A deeper dive into the evidence for some of the selected health outcomes

Moderated by Jeff Brook, University of Toronto and HEI Research Committee

Birth outcomes	Danielle Vienneau, Swiss Tropical and Public Health Institute
Respiratory	Audrey Smargiassi, University of Montreal
Cardiometabolic	Barbara Hoffmann, University of Düsseldorf
Mortality	Gerard Hoek, Utrecht University
Neurodevelopmental	Sharon Sagiv, University of California - Berkeley
Neurodegenerative	Jennifer Weuve, Boston University

HEI

Selected birth outcomes:

Fetal growth and growth restriction

- Term low birth weight (TLBW)
- Term birth weight (TBW)
- Small for gestational age (SGA)

Length of gestation

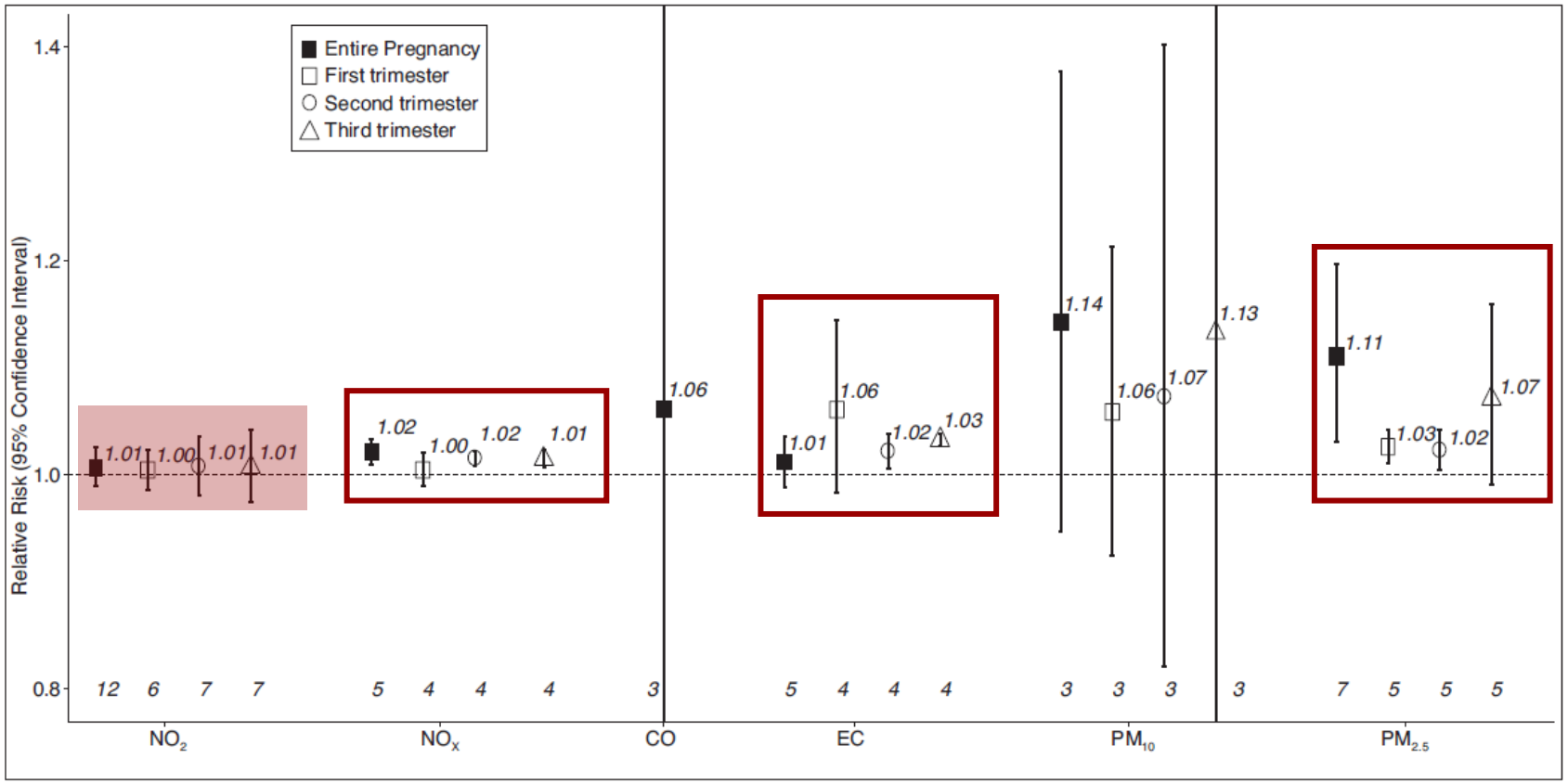
- Preterm birth

86 studies included:

- Cohort design
- Whole pregnancy window
- In North America & Europe
- Birth registry data
- High traffic specificity

HEI

TRAP and term low birth weight (TLBW)



Increments: 10 µg/m³ for NO_2, 20 µg/m³ for NO_x, 1 mg/m³ for CO, 1 µg/m³ for EC, 10 µg/m³ for PM_{10} and 5 µg/m³ for $PM_{2.5}$

- Strongest for **$PM_{2.5}$**
- **NO_x and EC** weaker, **NO_2** null
- **NO_2** stronger high vs. moderate traffic specificity
- Regional differences: stronger **NO_2, EC** and **$PM_{2.5}$** for Western Europe
- Some studies with monotonic exposure-response function

Summary:

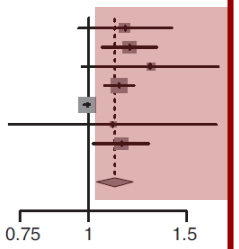
- Meta-analysis: **moderate confidence** in presence of an association
- Consistent:
  - studies not included in meta-analyses

Consistent association of PM for growth restriction

$PM_{2.5}$ and term LBW

Study	Study Name	RR	95%-CI	Weight
Brauer et al. 2008	BC 99/02 Birth Cohort	1.16	[0.95; 1.41]	9.4%
Pedersen et al. 2013	ESCAPE	1.18	[1.05; 1.32]	16.5%
Dadvand et al. 2014	Barcelona Birth Cohort	1.29	[0.97; 1.71]	5.5%
Coker et al. 2015	LA County Birth Registry 95/06	1.13	[1.07; 1.20]	22.9%
Laurent et al. 2016b	California Birth Registry 01/08	0.99	[0.98; 1.00]	26.9%
Kingsley et al. 2017	Rhode Island Birth Outcomes	1.10	[0.72; 1.69]	2.7%
Smith et al. 2017	London Birth Registry 06/10	1.14	[1.02; 1.28]	16.1%
Random effects model		**1.11**	**[1.03; 1.20]**	**100.0%**
Prediction interval			[0.91; 1.36]	

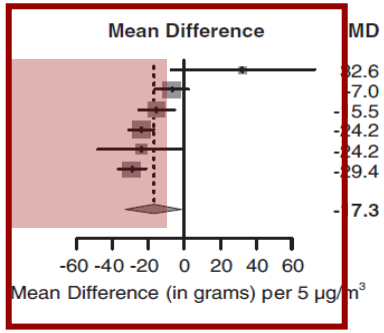
Heterogeneity: $I^2 = 84\%$, $\tau^2 = 0.0053$, $p < 0.01$



$PM_{2.5}$ and term BW

Study	Study Name	MD	95%-CI	Weight
Gehring et al. 2011	PIAMA	32.6	[-7.7; 72.9]	4.8%
Pedersen et al. 2013	ESCAPE	-7.0	[-16.5; 2.5]	20.6%
Gehring et al. 2014	BC 99/02 Birth Cohort	- 5.5	[-25.5; -5.5]	20.1%
Savitz et al. 2014	NYC Birth Registry 08/10	-24.2	[-31.2; -17.2]	22.6%
Kingsley et al. 2017	Rhode Island Birth Outcomes	-24.2	[-48.3; -0.1]	10.1%
Smith et al. 2017	London Birth Registry 06/10	-29.4	[-37.3; -21.5]	21.9%
Random effects model		**- 7.3**	**[-33.2; -1.5]**	**100.0%**
Prediction interval			[-49.8; 15.2]	

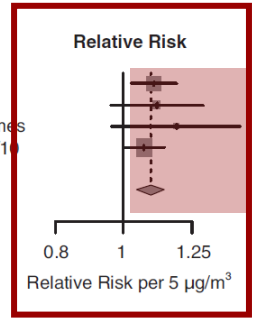
Heterogeneity: $I^2 = 77\%$, $\tau^2 = 99.0936$, $p < 0.01$



$PM_{2.5}$ and SGA

Study	Study Name	RR	95%-CI	Weight
Brauer et al. 2008	BC 99/02 Birth Cohort	1.10	[1.03; 1.19]	38.4%
Dadvand et al. 2014	Barcelona Birth Cohort	1.12	[0.96; 1.30]	9.2%
Kingsley et al. 2017	Rhode Island Birth Outcomes	1.19	[0.96; 1.47]	4.7%
Smith et al. 2017	London Birth Registry 06/10	1.07	[1.00; 1.14]	47.8%
Random effects model		**1.09**	**[1.04; 1.14]**	**100.0%**
Prediction interval			[1.03; 1.16]	

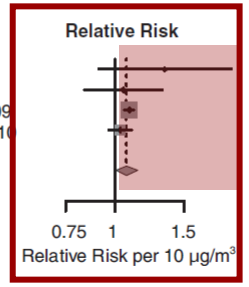
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.76$



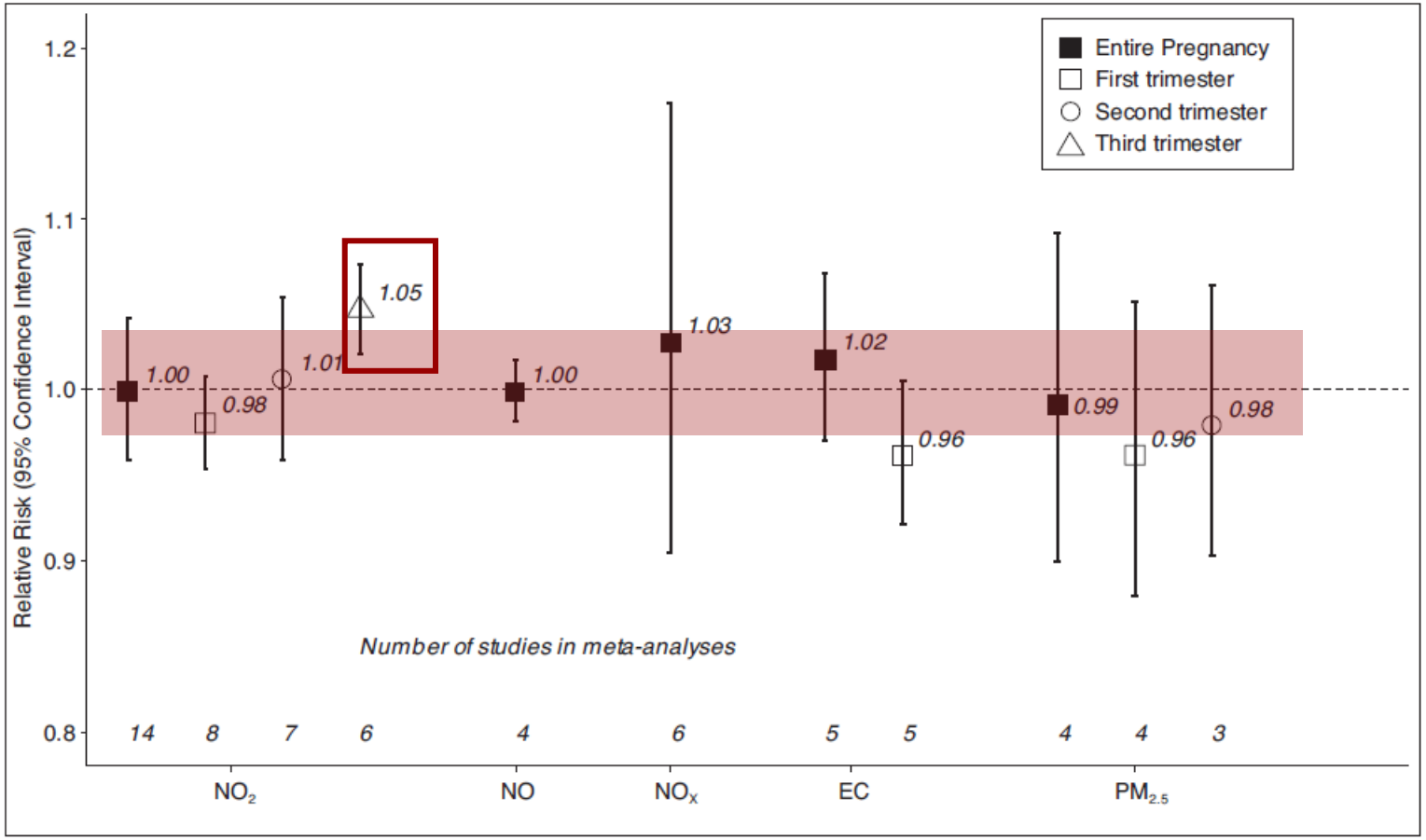
PM_{10} and SGA

Study	Study Name	RR	95%-CI	Weight
van den Hooven et al. 2012	Generation R	1.34	[0.91; 1.98]	1.2%
Dadvand et al. 2014	Barcelona Birth Cohort	1.05	[0.84; 1.32]	3.3%
Winckelmans et al. 2015	Flanders Birth Study 99/09	1.09	[1.06; 1.12]	67.0%
Smith et al. 2017	London Birth Registry 06/10	1.03	[0.97; 1.10]	28.5%
Random effects model		**1.08**	**[1.01; 1.14]**	**100.0%**
Prediction interval			[0.95; 1.22]	

Heterogeneity: $I^2 = 11\%$, $\tau^2 = 0.0005$, $p = 0.34$



TRAP and preterm birth



Increments: 10 µg/m^3 for NO_2, 10 µg/m^3 for NO, 20 µg/m^3 for NO_x, 1 µg/m^3 for EC and 5 µg/m^3 for $PM_{2.5}$

- Null associations for all pollutants
- Individual studies have effect estimates above and below unity
- Third trimester effect for **NO_2**
- 3 **traffic-$PM_{2.5}$** studies showed associations (i.e. PM from primary traffic emissions)

Summary:

- Meta-analysis: **low confidence** in presence of an association
- Supporting association:
  - 3 traffic-PM studies
  - distance to roadway

Confidence assessment

Legend

high	moderate	low	Very low

Health Outcome	NO_2 (per 10 µg/m³)	NO_x (per 20 µg/m³)	EC (per 1 µg/m³)	$PM_{2.5}$ (per 5 µg/m³)	Overall Assessment of Confidence in Association with TRAP
Term low birth weight	1.01 (0.99; 1.03) N=12	1.02 (1.01; 1.03) N=5	1.01 (0.99; 1.04) N=5	1.11 (1.03; 1.20) N=7	**Moderate**
Term birth weight	−3.2 (−11.0; 4.6) N=8	−3.4 (−11.7; 4.8) N=5	−2.6 (−6.1; 0.9) N=4	−17.3 (−33.2; −1.5) N=6	**Low**
Small for gestational age	1.00 (0.98; 1.02) N=11	Fewer than three studies	1.02 (0.92; 1.14) N=3	1.09 (1.04; 1.14) N=4	**Moderate**
Preterm birth	1.00 (0.96; 1.04) N=14	1.03 (0.90; 1.17) N=6	1.02 (0.97; 1.07) N=5	0.99 (0.90; 1.09) N=4	**Low**

Modified OHAT assessment: confidence in quality of the body of evidence

A deeper dive into the evidence for some of the selected health outcomes

Moderated by Jeff Brook, University of Toronto and HEI Research Committee

Birth outcomes	Danielle Vienneau, Swiss Tropical and Public Health Institute
Respiratory	Audrey Smargiassi, University of Montreal
Cardiometabolic	Barbara Hoffmann, University of Düsseldorf
Mortality	Gerard Hoek, Utrecht University
Neurodevelopmental	Sharon Sagiv, University of California - Berkeley
Neurodegenerative	Jennifer Weuve, Boston University

HEI

Description of studies

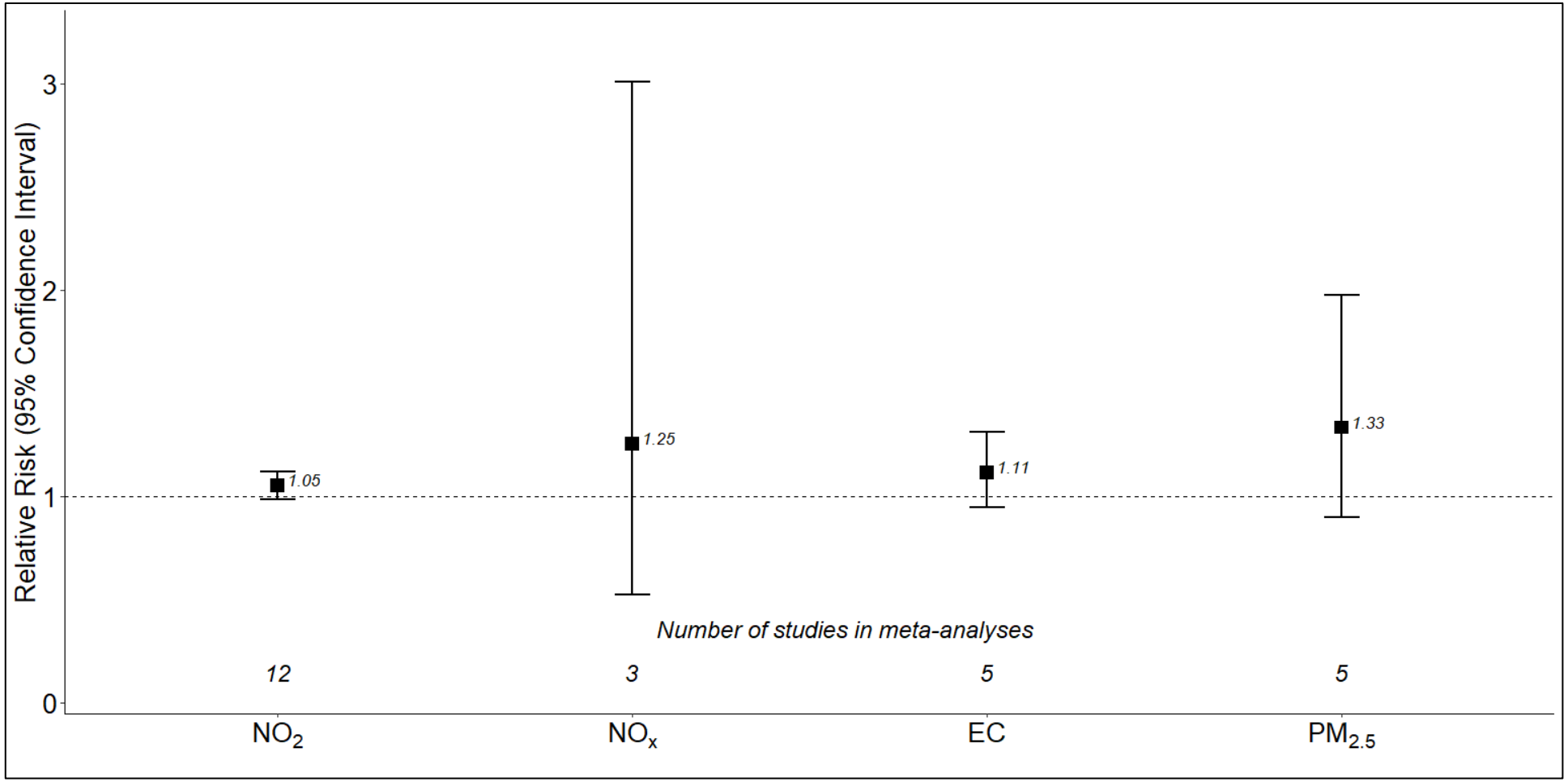
Health Outcome Category	Number of studies	Cohort	Case-control	Cross-sectional	Pub. before 2008	Exposure assessment method			High traffic specificity
						Monitoring (<5km)	LUR Modeling	Dispersion /CTM	
Respiratory effects - children	118	50 (42%)	17 (14%)	51 (45%)	35 (30%)	22 (19%)	41 (35%)	17 (14%)	89 (75%)
Respiratory effects – adults	50	19 (38%)	7 (14%)	24 (48%)	11 (22%)	2 (4%)	15 (30%)	15 (30%)	44 (88%)

Studies excluded if no control for inter-regional contrasts; Preference given to the earliest exposures (most estimates for exposure during pregnancy, at birth, or for the first year of life);

Most studies :

- from Europe / North America;
- controlled for lifestyle characteristics (ex. parental or individual smoking) except those based on administrative data (but control for area level SES);

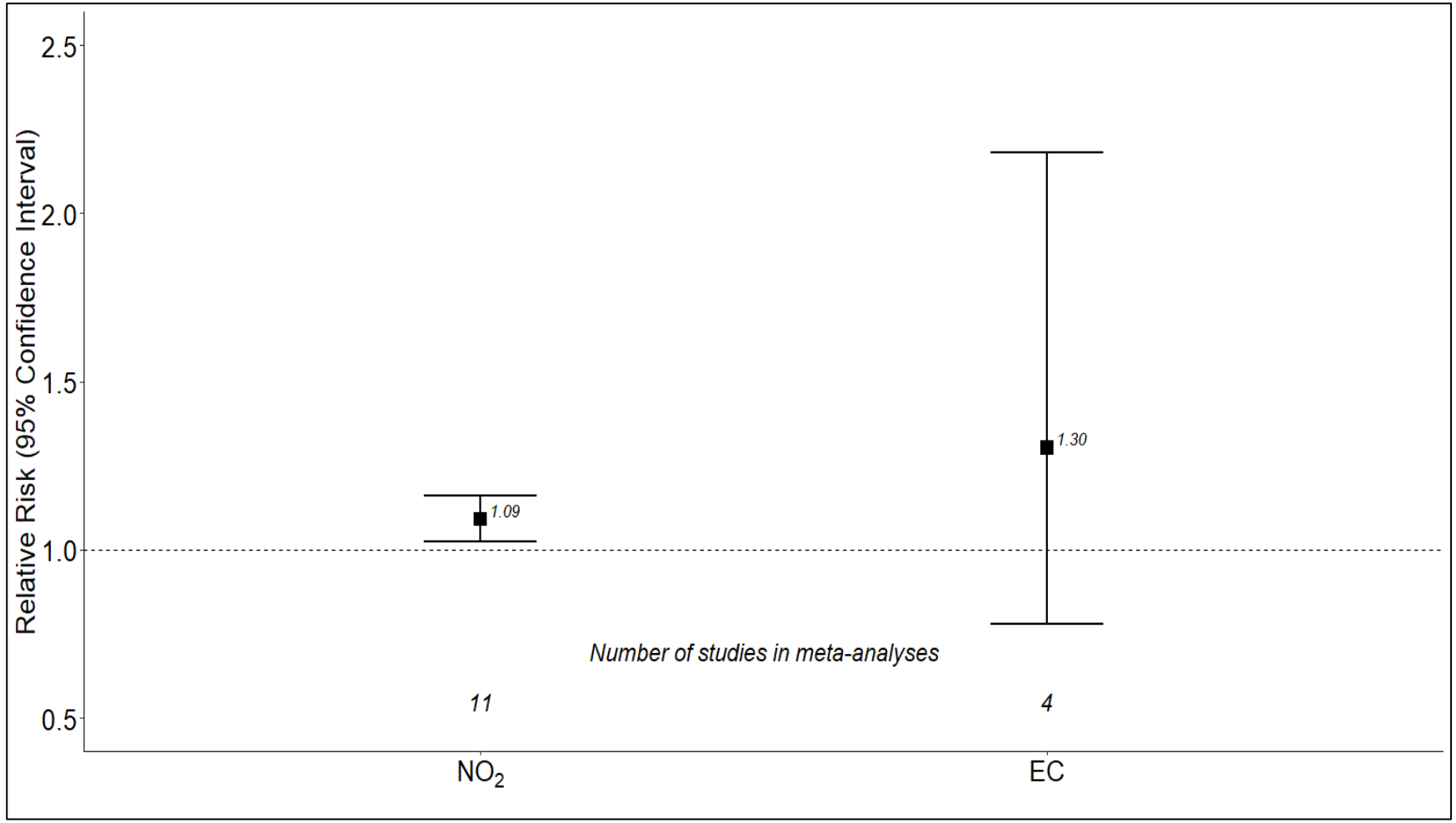
Meta-analysis of associations between TRAP and **asthma onset** in children



- Many cohorts based on questionnaires but minimal changes when removing such studies at moderate RoB
- Most estimates positive but some negative contributing to heterogeneity
- Smaller estimates from administrative cohorts, all from North America

Increments used: 10 µg/m^3 for NO_2, 20 µg/m^3 for NO_x, 1 µg/m^3 for EC and 5 µg/m^3 for $PM_{2.5}$

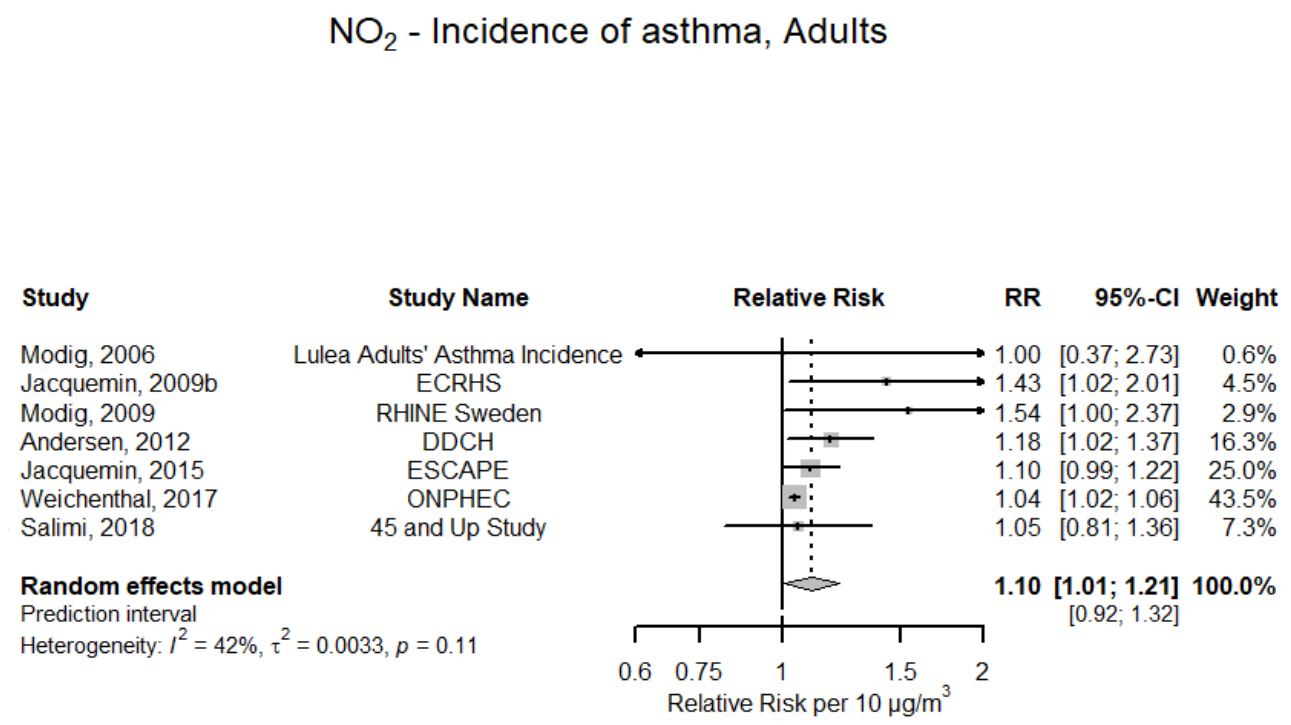
Meta-analysis of associations between TRAP and **ALRI** in children



- Cross-sectional and cohort studies based on questionnaires or administrative data
- Different infections considered
- Most estimates positive but some negative contributing to heterogeneity

Increments used: 10 µg/m^3 for NO_2 and 1 µg/m^3 for EC

Associations between NO_2 and **asthma onset** in adults: meta-analysis



- Mainly cohort studies (n=6/7)

Overall confidence in the evidence for an association between long-term exposure to TRAP and respiratory outcomes

		Narrative assessment	Confidence assessment of the body of evidence (modified OHAT)	Overall assessment
Children	Asthma onset	Moderate	High	Moderate to high
	Asthma ever	Moderate	Moderate	Moderate
	Active asthma	Moderate	Moderate	Moderate
	ALRI	High	Moderate	Moderate to high
Adults	Asthma onset	High	Moderate	Moderate to high
	ALRI	Low	Very low	Very low to low
	COPD	Low	Low	Low

- Mixed results from indirect traffic with asthma outcomes in children
- Limited information on associations with asthma exacerbations in children (n=6 with TRAP all positive estimates; no meta-analysis)
- Limited information and low confidence on associations in adults with asthma ever (n=5), active asthma (n=4) or exacerbations of COPD and asthma, with positive, negative and null findings

Aspects not covered in the modified OHAT assessment: number and size of the evidence base; strength (magnitude) of the association; different pollutants and indirect traffic measures.

A deeper dive into the evidence for some of the selected health outcomes

Moderated by Jeff Brook, University of Toronto and HEI Research Committee

Birth outcomes	Danielle Vienneau, Swiss Tropical and Public Health Institute
Respiratory	Audrey Smargiassi, University of Montreal
Cardiometabolic	Barbara Hoffmann, University of Düsseldorf
Mortality	Gerard Hoek, Utrecht University
Neurodevelopmental	Sharon Sagiv, University of California - Berkeley
Neurodegenerative	Jennifer Weuve, Boston University

HEI

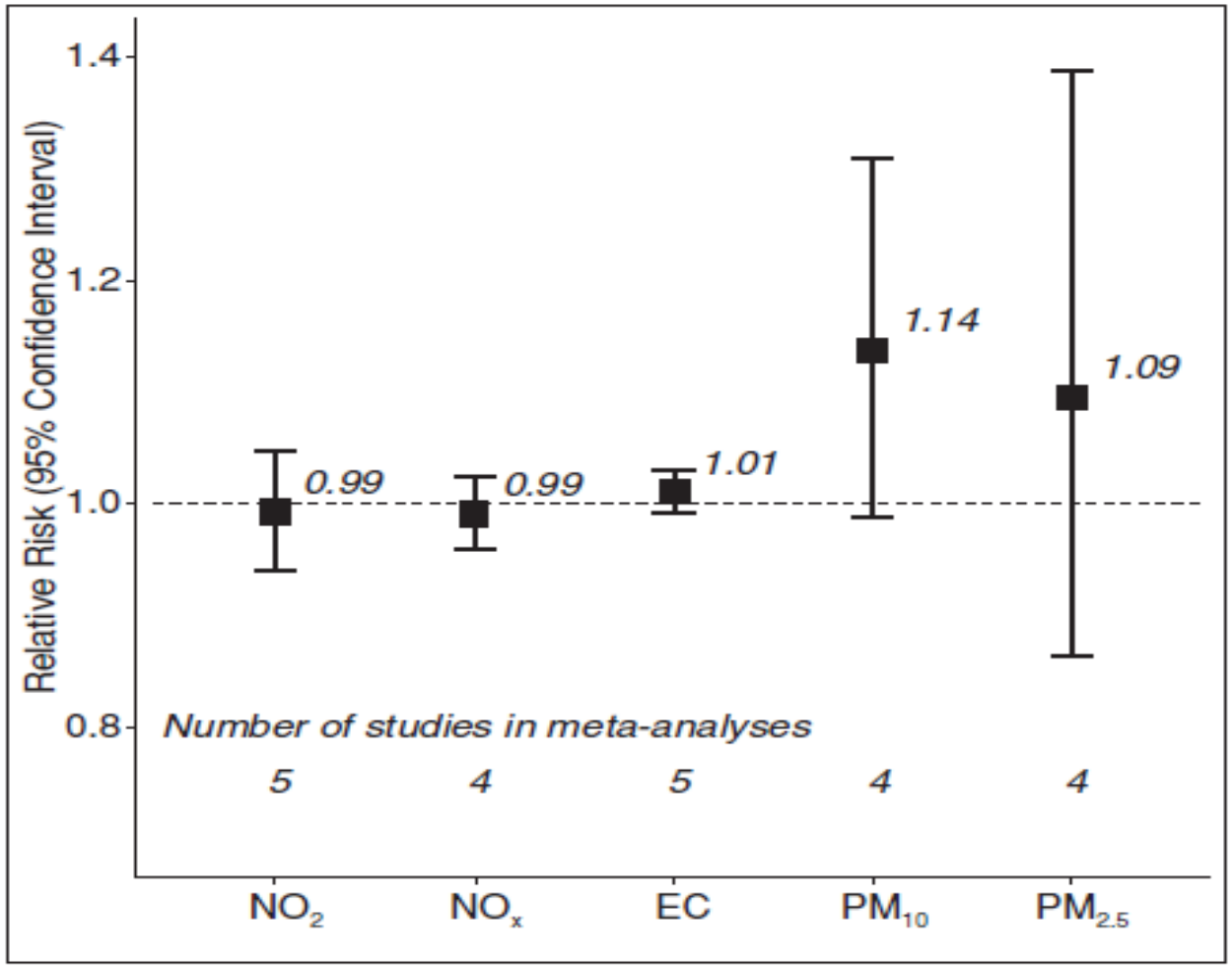
Substantial increase in published studies

Health outcome Category	Subcategory	Total number of studies	Total number of studies in meta-analyses
Cardiometabolic outcomes	Ischemic Heart Disease	20	11
	Coronary events	11	7
N=57 studies	Stroke events	20	13
	Type 2 diabetes mellitus – incidence	11	10
	Type 2 diabetes mellitus - prevalence	12	8

- Evidence base dominated by studies from Europe and North America
- Most studies incidence studies (exception: Diabetes studies), exclusion of diseased individuals at baseline (in contrast to mortality chapter)
- Many studies not included in meta-analysis because only indirect traffic measures available or less than 3 per pollutant
- Where possible, stratified analyses according to fatality of outcome

HEI

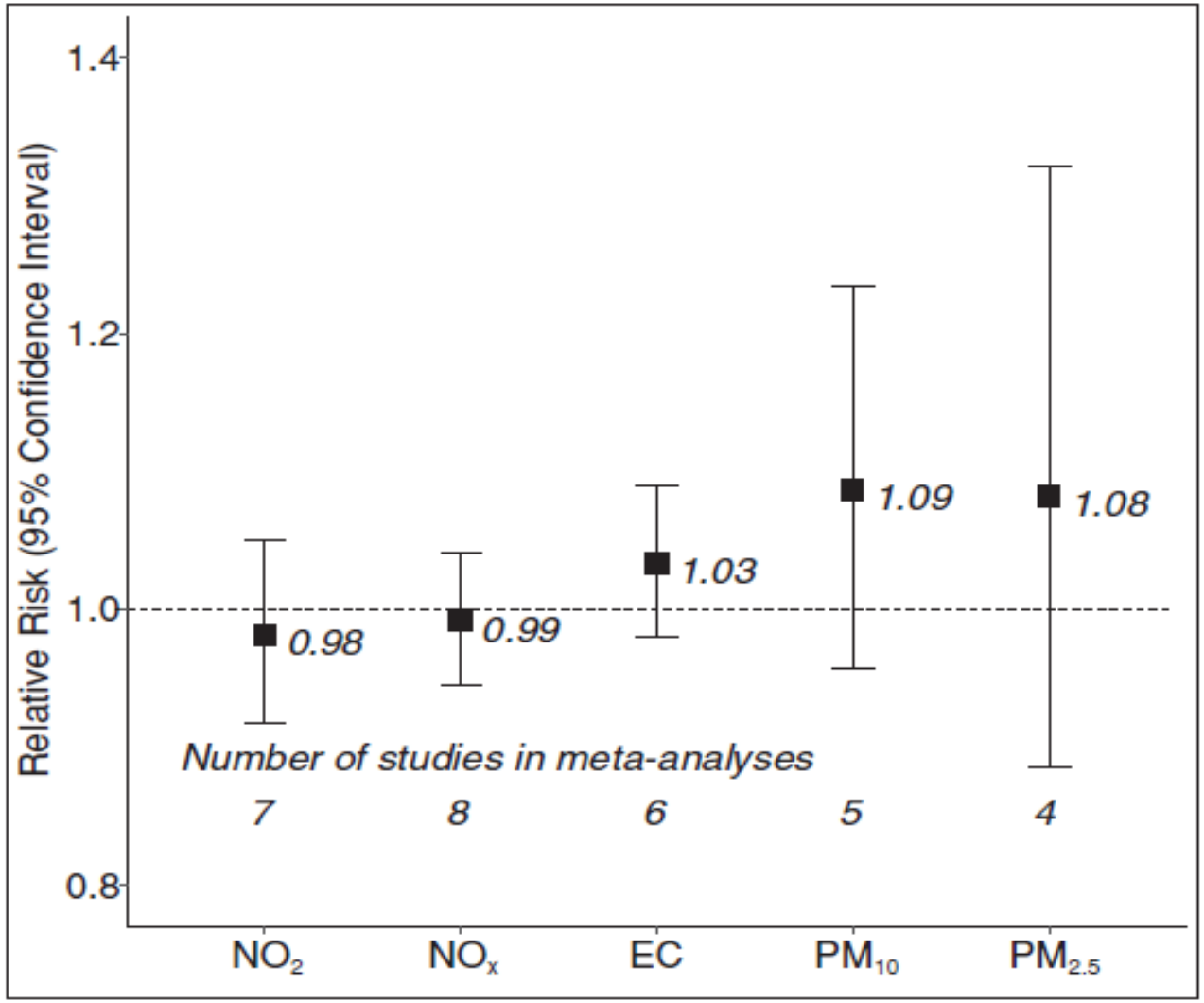
Ischemic Heart Disease



- Clear null associations for gaseous pollutants NO_2 and NO_x
- Subgroup analyses showed stronger and more consistent estimates for fatal disease
- Several studies with monotonic exposure-response function
- Additional support for indirect traffic measures, PM_{coarse} and PM nontailpipe indicators
- 4 out of 4 robust to noise adjustment

Increments used: 10 µg/m^3 for NO_2, 20 µg/m^3 for NO_x, 1 µg/m^3 for EC, 10 µg/m^3 for PM_{10} and 5 µg/m^3 for $PM_{2.5}$

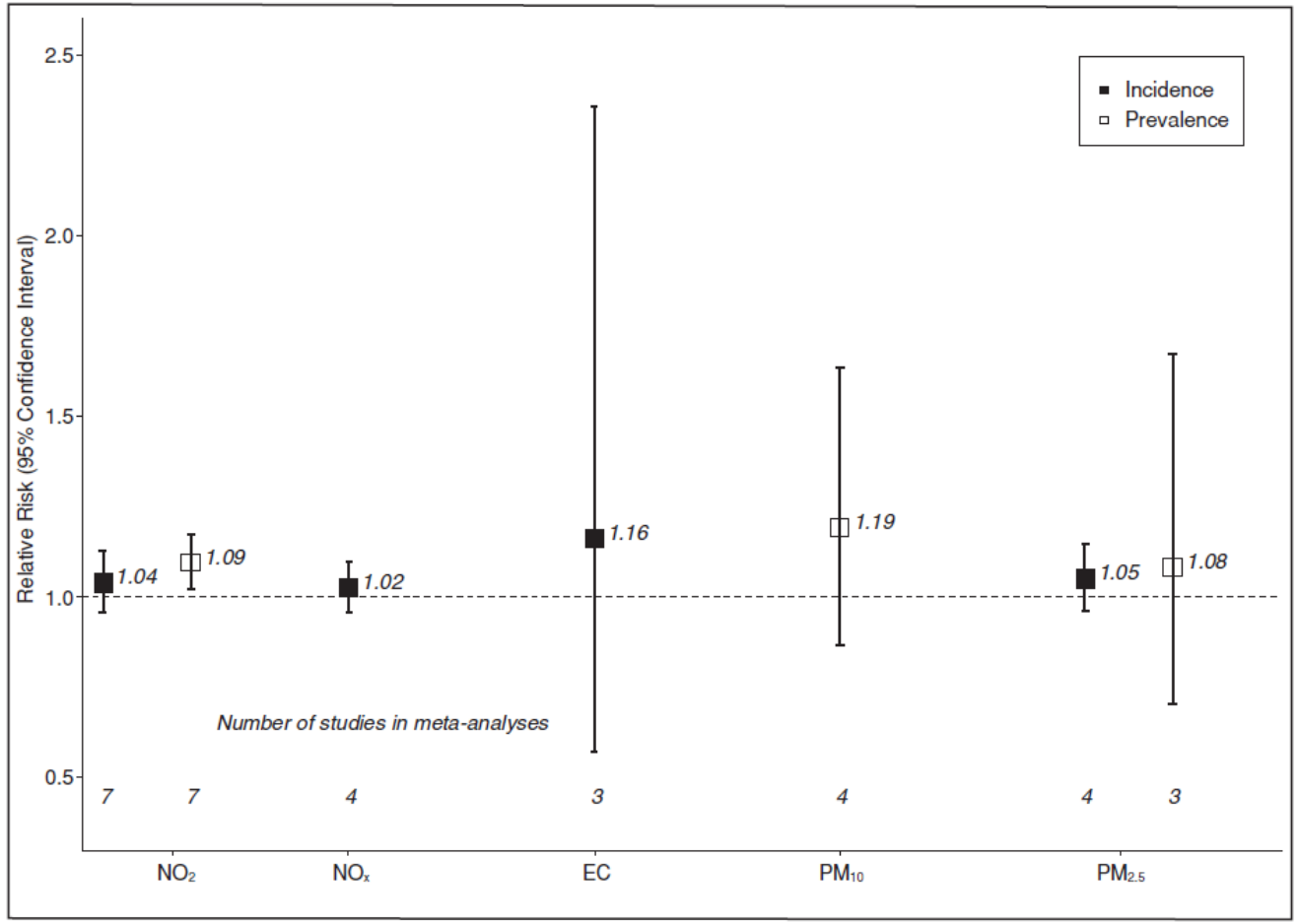
Stroke



- Clear null associations for gases NO_2 and NO_x
- Additional support for traffic-specific PM fractions
- Robust upon adjustment for noise (4 out of 4)

Increments used: 10 µg/m^3 for NO_2, 20 µg/m^3 for NO_x, 1 µg/m^3 for EC, 10 µg/m^3 for PM_{10} and 5 µg/m^3 for $PM_{2.5}$

Diabetes mellitus



- Indirect traffic measures (6 out of 7)
- Additional support for NO, UFP and traffic-specific PM fractions
- Robust upon adjustment for noise (4 out of 5)
- Studies with more extensive confounder control and outcome assessment with clinical exams yielded higher estimates and lower heterogeneity – upgrade in OHAT (1)

Increments used: 10 µg/m^3 for NO_2, 20 µg/m^3 for NO_x, 1 µg/m^3 for EC, 10 µg/m^3 for PM_{10} and 5 µg/m^3 for $PM_{2.5}$

Overall assessment

	Narrative assessment	Confidence assessment of the body of evidence (modified OHAT)	Overall assessment
Ischemic Heart Disease	**Moderate**	**Moderate**	**Moderate**
Coronary events	**Low**	**Low**	**Low**
Stroke events	**Moderate**	**Low**	**Low to moderate**
Type 2 diabetes mellitus	**Moderate**	**Moderate**	**Moderate**

- Generally stronger effects for fatal disease – in line with high ratings for cause-specific mortality outcomes (circulatory and ischemic heart disease)
- Exclusion of nonfatal (sub)clinical precursor conditions and short-term studies
- Repeated search conducted in 2022 for stroke and diabetes strengthens conclusions of moderate evidence
- Need for more toxicological / mechanistic evidence for nitrogen oxides and cardiometabolic disease

HEI

A deeper dive into the evidence for some of the selected health outcomes

Moderated by Jeff Brook, University of Toronto and HEI Research Committee

Birth outcomes	Danielle Vienneau, Swiss Tropical and Public Health Institute
Respiratory	Audrey Smargiassi, University of Montreal
Cardiometabolic	Barbara Hoffmann, University of Düsseldorf
Mortality	Gerard Hoek, Utrecht University
Neurodevelopmental	Sharon Sagiv, University of California - Berkeley
Neurodegenerative	Jennifer Weuve, Boston University

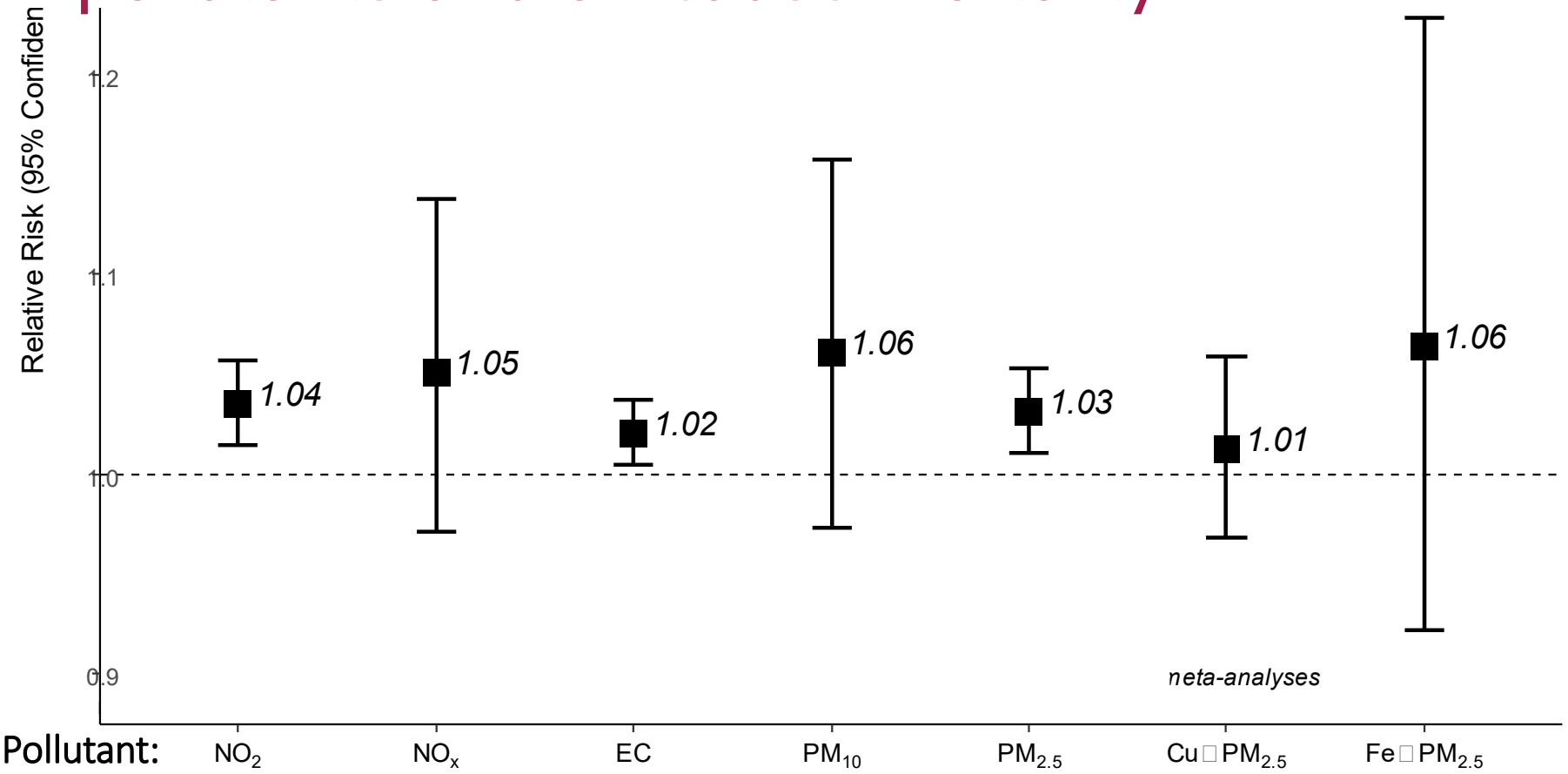
HEI

Many more studies on mortality than in 2010 HEI review

- 48 studies for all-cause (natural) and cause-specific mortality
- 31 studies for all-cause mortality
- Many cohort studies on air pollution not selected as not sufficiently traffic-specific (especially on $PM_{2.5}$ such as ACS, Medicare)
- Most selected were from Europe and North-America
- Studies with detailed lifestyle and very large population-based studies

HEI

Meta-analysis of associations between traffic-related air pollutants and all-cause mortality

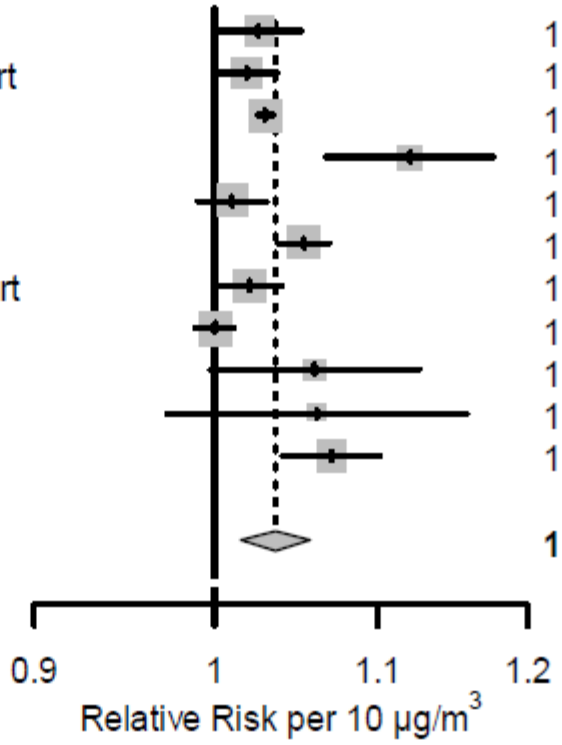


Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure. The individual pollutants are considered as indicators of the TRAP mixture.

Meta-analysis NO_2 – All cause mortality

Study	Study Name	RR	95%-CI	Weight
Beelen et al. 2008	NLCS-AIR	1.03	[1.00; 1.05]	9.8%
Carey et al. 2013	English National Cohort	1.02	[1.00; 1.04]	10.8%
Cesaroni et al. 2013	Rome Longitudinal	1.03	[1.02; 1.04]	12.2%
Yorifuji et al. 2013	Shizuoka Elderly	1.12	[1.07; 1.18]	6.1%
Beelen et al. 2014	ESCAPE	1.01	[0.99; 1.03]	10.6%
Crouse et al. 2015	1991 CanCHEC	1.05	[1.04; 1.07]	11.3%
Nieuwenhuijsen et al. 2018	Barcelona Mega Cohort	1.02	[1.00; 1.04]	10.6%
Yang et al. 2018	Hong Kong Elderly	1.00	[0.99; 1.01]	11.7%
Dirgawati et al. 2019	HIMS	1.06	[1.00; 1.13]	4.8%
Hanigan et al. 2019	45 and Up Study	1.06	[0.97; 1.16]	2.9%
Hvidtfeldt et al. 2019	DDCH	1.07	[1.04; 1.10]	9.3%
Random effects model		**1.04**	**[1.01; 1.06]**	**100.0%**
Prediction interval			[0.98; 1.10]	

Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.0006$, $p < 0.01$



Narrative assessment: high confidence

- Consistent associations multiple pollutants
- Sizable number of well-conducted (large) cohort studies
- Generally adjusting for major covariates
- In different locations: confounding less likely as pollution and lifestyle / SES have different direction of association with exposure
- Robust to adjustment for noise
- Different research groups
- Support from studies on traffic intensity / distance to major roads
- Some support from studies not included in meta-analysis such as studies in patient populations

HEI

Modified OHAT assessment for TRAP and all-cause mortality

- Few downgrades (imprecision, Risk of bias)
- Upgrades for monotonic exposure response function (NO_2, $PM_{2.5}$, NO_X and PM_{10}) and consistency across regions (NO_2)

• $PM_{2.5}$, NO_2, EC	high confidence
• NO_x and PM_{10}	moderate confidence
• Cu, Fe	low confidence
• **TRAP combined**	**high confidence**

HEI

Conclusions

- High confidence in an association between TRAP and all-cause mortality
- Despite issues formal and narrative assessment broadly agreed
- Broadly agree with other assessment on $PM_{2.5}$ and NO_2 pollutants by WHO, IARC and EPA (Integrated Science Assessment)
- Policies reducing TRAP will deliver health benefits

HEI

A deeper dive into the evidence for some of the selected health outcomes

Moderated by Jeff Brook, University of Toronto and HEI Research Committee

Birth outcomes	Danielle Vienneau, Swiss Tropical and Public Health Institute
Respiratory	Audrey Smargiassi, University of Montreal
Cardiometabolic	Barbara Hoffmann, University of Düsseldorf
Mortality	Gerard Hoek, Utrecht University
Neurodevelopmental	Sharon Sagiv, University of California - Berkeley
Neurodegenerative	Jennifer Weuve, Boston University

HEI

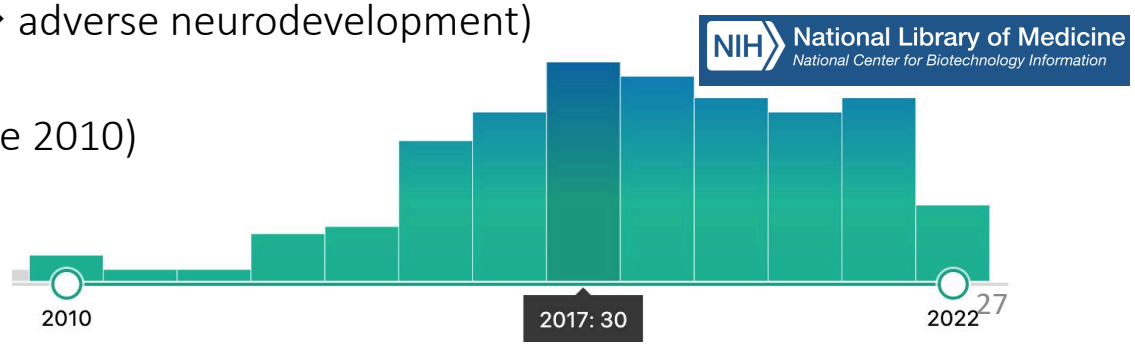
Neurodevelopment

- Brain development across multiple dimensions of cognitive function, behavior

- 3 categories of outcomes selected for TRAP review
  - Cognitive function (intellectual function, attention, executive function)
  - Attention deficit hyperactivity disorder (ADHD)
  - Autism spectrum disorders (ASD)

- No formal meta-analysis/confidence assessment for these outcomes

- Rationale for inclusion as secondary outcome in HEI review
  - Rapid development in early life → period of heightened vulnerability to environmental insult
    (legacy chemicals: prenatal/early life lead, mercury → adverse neurodevelopment)
  - Rapid growth in literature
    (e.g., 174 publications on air pollution* & autism since 2010)



* Not restricted to TRAP

Cognitive function

- Poorer performance or slower development along a range of cognitive domains
  - general, verbal, and nonverbal IQ, learning, memory, language, visuospatial skills, visual-motor abilities, attention, and dimensions of executive function, including working memory and response inhibition
- 30 studies included (age at cognitive assessment: 1-20 years)
  - 18 different study populations; all but 1 study set in Europe and N. America
  - 14 prospective cohort studies, 5 cross-sectional studies, range n=176 to 9,482
- MODERATE confidence in presence of association with TRAP
  - NO_2, EC, $PM_{2.5}$: approx. half of studies reported associations with cognitive function
    - both gestational and childhood exposure
    - mostly with general intelligence, attention, and working memory
  - null or scant evidence for NO_X, $PM_{10\&course}$, UFPs
  - mixed associations with indirect traffic measures (stronger for traffic density)

HEI

Attention deficit hyperactivity disorder (ADHD)

- ADHD diagnosis and related behaviors
  - inattention, hyperactivity, impulse control
- 8 studies included (age of ADHD assessment/diagnosis: 4 to 15 years)
  - 7 different study populations; all set in Europe and N. America
  - prospective cohorts except for 1 case-control study, range n=284 to 29,127
- LOW confidence in presence of association with TRAP
  - most studies reported null associations
  - small number of studies reported modest associations of childhood exposure to NO_2, EC, and $PM_{2.5}$ with ADHD behaviors

HEI

Autism Spectrum Disorders (ASD)

- ASD diagnosis and related behaviors
  - social cognition, restricted and repetitive behaviors
- 14 studies included (age at ASD assessment/diagnosis: 2 to 13)
  - 11 different study populations; most in Europe and N. America, also China, Israel
  - 7 case-control studies, 4 prospective cohorts, range n=430 to 126,402
  - all but 2 studies examined ASD diagnosis
- MODERATE TO HIGH confidence in presence of association with TRAP
  - NO_2: 4 of 5 studies reported higher ASD risk with gestational and early infancy exposure
  - $PM_{2.5}$: 3 of 4 studies reported higher ASD risk with exposure in first few years of life
  - null or mixed for other TRAP pollutants and indirect traffic
  - geographical heterogeneity in findings (+ N. America, Ø for Europe)

HEI

Discussion

- 49 studies representing 30 study populations included in review
- Confidence in presence of an association ranged from low (ADHD) to moderate/high (ASD)
- Limitations → directions for future study
  - Heterogeneity of outcomes, especially cognitive function → common set of endpoints
  - Sample sizes limited for many studies → larger studies, quantitative traits
  - Variable covariate inclusion → commons set of confounders
  - Critical window unclear (gestation, early life) → better identification of window of exposure, age at outcome assessment, biologic mechanisms
- Rapid growth in literature on air pollution and neurodevelopment
  - Formal meta-analysis/confidence assessment possible in the near future

HEI

A deeper dive into the evidence for some of the selected health outcomes

Moderated by Jeff Brook, University of Toronto and HEI Research Committee

Birth outcomes	Danielle Vienneau, Swiss Tropical and Public Health Institute
Respiratory	Audrey Smargiassi, University of Montreal
Cardiometabolic	Barbara Hoffmann, University of Düsseldorf
Mortality	Gerard Hoek, Utrecht University
Neurodevelopmental	Sharon Sagiv, University of California - Berkeley
Neurodegenerative	Jennifer Weuve, Boston University

HEI

Outcomes, methods, rationale

- Neurodegenerative outcomes included
  - Dementia and related cognitive outcomes (function and decline)
  - Parkinson disease

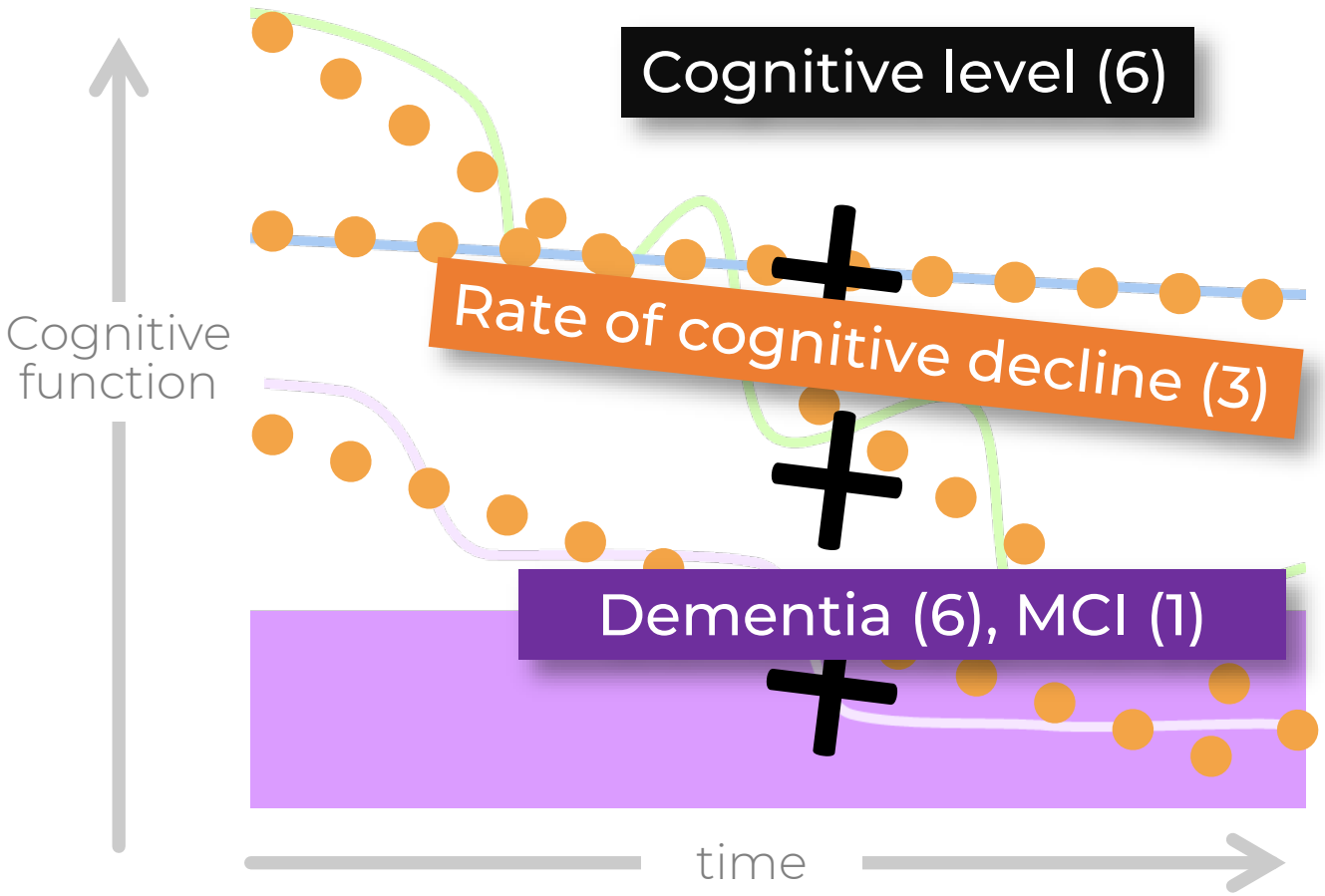
- No formal meta-analysis/confidence assessment for these outcomes

- Rationale for assessing as secondary outcomes
  - Public health burden:

    54.7M with dementia (2019); **6.1M with Parkinson disease** (2016)
  - Rapid growth in evidence base since 2010

HEI

Dementia and related cognitive outcomes: studies



15 studies in 10 cohorts

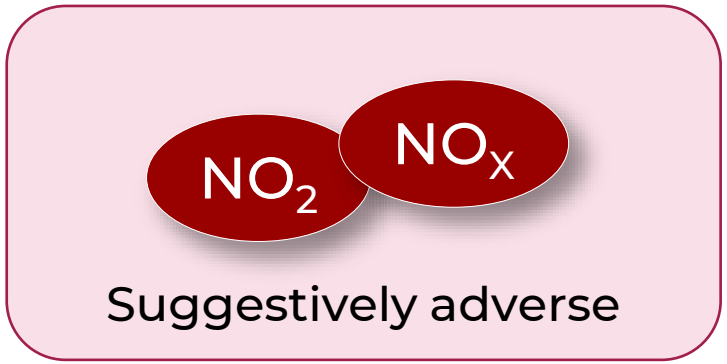
- N = 387 to >2 million
- Europe, N America
- Mostly cohort designs, some cross-sectional

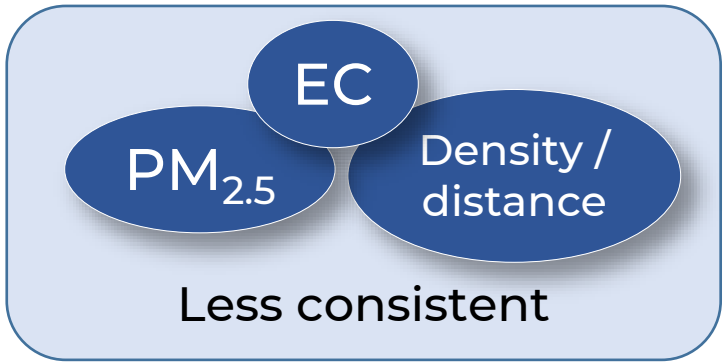
TRAP measures used

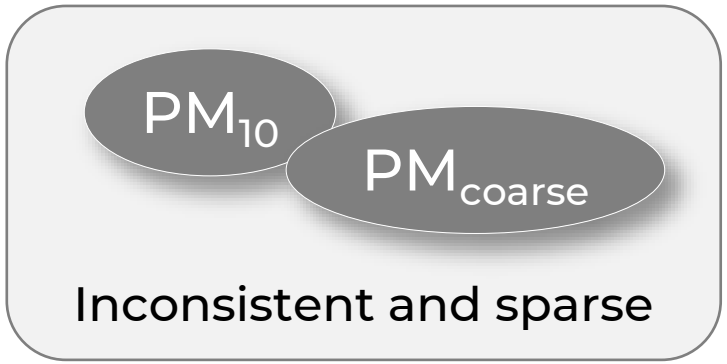
- Density/distance
- EC, NO_2
- $PM_{2.5}$, NO_x
- PM_{10}
- PM_{coarse}

Dementia and related cognitive outcomes: findings

Association patterns







Challenges

- Methodologic: selection bias, dementia misclassifcation in EMR
- Sparse numbers of specific pollutant-outcome pairs
- All associations with decline were null.

Low to moderate confidence in the presence of adverse association of TRAP with dementia-related outcomes

Parkinson disease: studies

6 studies in 5 cohorts

- N = 1290 to >2 million
- Europe, N America
- 3 cohort, 3 case-control

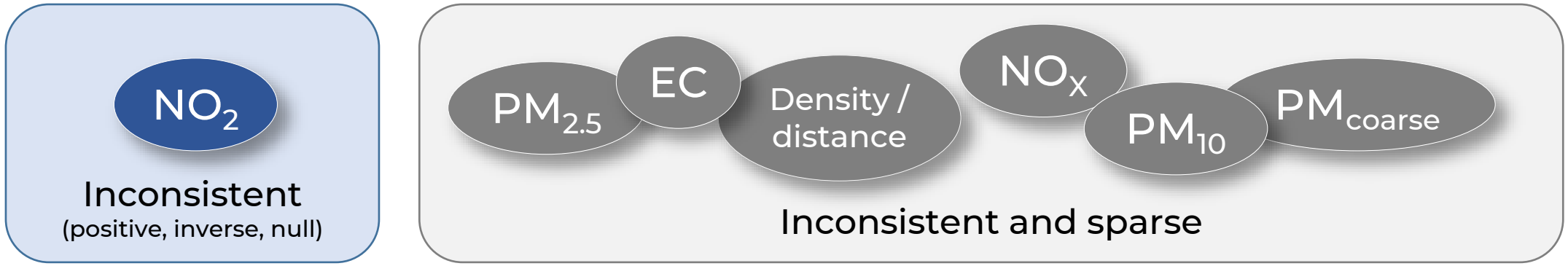
TRAP measures used

- ■■■■■ NO_2
  - ■■ $PM_{2.5}$, NO_x, PM_{10}, PM_{coarse}, density/distance

HEI

Parkinson disease: findings

Association patterns



Challenges

- Methodologic: selection bias, Parkinson misclassification, confounding by smoking
- Sparse numbers of specific pollutant-outcome pairs

Low confidence in the presence of adverse association of TRAP with Parkinson disease