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1 **Autism spectrum disorder and air pollution:**
2 **a systematic review and meta-analysis**

3
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32 **Abstract**

33 Despite the widely-known effects of air pollution, pollutants exposure surrounding pregnancy
34 and the risk for autism spectrum disorder (ASD) in newborns remains controversial. The
35 purpose of our study was to carry out a systematic review and meta-analyses of the risk of
36 ASD in newborns following air pollution exposure during the perinatal period (preconception
37 to second year of life). The PubMed, Cochrane Library, Embase and ScienceDirect databases
38 were searched for articles, published up to July 2020, with the keywords “air pollution” and
39 “autism”. Three models were used for each meta-analysis: a global model based on all risks
40 listed in included articles, a pessimistic model based on less favorable data only, and an
41 optimistic model based on the most favorable data only. 28 studies corresponding to a total of
42 758 997 newborns were included (47190 ASD and 703980 controls). Maternal exposure to all
43 pollutants was associated with an increased risk of ASD in newborns by 3.9 % using the
44 global model and by 12.3% using the optimistic model, while the pessimistic model found no
45 change. Each increase of $5\mu\text{g}/\text{m}^3$ in particulate matter $<2.5\mu\text{m}$ (PM2.5) was associated with
46 an increased risk of ASD in newborns, regardless of the model used (global +7%, pessimistic
47 +5%, optimistic +15%). This risk increased during preconception (global +17%), during
48 pregnancy (global +5%, and optimistic +16%), and during the postnatal period (global +11%
49 and optimistic +16%). Evidence levels were poor for other pollutants (PM10, NO_x, O₃,
50 metals, solvents, styrene, PAHs, pesticides). PM2.5 was associated with a greater risk than
51 PM10 (coefficient 0.20, 95CI -0.02 to 0.42), NO_x (0.29, 0.08 to 0.50) or solvents (0.24, 0.04
52 to 0.44). All models revealed that exposure to pollutants, notably PM2.5 during pregnancy,
53 was associated with an increased risk of ASD in newborns. Pregnancy and postnatal periods
54 seem to be the most at-risk periods.

55

56 **Keywords:** Air pollution - Autism Spectrum Disorder – pregnancy

57 Capsule: air pollution surrounding pregnancy increases the risk of ASD in newborns.

58

59 **Introduction**

60 Air pollution is a major public health ¹ and economic ² issue. associated with increased risk of
61 mortality ² and morbidity in multiple diseases, such as cancer ³, inflammatory ⁴, neurological ⁵
62 and respiratory and cardiometabolic diseases ⁶⁻⁸. Despite the considerable number of studies
63 demonstrating the adverse health effects of air pollution, exposure to ambient air pollution
64 surrounding pregnancy and the risk for Autism Spectrum disorder (ASD) in newborns
65 remains controversial ⁹⁻¹². Genetic and environmental factors specifically during perinatal
66 periods (preconception, pregnancy (first, second, third trimester), postnatal until 2nd year of
67 life) have been found to increase risk of pathology and malformation in children ¹³⁻¹⁵. Air
68 pollution is composed of a wide range of pollutants such as particulate matter (PM), nitrogen
69 oxide (NOx), volatile organic compounds, pesticides, ozone (O₃) and metals ^{16,17}. Though
70 few studies have focused on pregnancy and risk of ASD, air pollutants such as PM (PM₁₀,
71 with an aerodynamic diameter $\leq 10 \mu\text{m}$), appear to have the highest levels of toxicity ^{18,19}.
72 Among PM₁₀ ²⁰, PM_{2.5} which have an even smaller aerodynamic diameter $\leq 2.5 \mu\text{m}$ are
73 particularly harmful, penetrating more rapidly, easily and deeply into the organism ^{18,19}.
74 Despite a recent article ²¹, no meta-analysis to date has provided an overview or comparison
75 of the effects of classes of air pollutants ²², or the effects of sociodemographic risk factors
76 such as parental ages, gender of newborns, or smoking ²³⁻²⁵. In addition, there are no
77 published guidelines as yet on how to manage different data relating to a same risk within an
78 included article (e.g. crude odds ratio, or adjusted on different covariables) ²² and no meta-
79 analysis presented both risks quantified either as continuous (per increment of air pollutants)
80 or as categorical variables (high versus low exposure).

81 We hypothesized that there was an increased risk of developing ASD associated with air
82 pollution during pregnancy. This meta-analysis focused on the association between children
83 with ASD and exposure to air pollutants during the perinatal period (from preconception to
84 the second year of life) and involved three models for each meta-analysis by air pollutant; a
85 global model using all risks listed in included articles, a pessimistic model using less
86 favorable data only, and an optimistic model using the most favorable data only. We also
87 investigated related sociodemographic influences.

88

89 **Methods**

90 **Literature search**

91 We reviewed all studies reporting an association between air pollutants and ASD. The
92 PubMed, Cochrane Library, ScienceDirect and Embase databases were searched for all
93 original articles published up to July 2020, using the keywords “air pollution” and “autism” or
94 synonyms (see Appendix 1 for detailed search strategy). Inclusion criteria included articles
95 written in English or French, and that described our primary outcome variable i.e. the
96 association between perinatal exposure to ambient air pollution and risk of ASD. The
97 perinatal period included the preconception period to the second year of life. Studies were
98 required to report risk estimates in the form of odds ratios (OR) with 95% confidence interval
99 (95CI) or to provide data that allowed OR calculation. In order to identify studies not found
100 through our database search strategy, a manually search of new articles was carried out using
101 reference lists from all publications meeting inclusion criteria and systematic reviews. Our
102 search strategy is presented in [Figure 1](#) and [Appendix 1](#). Two authors (AC and FD) separately
103 conducted all literature searches, collated and, reviewed the abstracts based on selection
104 criteria and decided on the suitability of articles for inclusion. When questions arose over

105 article suitability, a third author (NB) reviewed the articles. Having reached a consensus, all
106 included articles were reviewed by the three authors.

107

108 **Quality of assessment**

109 The methodological quality of the studies was further evaluated using the Scottish
110 Intercollegiate Guidelines Network (SIGN) model for case control and cohort studies ²⁶. The
111 following 15 items were assessed: appropriate and clearly focused question, selection bias (2
112 items), performance bias (1 item), attrition bias (2 items), detection bias (6 items), confusion
113 bias (1 item), presence of confidence intervals, and general level of evidence (Figure 2).
114 Similar items were used to evaluate case control studies (Figure 2). We also used the
115 Newcastle-Ottawa Quality Assessment Scale (NOS) model ²⁷ with the following 9 items:
116 selection bias (4 items), comparability bias (2 items) and outcome bias (3 items)
117 (Supplementary Figure 1). Each item was assigned a judgment of “Yes” (+), “No” (-), “Can’t
118 say” (?), or “Not applicable” (NA), with the exception of item 2.1 (to minimize risk of bias or
119 confounding) and the final item concerning evidence level of the SIGN checklist, which was
120 assigned “0”, “+”, or “++”. Any disagreements over suitability were discussed with a third
121 author (BP) and a consensus reached. Assessment of article quality was carried out for the
122 two checklists by two authors (AC and FD).

123

124 **Data analysis**

125 The following data from articles were recorded: title, name of first author, journal and year of
126 publication, main objective, time of exposure to air pollution (perinatal period, full pregnancy
127 or during, first, second and/or third trimester of pregnancy and postnatal period), type and
128 concentration of pollutants, crude and/or adjusted OR and lower and upper limits, and

129 population characteristics (number of participants per study, parental mean age at birth,
130 gender of newborns, level of parental education, smoking).

131

132 **Statistical considerations**

133 Statistical analysis was conducted using Stata software (version 15, StataCorp, College
134 Station, US)^{28–33}. Characteristics of pollutant exposure, of individuals or other variables were
135 reported for each study as mean ± standard-deviation (SD) and number (%) for continuous
136 and categorical variables respectively (Table 1). When data could be pooled, we conducted
137 random effects meta-analyses (DerSimonian and Laird approach)³⁴ on the risk (OR) of ASD
138 in newborns following air pollutants exposure, centered at one. Particular attention was paid
139 to the type of statistics retrieved from the included articles (OR or other risk measurements).
140 Air pollutants exposure were quantified either as a continuous (per increment of air
141 pollutants) or as categorical variables (high versus low exposure). For the highest level of
142 proof, we first normalised all OR for a standardized increment in pollutant concentration (for
143 example per 5 µg/m³ increase in PM_{2.5}). We took into account the original increment of the
144 pollutant and we assumed a linear exposure outcome relationship³⁵ using the following
145 equation: $OR_{standardized} = e^{[Ln(OR_{original}) * 10 / (Increment_{original})]}$ ³⁶. When air
146 pollutant levels were expressed in parts per billion (ppb), we transformed those levels in
147 µg/m³ (for example NO₂: 1 ppb = 1.88 µg/m³; O₃: 1ppb = 2 µg/m³)³⁷ The effects expressed as
148 interquartile (or quintile, or percentile differences) were converted into effects per
149 concentration unit increase with the previous equation (³⁶ Meta-analyses were computed by
150 type of air pollutants (PM_{2.5}, PM₁₀, NO_x, O₃, metals, solvents, styrene, polycyclic aromatic
151 hydrocarbons (PAHs), pesticides), periconceptional periods, and pregnancy trimester where
152 sufficient data were available. For each meta-analysis, three models were used (a global
153 model of all risks listed in the included articles, a pessimistic model using less favorable data

154 only, and an optimistic model using the most favorable data only). Finally, we computed the
155 aforementioned meta-analyses categorical using OR based on categorical exposure (high
156 versus low exposure). For air pollutants that were the most reported, we also computed
157 sensitivity analyses depending on the methods to measure air pollutants. Heterogeneity
158 between studies was evaluated through forest plots, and their confidence intervals (CI), and I-
159 squared (I^2) – varying from 0 to 100%. Heterogeneity is considered low for $I^2 < 25\%$, modest
160 for $25 < I^2 < 50\%$, and high for $I^2 > 50\%$. For example, a significant heterogeneity may be due to
161 the variability between the characteristics of the studies, such as the exposure to air pollutants
162 (type of air pollutants), periconceptional periods (preconception, pregnancy, postnatal),
163 pregnancy trimester (first, second, third), characteristics of individuals (age of mothers and
164 fathers, smoking, gender of newborns, etc). To ensure the robustness of our results, we
165 conducted sensitivity analysis by searching for potential publication bias through funnel plots
166 (metafunnels) of aforementioned meta-analyses. Then, we reperformed meta-analyses without
167 the studies that were not evenly distributed around the funnel base ³⁸. When sample size
168 allowed, meta-regressions were performed to investigate the relationship between risk of ASD
169 in newborns following air pollutant exposure and putative variables such as type of air
170 pollutant, periconceptional period, pregnancy trimester and population characteristics. Results
171 were expressed as regression coefficients and 95% CI.

172

173 **Results**

174 An initial search identified 913 possible articles for inclusion (Figure 1). Following
175 application of selection criteria and removal of duplicates 28 articles were selected ^{9–12,17,39–61}
176 (Table 1), all of which were written in English.

177

178 **Quality of articles**

179 Use of the SIGN model, notably revealed selection and attrition bias in included studies. Most
180 studies had a high level of evidence. Detailed characteristics of methodological quality
181 assessment for each included study are provided in [Figure 2](#). Overall, for the SIGN model,
182 most studies were shown to have a high level of evidence but performed, with lowest
183 performance found response rate. The NOS model was also used to analyse the quality of
184 included articles ([Supplementary Figure 1](#)).

185

186 **Aims of included studies, study designs, and settings**

187 All studies shared a similar *objective* i.e. the association of exposure to air pollution (PMs,
188 NOx, O3, metals, PAHs, solvents, pesticides) during the perinatal period and the development
189 of ASD. Six studies described a cohort *study design*^{11,12,40,41,56,58} using a historical birth/child
190 cohort. The 22 remaining studies^{9,10,17,39,42–54,57,59–61} described case control studies. Most
191 studies assessed exposure over several consecutive years with the exception of four studies
192 which analyzed data from one year^{10,40,42,50,60}. *Countries of exposure* included North America
193 for 20 studies (U.S^{17,39–44,46,48–53,56,57,59–61}, Canada¹²), Europe for 5 studies (Denmark⁴⁷,
194 Sweden^{9,10,58} and other European countries¹¹), and Asia for 3 studies (Iran⁵⁵, Israel⁴⁵, China
195⁵⁴).

196

197 **Population**

198 *Sample size* for children with ASD ranged from 124⁵⁴ to 15 387⁴⁵. Population size for
199 controls (children without ASD) ranged from 156⁵² to 130 949¹². In total 751 170
200 individuals (47190 ASD and 703980 controls) were included in this meta-analysis.

201 *Age of mothers at birth* was expressed as a mean value in 11 articles^{9–12,45–50,56}, ranging from
202 29.5 ± 5.0 ⁴⁷ to 34.0 ± 4.0 years old⁴⁶ for mothers of ASD (mean age 31.6, 95CI 28.3 to
203 34.9), and 28.5 ± 6.0 ⁵⁰ to 33.7 ± 3.7 ⁴⁶ years for mothers of controls (mean age 31.7, 95CI

204 28.6 to 34.7). Twelve articles reported different classes of age^{17,39,42–44,51,54,55,57–60}, precluding
205 further analyses. Five articles did not mention age of mothers (37,48,49,57,60).

206 *Age of fathers at birth* was not reported in most (19/28) articles^{9,11,12,17,40–44,48,51–54,56–59,61}.
207 Three articles expressed age of fathers at birth as classes^{39,55,60}, and six as mean values^{10,45–}
208 ^{47,49,50}, ranging from 32.2 ± 6.1 ⁴⁷ to 36.8 ± 5.3 years⁴⁶ for fathers of ASD (mean age 33.9,
209 95CI 28.6 to 39.4), and 31.4 ± 6.6 ⁵⁰ to 33.7 ± 5.6 ⁴⁹ years for fathers of controls (mean age
210 33.9, 95CI 29.3 to 38.7).

211 *Gender*: All articles except two^{53,61} reported child with ASD gender, ranging from 29%⁵¹ to
212 87%⁵². Seven articles did not report child without ASD gender^{17,40–42,52,53,61}. 77% (95CI 73 to
213 81%) of children with ASD and 60% (95CI 55 to 65%) of children without ASD were boys.

214

215 **Characteristics of air pollutant exposure**

216 **Types of pollutants** analyzed in these articles included PM_{2.5} in 13 studies
217 11,12,39,44,46,47,49,52,54,56,57,59,61, PM₁₀ in 12 studies^{9–11,39,43,47,52,54–56,59,61}, NO_x in 12 studies^{9–}
218 12,39,45,47,52,56,58,59,61, O₃ in 7 studies^{39,44,52,56,57,59,61}, metals in 7 studies^{17,40–42,48,50,60}, solvents in
219 5 studies^{17,42,50,55,60}, styrene in 3 studies^{17,42,50}, PAHs in 3 studies^{17,42,50}, and pesticides in 3
220 studies^{17,42,50}.

221 **Type of exposure** included a general outdoor exposure in 19 studies^{11,12,17,40–43,45–}
222 48,52,53,56,57,59,61, in cities or regions of high human density in ten studies^{9,10,39,44,49,50,54,55,58,60},
223 with one study focusing on distance from homes to freeway and major roads⁵¹.

224 **Perinatal periods of exposure**: 6 studies analyzed exposure to air pollutants during
225 preconception^{41–43,46,49,57}, 25 during pregnancy^{9–12,17,39–41,43–47,49–53,55–61}, 9 during the postnatal
226 period^{9,10,43,46,48,49,54,56,57} and 5 during the two first years of life^{44,45,47,52,61}.

227 **Quantification of exposure**: Most studies^{9,11,12,17,39,40,43,45,47,48,50,54,55,57–59} assessed exposure
228 to pollutants first by geocoding birth certificate residential addresses, followed by use of

229 different models (NATA for National-scale air toxics assessment ^{17,40,48,50}; LUR model for
230 Land Use Regression ^{12,39,55}; CALINE4 line source air quality dispersion model ^{53,61}) to
231 estimate average pollutant concentration at participants' home address at time of birth..

232

233 **Meta-analysis by air pollutants**

234 **PM 2.5:** Each increase of $5\mu\text{g}/\text{m}^3$ in PM2.5 was associated with an increased risk of ASD in
235 newborns, regardless of the model used (global +7%, pessimistic +5%, optimistic +15%).
236 This risk increased during preconception (global +17%), during pregnancy (global +5%, and
237 optimistic +16%), and during the postnatal period (global +11% and optimistic +16%) ([Figure](#)
238 [3](#)). The risk was increased during the first and third trimesters regardless of the model used
239 (global +7% and +6%, pessimistic +7% and +7%, optimistic +7% and +7%, respectively)
240 ([Figure 4](#)). Results by periconceptional periods (preconception, pregnancy, postnatal)
241 ([Supplementary Figure 2](#)), and by pregnancy trimester (first, second, third) were similar using
242 categorical data (high exposure versus low exposure): the risk of ASD in newborns increased
243 regardless of the model used (global +11%, pessimistic +6%, optimistic +16%). Results were
244 also similar ([Supplementary Figure 3](#)).

245 **PM 10:** Each increase of $5\mu\text{g}/\text{m}^3$ in PM10 was not associated with risk of ASD using the
246 global model (-1%, non-significant), and was associated with a decreased risk of ASD using
247 the pessimistic model (-3%), and with an increased risk using the optimistic model (+1%).
248 Meta-analysis by periconception periods was associated with a decreased risk using the
249 pessimistic model for the pregnancy period only (-4%) and with an increased risk using the
250 optimistic model for the postnatal period only (+2%) ([Figure 3](#)). There was not enough data to
251 perform meta-analysis by trimester using incremental risk (continuous data). Results were
252 also similar by periconceptional periods (preconception, pregnancy, postnatal)

253 (Supplementary Figure 2) using categorical data. Meta-analysis by trimester did not reveal
254 any significant increase in risk, regardless of the model used (Supplementary Figure 3).

255 **NO_x**: Each increase of 10µg/m³ in NO_x was associated with an overall increased risk of ASD
256 using the global (+2%) and optimistic models (+5%), as well as during pregnancy period. No
257 significant results were found using the pessimistic model in all periods (Figure 3). Meta-
258 analysis using categorical risks showed similar results (Supplementary Figure 2).

259 **O₃**: Using categorical risks, overall risk of ASD following O₃ exposure increased using the
260 global (+3%) and optimistic models (+11%). Similarly, exposure during pregnancy led to an
261 increase in risk, using the global (+3%) and optimistic (+10%) models only (Supplementary
262 Figure 2).

263 **Metals**: Using categorical risks, exposure to metals did not lead to an increase in risk of ASD
264 using the global model but decreased using the pessimistic model, and increased using the
265 optimistic model (Supplementary Figure 2).

266 The meta-analysis on **solvent**, **styrene**, **PAH**, and **pesticide** exposure was based on a
267 maximum of five studies. Solvent and styrene exposure was found to increase the risk of ASD
268 using both the global and optimistic models, whereas the pessimistic model showed a
269 decreased risk following solvent exposure. Pesticide exposure was associated with a
270 decreased risk using the global and pessimistic model. PAH exposure did not modify the risk
271 of ASD (Supplementary Figure 2).

272 All individual meta-analysis are compiled in Supplementary Figure 4 for normalized OR
273 (continuous data) and in Supplementary Figure 5 for categorical data (high versus low
274 exposure).

275

276 **Overall meta-analysis**

277 Taking into account all air pollutants levels as categorical levels (high versus low exposure),
278 maternal exposure to air pollution was associated with an increased risk of ASD in newborns
279 by 3.9 % using the global model (OR = 1.039, 95% CI 1.031 to 1.048, I²=70.9%), and by
280 12.3% using the optimistic model (1.123, 1.098 to 1.147, I²=83.0%), but not to increase when
281 using the pessimistic model (0.975, 0.960 to 0.991, I²=70.4%). Meta-analysis by
282 periconception periods demonstrated an increased risk during preconception with the
283 optimistic model only, an increased risk during pregnancy with both the global and optimistic
284 models, and an increased risk regardless of the model used during the postnatal period.

285

286 **Metaregressions and sensitivity analyses**

287 Using categorical levels of exposure, PM_{2.5} tended to lead to greater increased risk of having
288 a child with ASD compared with exposure to PM₁₀ (coefficient 0.20, 95CI -0.02 to 0.42,
289 p=0.073), NO_x (coefficient 0.29, 95CI 0.08 to 0.50, p=0.006), and solvents (coefficient 0.24,
290 95CI 0.04 to 0.44, p=0.017). No other differences between air pollutants exposure were noted,
291 nor between periconceptional periods or trimesters. Neither parental age or gender of
292 newborns were found to influence the risk of ASD (Figure 5). Due to insufficient data other
293 sociodemographic variables were not analyzed. Results were similar using continuous levels
294 of exposure. For PM_{2.5} and PM₁₀, meta-analysis depending on the methods to measure air
295 pollutants showed similar results.

296

297

298 **Discussion**

299 The main findings revealed that air pollution particularly that of PM_{2.5} during the
300 periconception period was associated with an increased risk of ASD in newborns, in all
301 models used. The level of evidence is poor for other air pollutants. Exposure during

302 pregnancy (first and third trimesters) and postnatal periods may be the most at-risk periods.
303 The increased risk of ASD following exposure to air pollutants surrounding pregnancy was
304 not linked with sociodemographic factors.

305

306 **Air pollution and risk of ASD in newborns**

307 We demonstrated that global air pollution exposure in the perinatal period is a risk factor for
308 ASD in newborns. Despite a previous meta-analysis ²¹, there is the first to report a risk based
309 on consideration of all air pollutants. As, exposures are in general multiple when quantifying
310 risk, it is likely that overall risk is of most interest as reported by other authors ⁵¹⁻⁵³. ASD was
311 first described as a disorder in children with problems relating to others, highly sensitive to
312 changes in their environment ⁶². Prevalence of ASD appears to have increases over time ^{63,64}
313 possibly due to a modified definition of ASD, enhanced awareness and improved diagnosis
314 ^{65,66}, but also to a global increase in air pollutants in most megalopolis ^{67,68}. The rigorous and
315 sensitive statistical approach used in this meta-analysis allowed analysis of several included
316 studies presenting different data for the same risk (e.g. several models adjusted on different
317 covariables). There are presently no guidelines on how to manage this issue ²². To avoid
318 potential limitations, we created three models for each meta-analysis; a global model based on
319 all risks reported in included articles, a pessimistic model using less favorable risks only
320 (statistically speaking), and an optimistic model using the most favorable risks only.
321 Unsurprisingly, use of optimistic models led to stronger results, but notably, we were unable
322 to demonstrate an increased risk using the pessimistic model based on all air pollutants.

323

324 **PM2.5: a public health issue**

325 Risk of developing ASD in newborns increased using the global and optimistic models only
326 for all air pollutants, with a strong high risk following exposure to PM2.5 whatever the model.
327 Even use of the pessimistic model based on the least favorable data (those with the least

328 increased risk) revealed a minimum increased risk of 6% (up to 15% using the optimistic
329 model). Nearly all individual studies showed that maternal exposure to PM2.5 was associated
330 with increased risk of newborns with ASD ^{39,44,46,47,49,53,54,56,57,59,61}. Thus indicating the high
331 level of evidence concerning the deleterious effects of PM2.5 and related risk of ASD. PM2.5
332 particles appear to be the most dangerous pollutant due to their small size, and high volatility
333 ⁶⁹, able to be transported over longer distances ⁶⁹. They also have a lower sedimentation
334 velocity than other larger particles such as PM10 ⁶⁹. PM are primarily composed of toxic
335 particles such as PAHs, inorganic particles (sulfate, nitrate, ammonium), or organic carbon
336 metals (copper, iron, nickel) ^{70,71}. As road traffic is one of the primary sources of PM emission
337 ^{19,70,72} and predicted to double over the next twenty years ⁷³, the impact of PM2.5 on health
338 may become a major public health issue ⁷⁴. As diesel is considered to emit more fine PM than
339 gasoline ^{72,75}, it may become a target for future preventive strategy. Levels of evidence are
340 poor for the other air pollutants investigated.

341

342 **Late pregnancy and early postnatal period: a key developmental periods**

343 Late pregnancy and early postnatal periods were found to be the most at-risk periods for
344 developing ASD following air pollution exposure. These periods are crucial in the
345 development of the infant ¹³, and can influence long-term health outcomes ⁷⁶. Late pregnancy
346 is important for placental function, fetal growth and brain developments and is also the period
347 when maternal and fetal complications can occur, such as gestational diabetes, pre-eclampsia,
348 hypoxia or brain injury ⁷⁷⁻⁸⁰. Our result showing increased risk of ASD during late pregnancy
349 is in accordance with previous meta-analyses ²¹. Similarly, the early postnatal period can also
350 impact health outcomes as has been shown with breastfeeding which may impact a wide
351 range of parameters such as cognition, brain structure, structural development of the heart and
352 lungs, bone health, or atopy ^{81,82}. In comparison with the meta-analysis of Chun et al., we

353 highlighted the detrimental effects of air pollution leading to increased risk of ASD during the
354 postnatal period, being previously analyzed in relation to the prenatal period. Our results show
355 that the most at-risk periods for ASD were early and late pregnancy and the early postnatal
356 period. These results are in accordance with other studies on air pollution that have showed
357 these periods to also be the most at-risk for other birth outcomes such as hypertension,
358 preeclampsia, pre-term birth, or low birthweight⁸³⁻⁸⁵. Both late pregnancy and the early
359 postnatal period appear key phases as regards vulnerability to air pollution⁴³

360

361 **Influence of sociodemographic and other factors**

362 Most often, etiologies of ASD remain unknown. Although, genetic susceptibility has been
363 highlighted as a risk factor⁸⁶. No included studies in our meta-analysis indicated genetic
364 susceptibility. Two further highlighted risk factors concern parental age and the newborn
365 gender. Several studies have shown that maternal and/or paternal age^{87,88}, and male gender
366^{89,90} were associated with an increased risk of child neurodevelopmental outcomes such as
367 ASD. In our meta-analysis, neither parental age or newborn genders were found to influence
368 risk following exposure to air pollutants. However, our meta-regressions analyzed whether air
369 pollution modifies this risk depending on parental age or newborn genders. Other investigated
370 putative risk factors for ASD include maternal food intake⁹¹, low birthweight or preterm birth
371^{89,92}. As these factors were not assessed in the articles included in our meta-analysis, further
372 analyses were precluded.

373

374 **Limitations**

375 Our study has some limitations. Despite the large number of studies, some air pollutants were
376 only included in a few studies. Common air pollutants such as PM2.5, PM10, or NOx, were
377 however commonly assessed and as we included a large sample of 395 615 newborns, this

378 allowed the greater generalizability of our results. Our meta-analysis inherited the limitations
379 of the 28 included studies and was therefore subject to individual bias such as bias of
380 measures of exposure to air pollutants and bias of reporting of ASD. Despite the quality of
381 research reflected in the studies included in our meta-analyses, ASD covers a wide range of
382 severity that was not reported within included articles. Diagnostic method for ASD also
383 differed, limiting quality of data and precluding further analyses, although, most articles used
384 National ASD databases thus guaranteeing data accuracy. A further limitation concerns a
385 possible underestimation of our results. Diagnostic evidence of ASD can be underestimated
386 but is unlikely to be overestimated. Similarly, methods for detection or measurement of air
387 pollutant exposure differed between studies, thus precluding assessment of dose response
388 effects. In addition despite similarities, population characteristics between studies were not
389 identical. Data were collected in various countries, but excluded developing countries. The
390 majority of studies were conducted in the USA^{17,39–44,46,48–53,56,57,59–61}, and to a lesser extent in
391 Europe^{9–11,47,58}. The lack of data from Africa, Asia, and Oceania reduces potential
392 generalizability of our results, though. All ethnicities were included. Generalizability of our
393 results may also be lessened due to analysis of single-site studies, even if the majority of
394 included studies were multi-site. As studies differed in their study design, we performed
395 sensitivity analyses allowing demonstration of similar results whatever the design. In our
396 meta-analysis global model, some included studies appeared several times, with different data
397 for the same outcome depending on adjustment models. In the absence of clear consensus and
398 despite having more effect sizes within each meta-analyses when compared with studies
399 included in several highly-regarded published articles published^{93,94}, the weight of studies
400 may have required ponderation⁹⁵. This is one of the reasons for use of optimistic and
401 pessimistic models when only one data is available for each included article. A further
402 limitation of our meta-analysis concerns included studies using OR adjusted on different

403 factors between studies, even if adjusted OR may limit confusion bias. Finally, causality may
404 also be a limitation in retrospective or case-control studies.

405

406 **Conclusion**

407 Exposure to air pollution, notably PM_{2.5} during pregnancy was associated with an increased
408 risk of ASD in newborns regardless of the model used. The level of evidence concerning
409 other air pollutants is however poor. Exposure during pregnancy and the postnatal period
410 appear to be the most at-risk periods.

411

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Table 1. Characteristics of studies included in meta-analysis.

As: Arsenic; Ld: Lead; Hg: Mercury; * for median; #: see original articles (Gong 2014: see Figure 2; Kalkbrenner 2010: see Table 2 ; Kalkbrenner 2018: see Table 2)

Study	Country	Study design	Dates of inclusion	Perinatal periods	n ASD/ n total	Air pollutants		REF used for risk calculation	Concentration for REF of air pollutants	Type of risk	Adjustment of risk	Other variables
						Types	Mean levels (* for median)					
Becerra, 2013	USA	Case-control	1995-2006	Pregnancy	7594 / 83229	PM ₁₀ PM _{2.5} NO ₂ NO O ₃ , CO	-	IQR	PM ₁₀ : 8.3µg/m ³ PM _{2.5} : 4.7µg/m ³ NO ₂ : 10.5ppb NO: 29.7ppb O ₃ :11.5ppb	Odds ratio by IQR increase	Adjusted for maternal age, education, race/ethnicity, maternal place of birth, type of delivery, parity, insurance type, gestational weeks	Maternal place of birth, ethnicity, education, type of delivery, parity, insurance type
Chen, 2018	China	Case-control	2002-2011	Postnatal	124 / 1364	PM ₁ PM _{2.5} PM ₁₀	PM ₁₀ : 95.4µg/m ³ PM _{2.5} : 66.2µg/m ³ PM ₁ : 48.8µg/m ³	IQR	PM ₁₀ : 4.9µg/m ³ PM _{2.5} : 3.4µg/m ³ PM ₁ : 4.8µg/m ³	Odds ratio by IQR increase	Adjusted for birth weight; gestational weeks; disease, trauma, and mental health history; maternal age; familial history; parents' marital status, education, smoking, income; parental relationship; parenting	Gender
Dickerson, 2015	USA	Cohort	1992-2000	Pregnancy	2489 / 2489	Metals	-	>50 th centile of industrial facilities	>50 th centile: 46.9km from industry	Relative Risk by 10 th centile	Crude and adjusted for ethnicity and maternal education	Gender
Dickerson, 2016	USA	Cohort	2000-2008	Preconception Pregnancy	2489 / 2489	Metals	-	1 st quartile	As:<0.02ng/m ³ Ld:<1.49ng/m ³ Hg:<1.52ng/m ³	Relative Risk by quartile	Crude and adjusted for ethnicity, education, poverty	-
Gong, 2014	Sweden	Case-control	1992-2000	Pregnancy Postnatal	109 / 3051	PM ₁₀ NOx	PM ₁₀ : 3.3- 4.2µg/m ³ NOx: 5.4- 12.7µg/m ³	<5 th percentile	#	Relative Risk for >95 th percentile vs <5 th and by severity of ASD	Crude and adjusted for parity, gender, maternal age, smoking, marital status, education, income, neighborhood deprivation	Birth weight, ethnicity, gestational age, zygosity
Gong, 2017	Sweden	Case-control	1993-2007	Pregnancy Postnatal	5136 / 23373	PM ₁₀ NOx	PM ₁₀ : 4.2- 4.4µg/m ³ NOx: 9.8- 11.0µg/m ³	Arbitrary cut-off	PM ₁₀ : <10µg/m ³ NOx: <20µg/m ³	Odds ratio by 10µg/m ³ increase in PM ₁₀ and 20µg/m ³ in NOx	Crude and adjusted for sex; birth month; sibling order; parents' age, education, employment, income, birth countries; marital status; neighborhood deprivation	Birth weight, congenital malformation, intellectual disability
Goodrich, 2019	USA	Case-control	1997-2008	Pregnancy	346 / 606	PM ₁₀ PM _{2.5} NOx O ₃	-	< median	PM ₁₀ : <22.9 µg/cm ³ PM _{2.5} : <12.4µg/cm ³ NOx: <14.2ppb O ₃ : <33.4µg/cm ³	Odds ratio for > median vs < median	Adjusted for income, year of birth, vitamin A and zinc intake during pregnancy	Maternal age, education, birthplace; child ethnicity, sex; home ownership; preterm delivery; parity; gestational diabetes
Guxens, 2016	Europe (Italy, Spain, Nether- lands, Sweden)	Cohort	1992-2008	Pregnancy	541 / 8079	PM ₁₀ PM _{2.5} NO ₂	*PM ₁₀ : 15- 46µg/m ³ *PM _{2.5} : 8- 22µg/m ³ *NO ₂ : 17- 42µg/m ³ *NO _x : 34- 70µg/m ³	Arbitrary cut-off	*PM ₁₀ : <10µg/m ³ *PM _{2.5} : <5µg/m ³ *NO ₂ : <10µg/m ³ *NO _x : <20µg/m ³	Odds ratio by 10µg/m ³ increase in PM ₁₀ and NO ₂ , and 5µg/m ³ in PM ₅ and 20µg/m ³ in	Adjusted for maternal education, country of birth, age, body mass index, height, smoking, parity, urbanicity; child's sex, season at birth, age at ASD diagnosis	-

											NOx		
Jo, 2019	USA	Cohort	1999-2009	Pregnancy Postnatal	2471 / 246420	PM ₁₀ PM _{2.5} NO ₂ O ₃	PM ₁₀ : 38.1µg/m ³ PM _{2.5} : 17.9µg/m ³ NO ₂ : 25.1ppb O ₃ : 41.6ppb	<5 th percentile	#		Hazard ratio for >95 th vs <5 th percentile	Adjusted for birth year, medical center, maternal age, ethnicity, parity, education, comorbidities; household income, child sex	-
Kalkbrenner, 2010	USA	Case-control	1992-1994 1994-1996	Perinatal	383 / 2829	Metals Solvents Styrene Pesticides PAHs	# (0.00001-2108 µg/m ³ depending on air pollutants)	<20 th percentile	#		Odds ratio for >80 th percentile vs <20 th	Adjusted for maternal age, education, ethnicity, smoking; marital status; household income; urbanicity	Gender, first born, married
Kalkbrenner, 2015	USA	Case-control	1994-1996-1998-2000	Preconception Pregnancy Postnatal	645 / 13079	PM ₁₀	PM ₁₀ by groups: 21.8-24.3µg/m ³	Arbitrary cut-off	PM ₁₀ : <10µg/m ³		Odds ratio by 10µg/m ³ increase in PM ₁₀	Adjusted for maternal age, ethnicity, education; household income, urbanization, week of birth	Gender, smoking, married
Kalkbrenner, 2018	USA	Case-control	1994-2007	Pregnancy	1540 / 2017	Metals PAHs Solvents Styrene Pesticides	# (155 pollutants)	<25 th percentile (or <5 th), and log-transformed	#		Odds ratio for >75 th vs <25 th (or >95 th vs <5 th)	Adjusted for air toxic levels in the family, birth year, education, income, population density	Gender, ethnicity, maternal age, number in siblings
Kaufman, 2019	USA	Case-control	2006-2010	Pregnancy Postnatal	428 / 6420	PM _{2.5} O ₃	PM _{2.5} : 66.2µg/m ³ O ₃ : 48.8µg/m ³	<5 th percentile and IQR	<5 th percentile: data not shown IQR: PM _{2.5} : 3.5µg/m ³ O ₃ : 16ppb		Odds ratio for >95 th vs <5 th percentile and by IQR increase	Adjusted for year of birth; maternal education, body mass index, birth spacing, month of conception, pollutants	Gender; maternal age, ethnicity, smoking, body mass index; gestational age, birth weight, previous births
Kim, 2017	USA	Case-control	1999-2008	Pregnancy Postnatal	158 / 147	PM ₁₀ PM _{2.5} NO ₂ O ₃	PM ₁₀ : 6.2µg/m ³ PM _{2.5} : 3.7µg/m ³ NO ₂ : 5.7ppb O ₃ : 6.2 ppb	<75 th percentile	data not shown		Odds ratio for >75 th vs <75 th percentile	Adjusted for education, ethnicity, child's sex	-
MCGuinn, 2020	USA	Case-control	2003-2006	Preconception Pregnancy Postnatal	674 / 1529	PM _{2.5} O ₃	PM _{2.5} : 12.7µg/m ³ O ₃ : 35.1ppb	Arbitrary cut-off	PM ₁₀ : <1.6µg/m ³ O ₃ : <6.6 ppb		Odds ratio by 1.6 µg/m ³ in PM _{2.5} and 6.6 ppb in O ₃	Adjusted for maternal age, education, ethnicity, smoking; study site; month and year of birth; exposure time	Gender, preterm
Oudin, 2019	Sweden	Cohort	1999-2009	Pregnancy	768 / 47865	NOx	NOx: 17.7µg/m ³	<1 st quartile and arbitrary cut-off	1 st quartile: <11.3 µg/m ³ Arbitrary cut-off: NOx: 10µg/m ³		Odds ratio by quartile and by 10µg/m ³ in NOx	Adjusted for gender of child; maternal age, parity, smoking, body mass index, education, income, country of birth	-
Pagalan, 2018	Canada	Cohort	2004-2009	Pregnancy	1307 / 132256	PM _{2.5} NO NO ₂	PM _{2.5} : 5.0-5.7µg/m ³ NO ₂ : 13.5-16.0µg/m ³ NO: 11.0-16.0µg/m ³	IQR	PM _{2.5} : 1.5µg/m ³ NO ₂ : 4.8ppb NO: 10.7ppb		Odds ratio by IQR increase	Crude and adjusted for gender, income, urbanicity, month and year of birth, maternal age, birthplace	Gestational age, multiple birth, parity
Raz, 2015	USA	Case-control	1993	Preconception Pregnancy Postnatal	245 / 1767	PM _{2.5}	PM _{2.5} : 14.6µg/m ³	IQR	PM _{2.5} : 4.42µg/m ³		Odds ratio by IQR increase	Crude and adjusted for child sex, year and month of birth, parents age, income	Birth weight, education, marital status, prematurity, smoking
Raz, 2017	Israel	Case-control	2005-2009	Pregnancy Postnatal	2098 / 56289	NO ₂	*NO ₂ : 16.7ppb	IQR	NO ₂ : 5.85ppb		Odds ratio by IQR increase	Adjusted for year and month of birth, ethnicity, paternal age, poverty	Birth weight, gestational age, income, population group, multiplicity of birth

Ritz, 2018	Denmark	Case control	1989-2013	Pregnancy Postnatal	15387 / 83526	PM ₁₀ PM _{2.5} NO ₂ SO ₂	-	IQR	PM ₁₀ : 3.80µg/m ³ PM _{2.5} : 3.61µg/m ³ NO ₂ : 11.41µg/m ³ SO ₂ : 2.80µg/m ³	Odds ratio by IQR increase	Crude and adjusted for parental age, birth place, neighborhood employment and housing, maternal smoking, pollutants exposure periods	Gender, birth weight, gestational age
Roberts, 2013	USA	Case-control	1987-2002	Postnatal	325 / 22426	Metals	-	1 st quintile	<1 st quintile: data not shown	Odds ratio by quintile	Adjusted for maternal age, year of birth, parents' education, income, and year	Gender, state of residence at birth, smoking
Talbott, 2015a	USA	Case-control	2005-2009	Preconception Pregnancy Postnatal	211 / 430	PM _{2.5}	PM _{2.5} : 15µg/m ³	IQR	PM _{2.5} : 2.84µg/m ³	Odds ratio by IQR increase	Crude and adjusted for maternal education, smoking, ethnicity, and age	Year and country of birth, multiple birth, birth weight, preterm birth
Talbott, 2015b	USA	Case-control	2005-2009	Pregnancy	216 / 4971	Metals Solvents PAHs Pesticides	# (30 pollutants)	1 st quartile	<1 st quintile: #	Odds ratio by quartile	Adjusted for maternal age, education, smoking, ethnicity, child's birth year and sex	Country of birth
Volk, 2011	USA	Case-control	1997-2006	Pregnancy	304 / 259	PM ₁₀ PM _{2.5} NOx O ₃	-	Last quartile of distance from freeway	Last quartile: >1.4km from freeway	Odds ratio by quartile	Adjusted for child sex, ethnicity; parents education; maternal age and smoking	Preterm delivery
Volk, 2013	USA	Case-control	1997-2008	Pregnancy Postnatal	279 / 524	PM ₁₀ PM _{2.5} NOx O ₃	-	1 st quartile	1 st quartile: <9.7ppb of global traffic air pollution levels	Odds ratio by quartile	Crude and adjusted for child's sex, ethnicity; parents education; maternal age and smoking	-
Volk, 2014	USA	Case-control	1997-2009	Pregnancy	251 / 156	PM ₁₀ PM _{2.5} NOx O ₃	-	<25 th percentile	PM ₁₀ : <29.2µg/m ³ PM _{2.5} : <16.0µg/m ³ NOx ₅ : <17.5ppb O ₃ : <41.8ppb	Odds ratio for >75 th vs <25 th percentile	Adjusted for child's sex, ethnicity; parents education; maternal age and smoking; home ownership	-
Yousefian, 2018	Iran	Case-control	2004-2012	Pregnancy	134 / 388	PM ₁₀ SO ₂ Solvents	PM ₁₀ : 105.1-107.9µg/m ³ SO ₂ : 22.8-26.4ppb Solvents: 60.7µg/m ³	per 1-unit increase in pollutants	per 1-unit increase in pollutants	Odds ratio per 1-unit increase in pollutants	Adjusted for maternal age, smoking; parents education; cousin marriage; birth order, gestational age, multiplicity, parents comorbidities	Gender, type of delivery
Windham, 2013	USA	Case-control	1994	Pregnancy	284 / 943	Solvents Pesticides Metals	-	Exposed workers vs non-exposed workers	Non-exposed workers: no concentrations given	Odds ratio exposed versus non-exposed workers	Crude and adjusted for child ethnicity, maternal age and education	Gender; paternal age, education; parity; birth weight; prematurity

Figure Legends

Figure 1. Search Strategy

Figure 2. Methodological quality of included articles using the SIGN checklist

Figure 3. Meta-analysis on risk of autism by air pollutant depending on perinatal periods (preconception, pregnancy and postnatal), using normalized Odds ratio (continuous data - incremental risk).

When available (more than one study), we computed three models for each meta-analysis (a global model using all risks listed in included articles, a pessimistic model using only the less favorable data, and an optimistic model using only the most favorable).

95%CI: 95% confidence intervals. Each meta-analysis is represented in the forest-plot by a dot on a horizontal line, with the corresponding number of articles (n studies (subgroups)) included within the meta-analysis. The white dots represent the odds ratio (OR), and the length of each line around the dots represent its 95% confidence interval (95CI). An overall summary pooled-estimate (result of the meta-analysis of meta-analyses) is represented by a blue lozenge at the end of the graph. The black solid vertical line represents the null estimate (with a value of 1 for OR). Horizontal lines that cross the null vertical line (OR=1) represent non-significant studies.

Figure 4. Meta-analysis on risk of autism for PM2.5 depending on trimester of pregnancy (first, second, third), using normalized Odds ratio (continuous data - incremental risk).

When available (more than one study), we computed three models for each meta-analysis (a global model using all risks listed in included articles, a pessimistic model using only the less favorable data, and an optimistic model using only the most favorable).

95%CI: 95% confidence intervals. Each meta-analysis is represented in the forest-plot by a dot on a horizontal line, with the corresponding number of articles (n studies (subgroups)) included within the meta-analysis. The white dots represent the odds ratio (OR), and the length of each line around the dots represent its 95% confidence interval (95CI). An overall summary pooled-estimate (result of the meta-analysis of meta-analyses) is represented by a blue lozenge at the end of the graph. The black solid vertical line represents the null estimate (with a value of 1 for OR). Horizontal lines that cross the null vertical line (OR=1) represent non-significant studies.

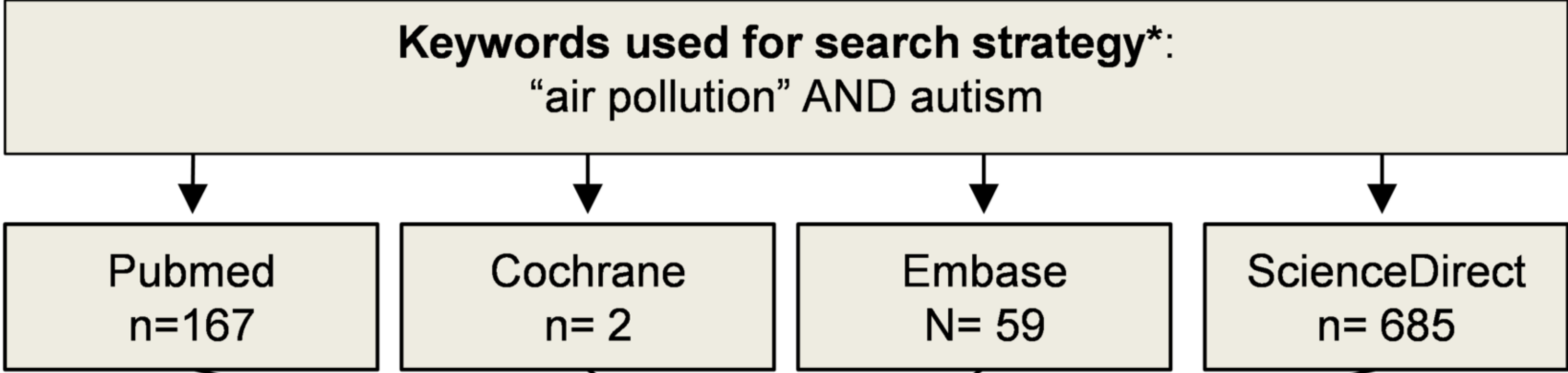
Figure 5. Meta-regressions

95%CI: 95% confidence intervals; t0: baseline; † Dropped because of collinearity.

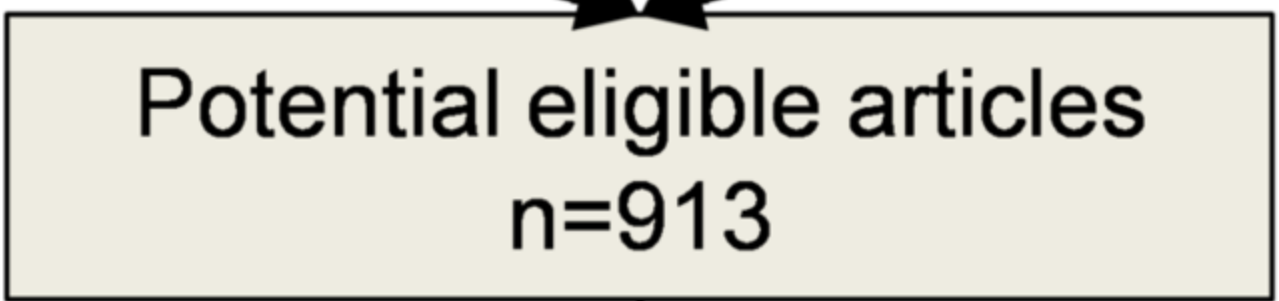
The effect of each variable on the outcome is represented in the forest-plot by a dot on a horizontal line. The white dots represent the coefficient for each variable, and the length of each line around the dots represent their

95% confidence interval (95CI). The black solid vertical line represents the null estimate (with a value of 0). Horizontal lines that cross the null vertical line are non-significant variables.

Identification

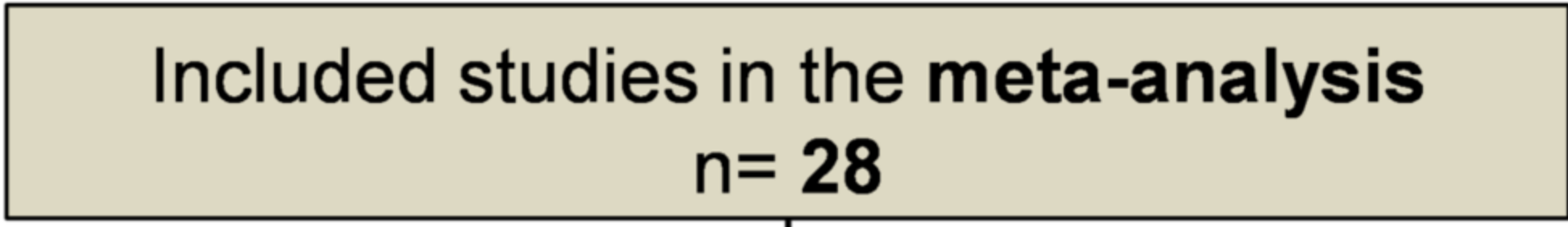
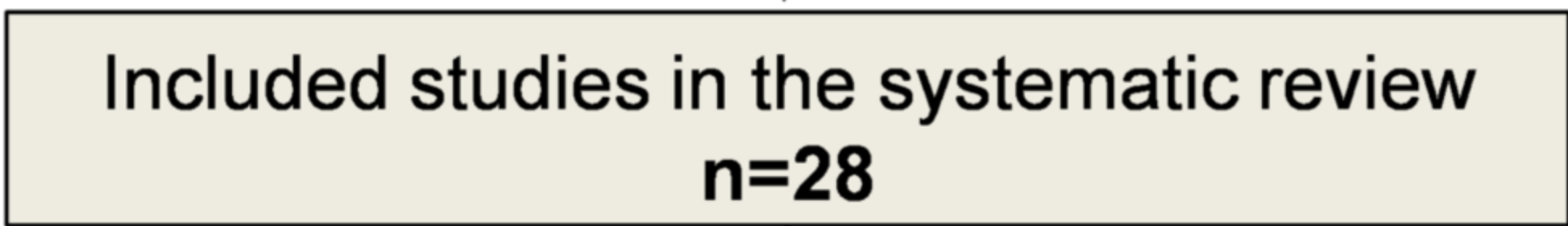


Screening

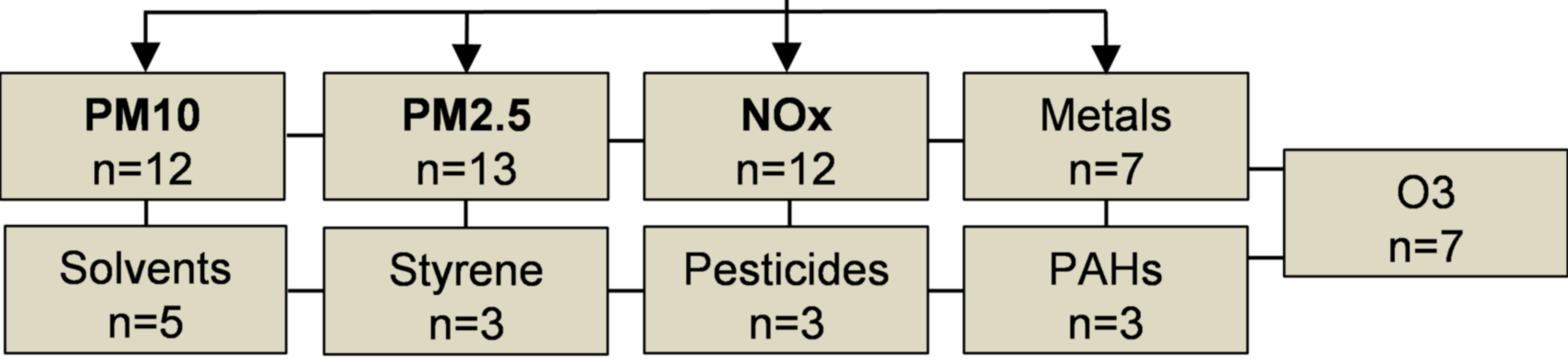


- Duplicates or triplicates removed n= 57
- Studies not in French or English n= 5
- Off topic studies n= 823

Eligibility



Included

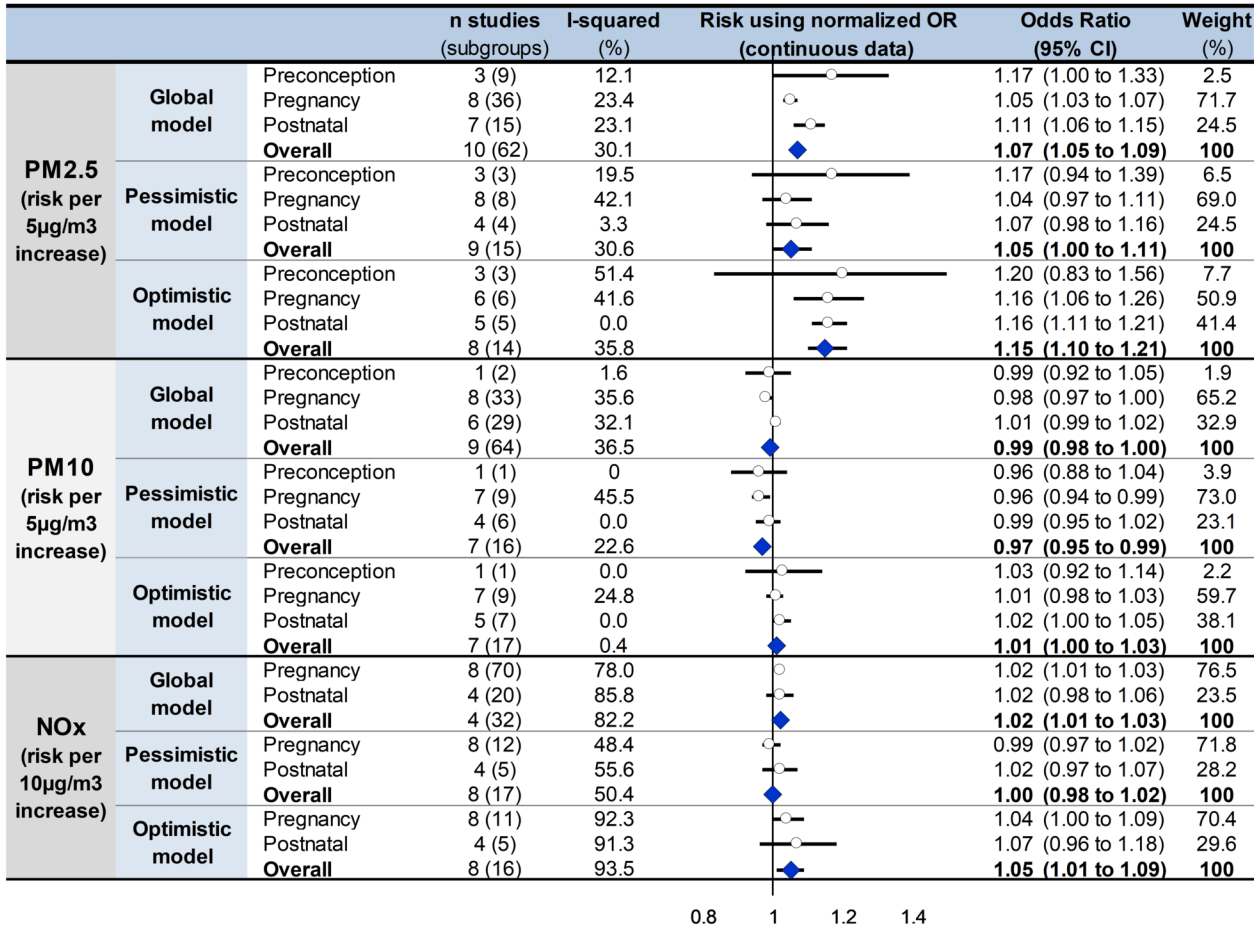


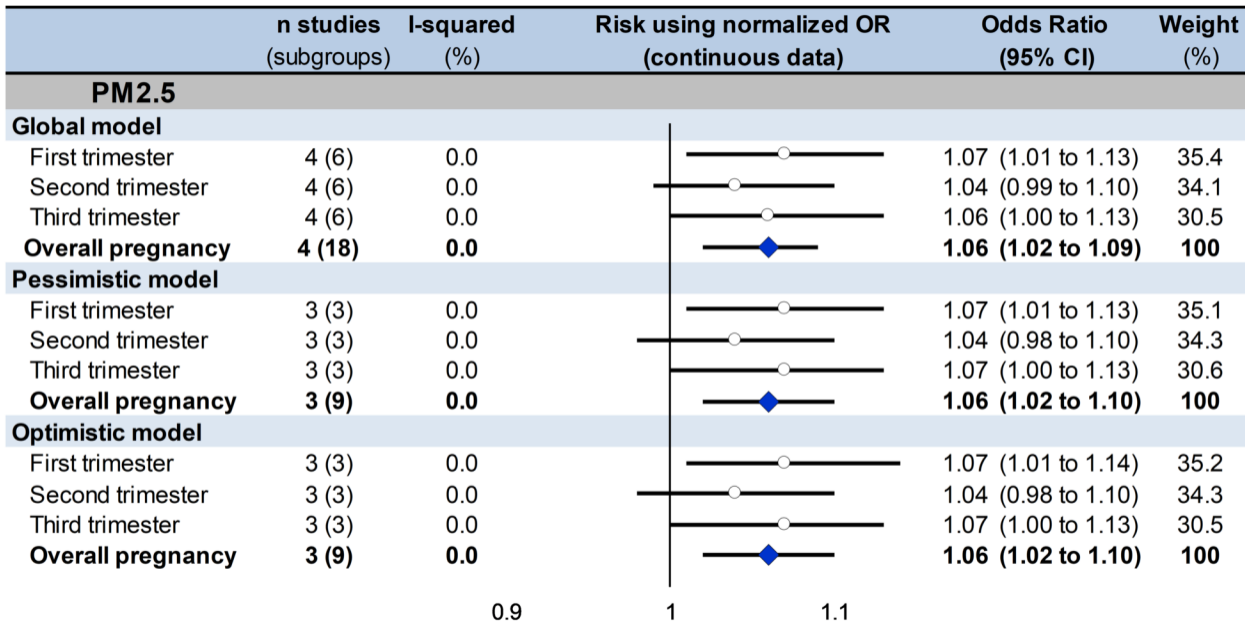
	Selection bias							Assessment bias	Confound- ing bias	Sta- tistics	Overall assess- ment				
	Appropriate and clearly focused question	Selection bias (comparable groups)	Selection bias (same exclusion criteria in both groups)	Selection bias (participation rate of both groups)	Attrition bias (comparison included/non-included)	Adequate case definition	Controls are non-cases ?	Detection bias (blind assessments)	Detection bias (exposure status is well measured)	Potential confounders taken into account	Confidence intervals are provided	To minimise the risk of bias or confounders	Overall effect is due to the study intervention	Results applicable to the patient group targeted	General level of evidence
Becerra 2013	+	+	+	100	+	+	+	NA	+	+	+	++	+	+	++
Chen 2018	+	+	+	100	+	+	+	NA	+	+	+	++	+	+	++
Gong 2014	+	+	+	69	+	+	-	NA	+	?	+	+	+	+	+
Gong 2017	+	+	+	100	+	+	+	NA	+	+	+	+	+	+	++
Goodrich 2019	+	+	+	80	+	+	+	NA	+	+	+	+	+	+	+
Guxens 2016	+	+	+	62	+	+	+	NA	+	+	+	++	+	+	++
Kalkbrenner 2010	+	+	+	?	?	+	+	NA	+	+	+	0	+	+	+
Kalkbrenner 2015	+	+	+	93	-	+	+	NA	+	+	+	+	+	+	+
Kalkbrenner 2018	+	+	+	100	+	+	+	NA	+	+	+	++	+	+	++
Kaufman 2019	+	+	+	?	+	+	+	NA	+	+	+	+	+	+	++
Kim 2017	+	+	+	79	?	+	+	NA	+	+	+	++	+	+	+
MCGuinn 2020	+	+	+	?	?	+	+	NA	+	+	+	++	+	+	++
Raz 2015	+	+	+	88	-	+	+	NA	+	+	+	+	+	+	++
Raz 2017	+	+	+	99	+	+	+	NA	+	+	+	+	+	+	++
Ritz 2018	+	+	+	71	+	+	+	NA	+	+	+	+	+	+	+
Roberts 2013	+	+	+	84	-	+	+	NA	+	+	+	+	+	+	++
Talbott 2015a	+	+	+	98	+	+	+	NA	+	+	+	+	+	+	++
Talbott 2015b	+	+	+	81	?	+	+	NA	+	+	+	+	+	+	+
Volk 2011	+	+	+	100	+	+	+	NA	+	+	+	+	+	+	+
Volk 2013	+	+	+	100	+	+	+	NA	+	+	+	+	+	+	++
Volk 2014	+	+	+	63	-	+	+	NA	+	+	+	+	+	+	+
Yousefian 2018	+	+	+	96	?	+	+	NA	+	+	+	+	+	+	+
Windham 2012	+	+	+	?	?	+	+	NA	+	+	+	0	+	+	+

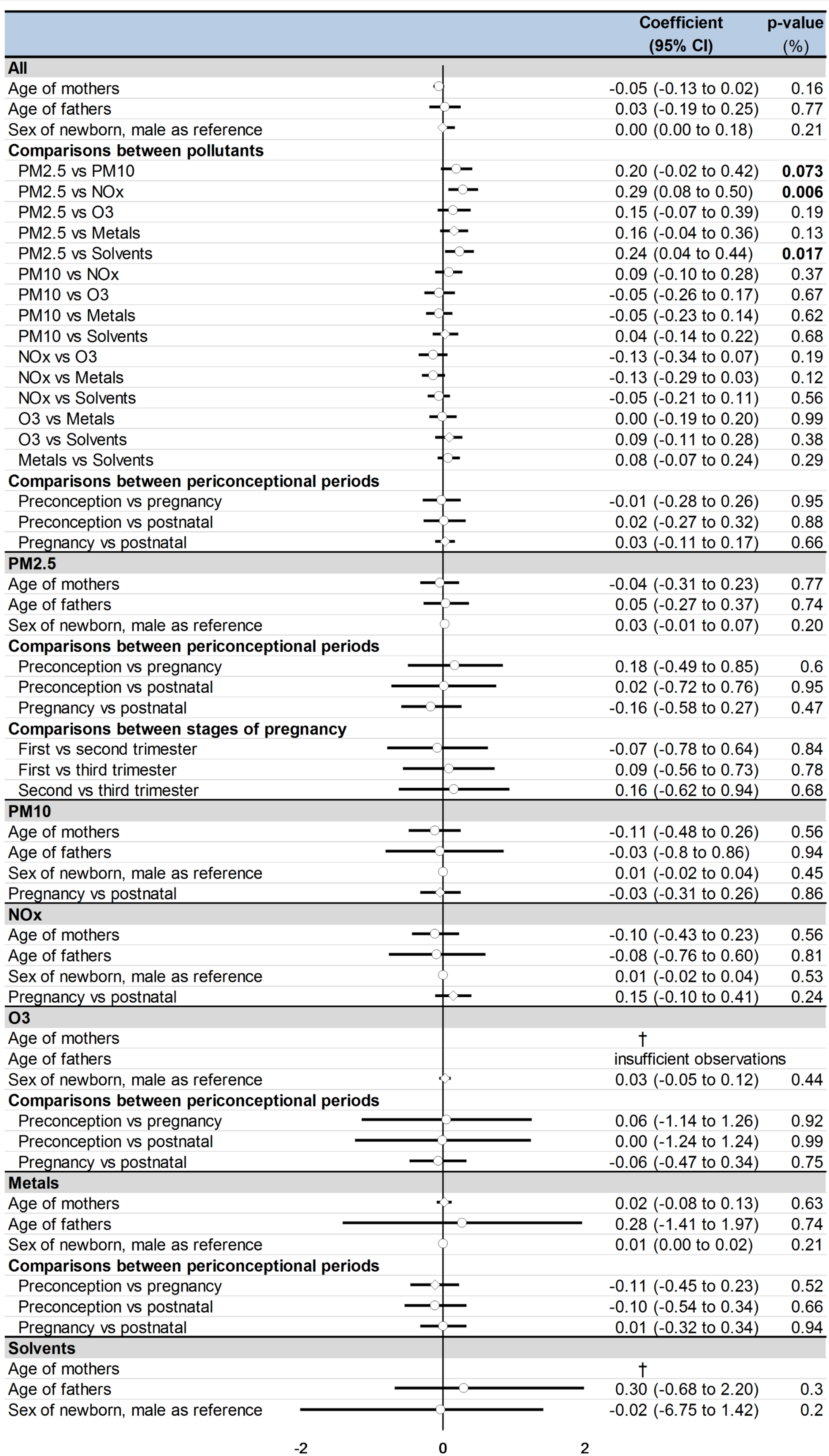
Case control studies

	Selection bias							Assess- ment bias	Con- found- ing bias	Sta- tistics	Overall assess- ment							
	Appropriate and clearly focused question	Selection bias (comparable groups)	Selection bias (participation rate)	Performance bias (use of sensitivity analyses)	Attrition bias (% of patients lost sight)	Attrition bias (comparison included/lost sight)	Outcomes clearly defined	Detection bias (blind assessments)	Detection bias (process measures are comparable)	Detection bias (measure of assessment is reliable)	Detection bias (outcome measures are defined)	Detection bias (exposure level is assessed)	Confusion bias (confounders taken into account)	Confidence intervals are provided	To minimise the risk of bias or confounders	Clear evidence of link between exposure & outcome	Results applicable to the patient group targeted	General level of evidence
Dickerson 2015	+	NA	+	+	0	NA	+	NA	NA	+	+	+	+	+	+	+	+	+
Dickerson 2016	+	NA	+	+	2.7	NA	+	NA	NA	+	+	+	+	+	+	+	+	+
Jo 2019	+	+	+	+	?	NA	+	NA	+	+	+	+	+	+	++	+	+	++
Oudin 2019	+	+	+	+	?	?	+	NA	+	+	+	+	+	+	++	+	+	++
Pagalan 2018	+	+	+	+	?	?	+	NA	+	+	+	+	+	+	++	+	+	++

Cohort studies







The risk of ASD following air pollutants exposure during pregnancy

