study design		-0.137	8.06	0.348		
Time-series	24				73.3	0.001
Case crossover	7				76.3	0.001
Location		-0.005	-3.46	0.564		
Asia	14				87.6	0.001
Non-Asia	17				64.0	0.001
COPD Subtype		-0.004	-1.28	0.674		
Mortality	6				90.9	0.001
Hospital Admission	25				74.7	0.001
Age		-0.001	-10.68	0.955		
≥65	25				62.4	0.004
All	8				74.7	0.001

C: Nitrogen dioxide

Stratified study	No. of studies	Meta-regression			Heterogeneity	
		Coef.	Adj R ² (%)	<i>p</i> -value	I ² (%)	<i>p</i> -value
Study design		-0.166	26.95	0.014		
Time-series	24				73.3	0.001
Case crossover	9				76.3	0.001
Location		0.038	-1.92	0.419		
Asia	16				87.6	0.001
Non-Asia	17				64.0	0.001
COPD Subtype		0.063	-1.72	0.405		
Mortality	7				21.9	0.311
Hospital Admission	27				74.7	0.001
Age		0.062	-3.82	0.470		
≥65	25				62.4	0.004
All	8				83.3	0.001

D: Ozone

Stratified study	No. of studies	Meta-regression			Heterogeneity	
		Coef.	Adj R ² (%)	<i>p</i> -value	I ² (%)	<i>p</i> -value
Study design		-0.072	13.31	0.017		
Time-series	24				90.0	0.001
Case crossover	10				84.0	0.001
Location		-0.047	4.87	0.094		
Asia	5				83.6	0.001
Non-Asia	10				88.4	0.001
COPD Subtype		0.030	-2.88	0.399		
Mortality	5				74.8	0.311
Hospital Admission	29				78.8	0.001
Age		0.0124	-3.15	0.685		
≥65	23				27.1	0.179
All	11				78.4	0.001

E: PM_{2.5}

Stratified study	No. of studies	Meta-regression			Heterogeneity	
		Coef.	Adj R ² (%)	<i>p</i> -value	I ² (%)	<i>p</i> -value
Study design		-0.024	4.11	0.300		
Time-series	8				78.6	0.001
Case crossover	7				79.5	0.001
Location		-0.011	19.32	0.137		
Asia	5				82.7	0.001
Non-Asia	10				76.3	0.001
COPD Subtype		-0.016	-6.73	0.602		
Mortality	2				47.2	0.165
Hospital Admission	13				80.7	0.001
Age		0.022	-5.43	0.344		
>=65	12				66.3	0.018
All	3				80.2	0.001

F: PM₁₀

Stratified study	No. of studies	Meta-regression			Heterogeneity	
		Coef.	Adj R ² (%)	<i>p</i> -value	I ² (%)	<i>p</i> -value
Study design		-0.008	0.99	0.224		
Time-series	27				78.6	0.001
Case crossover	11				73.1	0.001
Location		-0.004	-2.14	0.540		
Asia	13				72.7	0.001
Non-Asia	25				66.3	0.001
COPD Subtype		0.006	5.26	0.328		
Mortality	14				69.5	0.001
Hospital Admission	24				76.7	0.001
Age		0.001	-4.61	0.943		
>=65	15				69.2	0.001
All	26				87.1	0.001

Figure S1

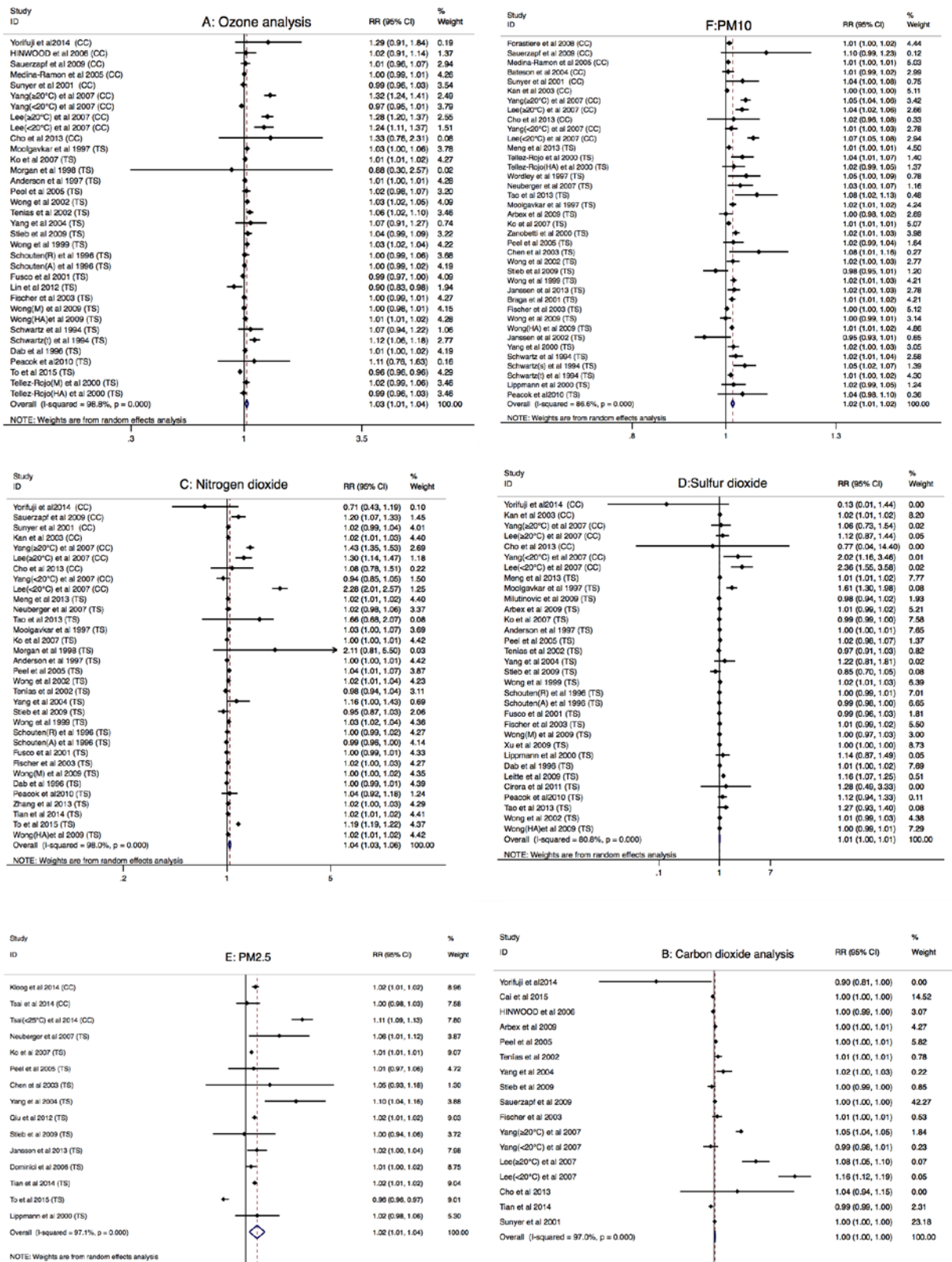
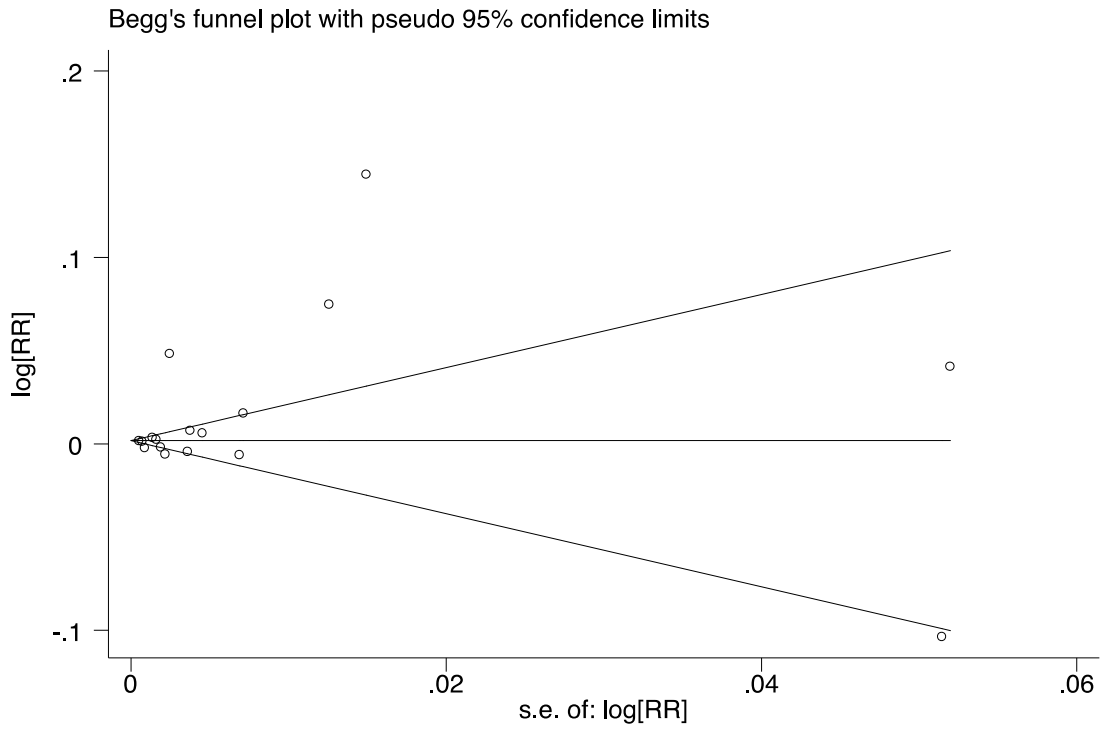
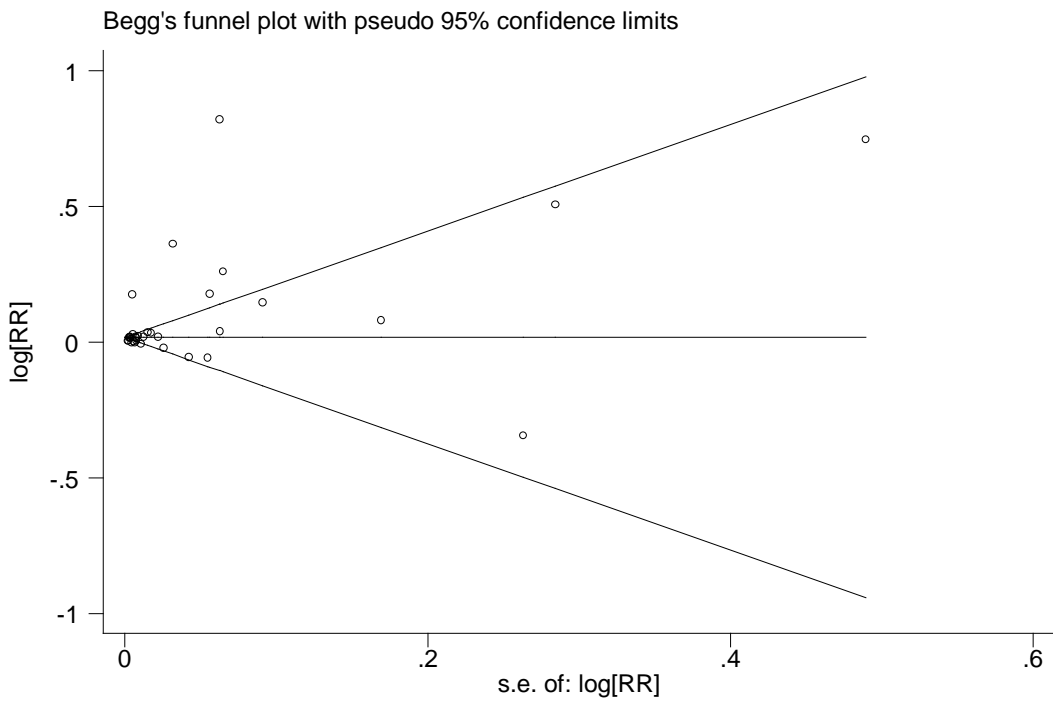


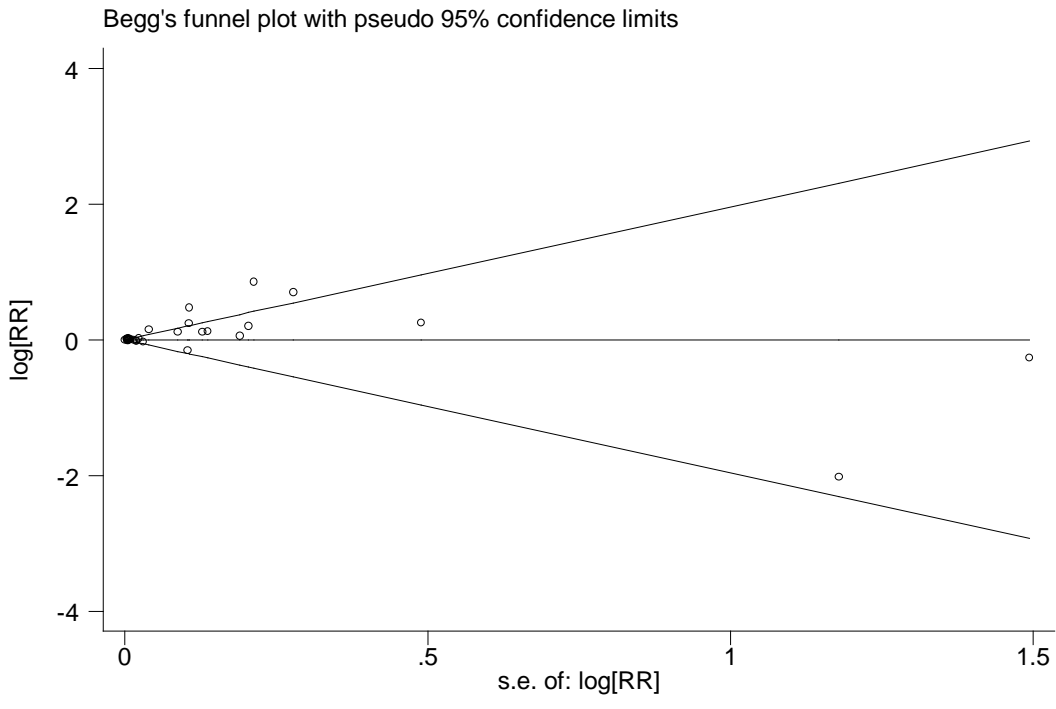
Figure S2



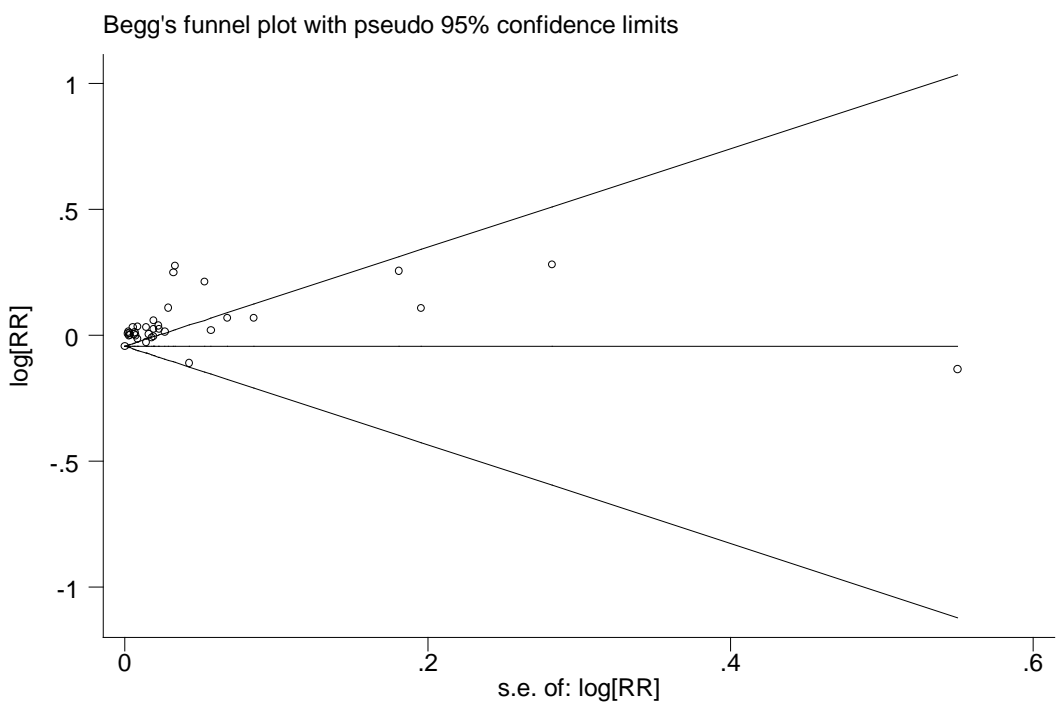
A: Carbon monoxide



B: Nitrogen dioxide

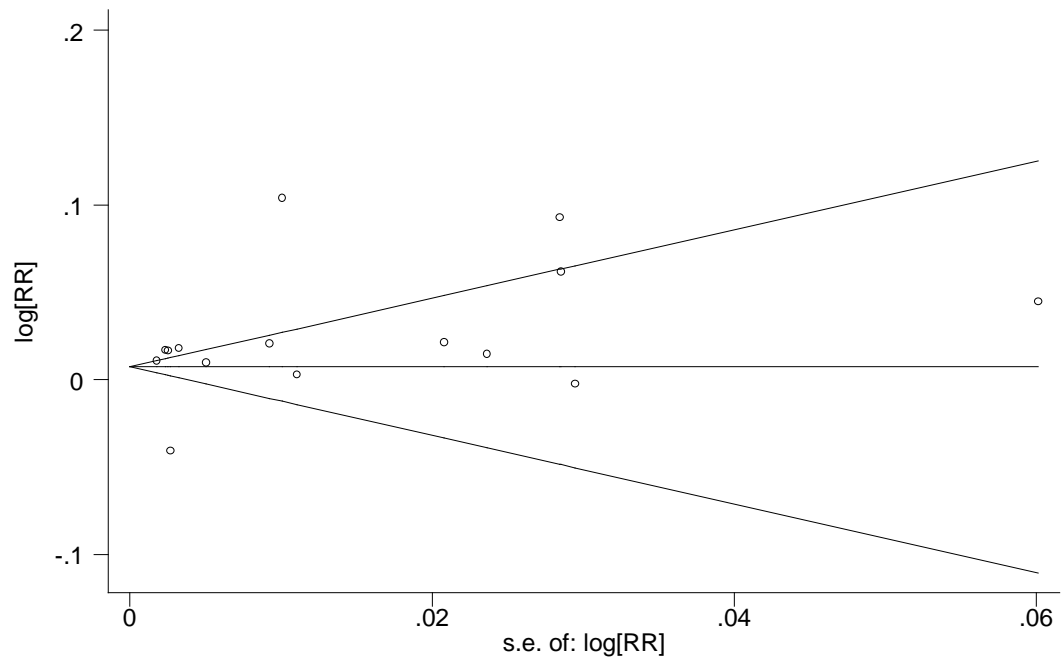


C: Sulphur dioxide



D: Ozone

Begg's funnel plot with pseudo 95% confidence limits



Supplementary Figure Legends

Figure S1 Association between air pollutants and hospitalization/mortality for COPD in overall analyses

Figure S2 Funnel plots for RR of mortality/ hospitalization for COPD exposure to air pollutants

Supplementary Included Reference

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