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1 **Metabolic syndrome and pesticides: a systematic review and meta-analysis.**

2 Hugo Lamat¹, Marie-Pierre Sauvant-Rochat³, Igor Tauveron², Reza Bagheri⁴, Ukadike C
3 Ugbolue⁵, Salwan Maqdasi², Valentin Navel⁶, Frédéric Dutheil⁷

4
5 ¹ Université Clermont Auvergne, University Hospital of Clermont–Ferrand, CHU Clermont–
6 Ferrand, Endocrinology-diabetology-nutrition, 63000 Clermont-Ferrand, France

7 ² Université Clermont Auvergne, CNRS, GReD, Inserm, University Hospital of Clermont-
8 Ferrand, CHU Clermont-Ferrand, Endocrinology, Clermont-Ferrand, France

9 ³ Université Clermont Auvergne, Clermont Auvergne INP, CNRS, Institut Pascal, F-63000
10 Clermont–Ferrand, France

11 ⁴ University of Isfahan, Exercise Physiology, Isfahan, Iran

12 ⁵ University of the West of Scotland, Health and Life Sciences, South Lanarkshire, Scotland,
13 UK

14 ⁶ Université Clermont Auvergne, CNRS, INSERM, GReD, CHU Clermont-Ferrand,
15 University Hospital of Clermont-Ferrand, Ophthalmology, Clermont-Ferrand, France

16 ⁷ Université Clermont Auvergne, CNRS, LaPSCo, Physiological and Psychosocial Stress,
17 University Hospital of Clermont–Ferrand, CHU Clermont–Ferrand, Occupational and
18 Environmental Medicine, WittyFit, F–63000 Clermont–Ferrand, France

19
20 ***Corresponding author:** Valentin Navel, University Hospital of Clermont-Ferrand, CHU
21 Clermont-Ferrand, Ophthalmology, Tel: +33 6 82 91 34 36, Fax: +33 4 73 75 14 61,
22 valentin.navel@hotmail.fr

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24 **Running title:** Metabolic syndrome and pesticides

25 **Abstract**

26 The relation between pesticides exposure and metabolic syndrome (MetS) has not been
27 clearly identified. Performing a systematic review and meta-analysis, PubMed, Cochrane
28 Library, Embase, and ScienceDirect were searched for studies reporting the risk of MetS
29 following pesticides exposure and their contaminants. We included 12 studies for a total of
30 6789 participants, in which 1981 (29.1%) had a MetS. Overall exposure to pesticides and
31 their contaminants increased the risk of MetS by 30% (95CI 22% to 37%). Overall
32 organochlorine increased the risk of MetS by 23% (14 to 32%), as well as for most types of
33 organochlorines: hexachlorocyclohexane increased the risk by 53% (28 to 78%),
34 hexachlorobenzene by 40% (0.01 to 80%), dichlorodiphenyldichloroethylene by 22% (9 to
35 34%), dichlorodiphenyltrichloroethane by 28% (5 to 50%), oxychlordan by 24% (1 to 47%),
36 and transnonchlor by 35% (19 to 52%). Sensitivity analyses confirmed that overall exposure
37 to pesticides and their contaminants increased the risk by 46% (35 to 56%) using crude data
38 or by 19% (10 to 29%) using fully-adjusted model. The risk for overall pesticides and types of
39 pesticides was also significant with crude data but only for hexachlorocyclohexane (36% risk
40 increase, 17 to 55%) and transnonchlor (25% risk increase, 3 to 48%) with fully-adjusted
41 models. Metaregressions demonstrated that hexachlorocyclohexane increased the risk of MetS
42 in comparison to most other pesticides. The risk increased for more recent periods
43 (Coefficient = 0.28, 95CI 0.20 to 0.37, by year). We demonstrated an inverse relationship
44 with body mass index and male gender. In conclusion, pesticides exposure is a major risk
45 factor for MetS. Besides organochlorine exposure, data are lacking for other types of
46 pesticides. The risk increased with time, reflecting a probable increase of the use of pesticides
47 worldwide. The inverse relationship with body mass index may signify a stockage of
48 pesticides and contaminants in fat tissue.

49 **Keywords:** metabolic syndrome, pesticide, exposure, public health, systemic review, meta-
50 analysis, meta-regression

51 **Introduction**

52 In 2020, the global production of pesticide reached 3.5 million tons.¹ Considering the damaging
53 consequences on human health,² many international measures have been taken to limit the
54 production and use of pesticides,³ but even those who have been prohibited still exist in the
55 environment leaving us with important exposure.^{4,5} Among the wide range of diseases enhanced
56 by pesticides,⁶ they are an evident risk factor for cardiovascular diseases,⁷ but also for metabolic
57 diseases such type 2 diabetes mellitus (T2DM)⁸ and obesity.⁹ Metabolic syndrome (MetS) is
58 considered as a plurimetabolic condition, linked with obesity and T2DM pathophysiology.¹⁰
59 However, if the level of proof is high regarding the increased risk of diabetes and obesity
60 following pesticides exposure, few studies have focused on the relationship between exposure to
61 pesticides and the risk of having MetS. Among hundreds of pesticides, the most used are
62 organochlorine pesticides (OCP), organophosphates, carbamates, pyrethroids and triazines.
63 Moreover, pesticides exposure is often accompanied by contaminants such as polychlorodibenzo-
64 p-dioxins and polychlorodibenzofuranes (PCCD/PCDF) and polychlorobiphenyls (PCB),¹¹ with
65 each of them having specific effects on human health.⁶ Furthermore, simultaneous exposure to
66 several pesticides and contaminants seems to increase the risk for multiple metabolic parameters
67 such as T2DM, dyslipidemia and insulin resistance.^{12,13} Such effects are yet to be demonstrated in
68 MetS. Considering that pesticides production are increasing to meet worldwide food demand,^{14,15}
69 the risk of MetS following pesticides exposure may have also increased over the last years. From a
70 physiological point of view, most pesticides are known to be lipophile compounds that accumulate
71 preferably in adipose tissue.¹⁶ Considering that MetS is closely related to visceral adiposity, the
72 influence of adiposity can be a very important factor in effects of pesticides exposure on MetS.¹⁷
73 Similarly, sociodemographic characteristics like age, sex and race have an evident impact on the
74 risk of MetS,^{18,19} as previously demonstrated for other pathologies like T2DM.²⁰

75 Therefore, we aimed to conduct a systematic review and meta-analysis based on the risk of MetS
76 following pesticides exposures. Secondary aims were to compare the risk depending on the type of
77 pesticides, the effects of multiple exposures to pesticides and their contaminants and the effect of
78 time of exposure and to assess the influence of characteristics of individuals (anthropometric,
79 sociodemographic, and lifestyle).

80

81 **Methods**

82

83 **Literature search**

84 We reviewed all studies reporting the risk of having MetS in relation with pesticides exposure.
85 The PubMed, Cochrane Library, ScienceDirect and Embase databases were searched until October
86 24th 2021, with the following keywords: “metabolic syndrome” and “pesticide” (details of the
87 search strategy is available in [Appendix 1](#)). The search was not limited to specific years and no
88 language restrictions were applied. To be included in the systematic review, articles needed to
89 describe our primary outcome variables i.e. the risk of MetS following exposure to pesticides or
90 reporting numbers to calculate this risk. Then, articles describing either an odds ratio, a relative
91 risk, or a hazard ratio, or giving data to calculate this risk, were included in the meta-analysis. In
92 addition, reference lists from all publications meeting the inclusion criteria were manually
93 searched to identify any further studies that were not found with the electronic search. The search
94 strategy is presented in ([Figure 1](#)). Two authors (H Lamat and S Maqdasy) conducted all literature
95 searches, collated, and reviewed the abstracts and based on the selection criteria, decided the
96 suitability of the articles for inclusion. A third author (F Dutheil) was asked to review the articles
97 where consensus on suitability was debated. All authors then reviewed the eligible articles. We
98 followed the guidelines outlined by PRISMA.

99

100 **Data collection**

101 The data collected included first author's name, publication year, study design, periods of studies,
102 aims, outcomes of included articles, sample size, mean age, sex (percentage of males), risk of
103 MetS (depending on method of calculation or adjustment model such as crude or adjusted odd
104 ratio, and types of risk such as odds ratio, relative risks, and prevalence ratio), characteristics of
105 pesticide and contaminants exposure (types, multi-exposure, years of exposure), and
106 characteristics of individuals (such as body mass index (BMI), age, sex, geographical zone,
107 smoking habits, alcohol consumption).

108

109 **Risk of bias and certainty of evidence**

110 The Newcastle-Ottawa Scale (NOS) was used to check the risk of bias of included articles.²¹ This
111 scale has an original version to evaluate case-control and cohort studies. Adapted version exists
112 and widely used to evaluate cross-sectional studies.²²⁻²⁴ Through different items, three dimensions
113 are evaluated: selection, comparability, and exposure for case-control studies; and selection,
114 comparability and outcome for cohort and cross-sectional studies. One point was given for each
115 item. The maximum score is 9 for case-control and cohort studies and 10 for cross-sectional
116 studies (Figure 2). The evidence synthesis for this review was conducted in accordance with the
117 Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines
118 (Appendix 2).²⁵

119

120 **Statistical considerations**

121 Statistical analysis was conducted using Stata software (v15, StataCorp, College Station, US).²⁶⁻³³
122 Baseline characteristics were summarized for each study sample and reported as mean (standard-
123 deviation) and number (%) for continuous and categorical variables respectively. Random effects

124 meta-analyses (DerSimonian and Laird approach) were conducted when data could be pooled.³⁴
125 We conducted meta-analysis on the risk of MetS following pesticides exposure using all odds
126 ratio, relative risk, or hazard ratio. We stratified these meta-analyses on the type of pesticides
127 (organochlorines and types of organochlorines, organophosphates, carbamates, pyrethroids,
128 triazines) and contaminants (OCP, PCB and PCCD/PCDF). We described our results by
129 calculating the hazard ratio of the risk of MetS after exposure to pesticides.³⁴ Hazard ratio were
130 centered at one if the risk of MetS after exposure to pesticides did not differ from the risk of MetS
131 without exposure to pesticides. Hazard ratio >1 denoted an increased risk of MetS, and hazard
132 ratio <1 reflected a decreased risk. Heterogeneity in the study results was evaluated by examining
133 forest plots, confidence intervals (CI) and using formal tests for homogeneity based on the I-
134 squared (I^2) statistic. I^2 is easily interpretable and the most common metric to measure the
135 magnitude of between-study heterogeneity. I^2 values range between 0% and 100% and are
136 typically considered low for <25%, modest for 25–50%, and high for >50%. For rigor, funnel
137 plots of these meta-analyses were also used to search for potential publication bias. In order to
138 verify the strength of the results, further meta-analyses were then conducted after exclusion of
139 outliers i.e. by excluding studies that were not evenly distributed around the base of the funnel,³⁵
140 as well as sensitivity analyses based on the type of risks (odds ratio, relative risk, or hazard ratio).
141 Moreover, when a study reported simultaneously both crude and adjusted risks, we also computed
142 first sensitivity analyses using only the most adjusted risks listed in included articles, and in a
143 second time, only crude or less adjusted risks. Therefore, for each meta-analysis, we computed
144 two models (a model using the most adjusted risks listed in included articles, and a model using
145 only crude or less adjusted risks). Lastly, because of a possible time-dependent cumulative effect
146 for the risk of MetS, we computed a separated subgroup sensitivity analyses by removing the
147 studies that included individuals over 70 years old. When possible (sufficient sample size), meta-
148 regressions were proposed to study the relationship between the risk of MetS and pesticides

149 exposure and clinically relevant parameters such as characteristics of exposure (type of pesticides,
150 multi-exposure, years of exposure) or those of individuals (BMI, age, sex, lifestyle). Results were
151 expressed as regression coefficients and 95% CI. P values less than 0.05 were considered
152 statistically significant.

153

154 **Results**

155 An initial search produced a possible 8595 articles ([Figure 1](#)). Removal of duplicates and use of
156 the selection criteria reduced the number of articles reporting MetS as an outcome of pesticides
157 exposure to 12 articles in the systematic review.³⁶⁻⁴⁷ One study reported only β coefficients³⁸ and
158 was not included in the meta-analyses.⁴⁸ Thus all 12 studies were included in the systematic
159 review and only 11 studies were included in the meta-analyses. All articles were written in
160 English.

161

162 **Risk of bias and certainty of evidence**

163 The assessment of the quality of the 12 included studies was performed using the Newcastle-
164 Ottawa quality scale to assess the risk of bias and GRADE to assess the certainty of evidence.²¹⁻²⁵
165 All studies had a low risk of bias. Overall, case-control studies performed better in the comparability
166 section and worse in the exposure section, while cohort and cross-sectional studies performed better in
167 comparability section and worse in selection section ([Figure 2](#)). All studies mentioned ethical
168 approval. The certainty of the evidence was rated as high for our main outcome and for most other
169 meta-analytic outcomes. The certainty of the evidence was low for mirex, aldrin, PCDD, and
170 PCDF ([Appendix 2](#)).

171

172 **Aims and outcomes of included articles**

173 Eight studies aimed to evaluate the association between pesticides exposure and the incidence or
174 the prevalence of MetS as a primary result^{36–39,42–44,47} while four studies evaluated this association
175 as a secondary result.^{40,41,45,46} Ten studies evaluated only pesticides. The two other studies
176 assessed the impact of other environmental pollutants.^{40,41}

177

178 **Study designs**

179 Our analysis was performed from six cross-sectional studies, three nested case-control studies, two
180 cohort studies and one case-control study. Duration of recruitment in cross-sectional studies
181 ranged from 6 months⁴² to 5 years,³⁸ and duration of follow up in prospective studies ranged from
182 2.6 years⁴⁴ to 10 years.⁴⁰ Five studies were conducted in Asia (South Korea,^{39,42,44,45} India³⁶), four
183 in Europe (Sweden,^{40,41} Spain,⁴⁶ Norway⁴⁷), and two in USA.^{37,43} Seven studies were
184 monocentric^{36,37,39–42,47} and five multicentric.^{38,43–46}

185

186 **Inclusions and exclusions criteria of included articles**

187 Diagnosis of MetS was based on NCEP-ATPIII definition in all studies except one that used
188 both NCEP-ATPIII and IDF definitions.⁴⁶ Some of the included articles targeted at the
189 population at advanced age^{40,41} or being overweight or obese,^{46,47} and therefore predisposed to
190 risk of MetS. Two studies included MetS patients.^{36,42} Inclusion criteria for other articles were
191 normal weight,⁴⁵ non-diabetic,^{37,39,43} non-MetS at baseline,^{40,44} or living in the same area.³⁸
192 All studies excluded participants with incomplete data on MetS or pesticides exposure. Other
193 main exclusion criteria were diabetes mellitus,^{37,39,43,47} underweight,⁴⁶ occupational
194 exposure.⁴³

195

196 **Recruitment**

197 Six studies recruited participants from other ongoing surveys^{37,38,43-46} whereas six studies
198 specifically recruited participants for their studies.^{14,19,35,45,49,50} Recruitment was from general
199 population,^{37,39-41,43,46} medical centres,^{36,47} high exposed area,³⁸ professional farmers⁴⁴ or
200 other targeted populations.^{40-42,45}

201

202 **Population**

203 **Sample size** ranged from 100^{36,39,45} to 1162.⁴⁴ We included 6789 individuals in total, among
204 which 1981 (29.1%) had MetS. Prevalence of MetS ranged from 20.4⁴⁰ to 64.0%.⁴⁷

205 **Age** was reported in all studies except one.³⁶ Mean age ranged from 18^{38,47} to 78⁴⁷ years.

206 **Gender** was reported in all studies except three.^{36,41,43} Proportion of men ranged from 32.0%³⁷ to
207 50%.⁵¹

208 **Body mass index (BMI) and waist circumference** were reported as mean±SD in all
209 studies except five,^{36,40,43,44,51} and ranged from 23.2±1.4⁴⁵ to 30.2±7.4³⁷ kg/m² for BMI, and from
210 75.3³⁹ to 99.9³⁶ cm for waist circumference. Only one study included only obese individuals'
211 grade 2 and 3, with a BMI of 42±5.1 kg/m² and a waist circumference of 125±13 cm.⁴⁷ Three
212 studies only reported proportions of normal, overweight, and obese participants.^{37,44,46}

213 **Blood pressure (BP)** was reported in all studies except four.^{41-43,46} Mean systolic BP ranged
214 from 114.9³⁹ to 147.1 mmhg⁴⁰ while mean diastolic BP ranged from 70.6³⁹ to 85.5⁴⁷ mmHg.

215 **Triglycerides and HDL** were reported in all studies except three.^{41,43,47} Mean levels were
216 reported in six studies,^{36,39,41,42,44,45} and ranged from 76.8³⁹ to 211.7³⁹ mg/dl for triglycerides, and
217 from 35.6³⁹ to 62.0⁴⁵ mg/dl for HDL. Proportion of individuals with high triglycerides levels
218 (≥150 mg/dl) or with low HDL level (≤40 in men and ≤50 mg/dl in women) were reported in two
219 studies,^{37,46} ranging from 13.5%⁴⁶ to 38.0%³⁷ for TG level, and from 34.9%⁴⁶ to 59%³⁷ for HDL
220 level.

221 **Fasting glucose level** was reported in all studies except three.^{40,41,43} Mean glucose levels
222 ranged from 81.4³⁶ to 122.7³⁶ mg/dl.

223 **Smoking status** was reported in all studies except four.^{36,39,43,46} Proportion of smokers ranged
224 from 8.0⁴⁵ to 17.6%.⁴⁷

225 **Alcohol consumption** was reported in three studies.^{37,42,44} Percentage of consumers ranged
226 from 31.0³⁷ to 49.6%,⁴⁴ but studies used different cut-offs.

227 **Other descriptive variables** were marital status,^{37,44} education^{37,40,46} or occupation,⁴⁶
228 race,³⁷ physical activity^{40,42,45,46} or energy intake,⁴⁰ family history of diabetes^{37,45} or heart
229 disease,³⁷ or personal history of liver disease,³⁷ myocardial infarction⁴¹ or stroke,⁴¹
230 medications,^{40,41} other biological parameters (HOMA-IR,^{37,39,45,46} insulin,^{39,45} total
231 cholesterol,^{37,42} LDL,⁴⁰ CRP,^{46,47} or ALAT⁴⁷), and body composition.⁴⁵

232

233 **Measurements of pesticides exposure and risk of MetS**

234 All studies employed gas chromatography/isotope and high-resolution mass spectrometry
235 using the isotope dilution method to measure the concentration of pesticides in plasma^{40,41} or
236 serum^{36,37,39,42,43,45-47} blood sampling as exposure measurement except one study that used the
237 intensity level of pesticides exposure and cumulative exposure index.⁴⁴ Similarly, all studies
238 used either serum or plasma samples to measure the biological parameters of MetS (blood
239 glucose levels, HDL cholesterol and triglycerides). Risk of MetS were expressed as odds ratio
240 in all studies except three studies that used relative risks,⁴⁴ prevalence ratio,⁴⁶ or β -
241 coefficient.³⁸ All studies reported measurements of pesticides and their contaminants except
242 three where only pesticides were explored.^{36,39,44} Contaminants were measured using the same
243 methods.

244

245 **Meta-analysis on the risk of MetS following pesticides exposure**

246 Overall exposure to pesticides and their contaminants increased the risk of MetS by 30%
247 (OR=1.30, 95CI 1.22 to 1.37). All studies included exposure to organochlorine pesticides.
248 Organochlorine increased the risk of MetS by 23% (14 to 32%). Among organochlorine, most
249 pesticides increased the risk of MetS: hexachlorocyclohexane increased the risk by 53%
250 (OR=1.53, 95CI 1.28 to 1.78) (using data from six studies^{36,37,39,42,43,46}), hexachlorobenzene
251 by 40% (95CI 0 to 80%) (five studies^{37,39,42,46,51}), dichlorodiphenyldichloroethylene by 22%
252 (9 to 34%) (seven studies^{36,37,39,41-43,46}), dichlorodiphenyltrichloroethane by 28% (5 to 50%)
253 (five studies^{36,37,39,42,46}), oxychlordan by 50% (14 to 85%) (four studies^{37,39,42,43}), and
254 transnonchlor by 56% (22 to 90%) (five studies^{37,39,41-43}), with more than four studies for each
255 type of pesticides. Besides organochlorine pesticides, there were no data for the following
256 types of pesticides: organophosphates, carbamates, pyrethroids, triazines. Only one study
257 reported a risk for concomitant exposure to several pesticides, precluding further analyses.
258 Pesticides' contaminants increased the risk by 31% (19 to 42%), mainly represented by PCB
259 that increased the risk of MetS by 32% (18 to 45%) (Figure 3).

260

261 **Sensitivity analyses**

262 All mentioned meta-analysis gave similar results after exclusion of studies that were not evenly
263 distributed around the base of the metafunnel (Figure 4), as well as sensitivity analyses based on
264 the type of risks i.e. while removing the three studies that did not express the risk of MetS as odds
265 ratio. We also performed a meta-analysis only using crude odds ratio (Figure 5 and Supplementary
266 Figure 1) and only using fully adjusted odds ratio (Figure 5 and Supplementary Figure 2). The
267 meta-analysis using only crude odds ratio still showed an increased risk of MetS after exposure to
268 pesticides and their contaminants by 46% (35 to 56%), and for overall pesticides by 42% (29 to
269 55%). Nevertheless, meta-analysis using fully adjusted odds ratio were not significant for the risk

270 of MetS following pesticides exposure (OR=1.09, 95CI 0.98 to 1.19). However, the risk of MetS
271 was significantly increased following exposure to polychlorobiphenyls and overall contaminants.
272 Such an effect of contaminants was still apparent as a 19% (10 to 29%) increase of the fully
273 adjusted odds ratio for the combination of pesticides and contaminants. The only single pesticides
274 that showed increasing risk of MetS in the fully-adjusted meta-analysis were
275 hexachlorocyclohexane at an increased risk of 36% (17 to 55%) and transnonchlor at 25% (3 to
276 48%). Lastly, the results were also similar after exclusion of the two studies that included
277 individuals over 70 years old,^{46,47} i.e. an increased risk of MetS after exposure to pesticides and
278 their contaminants of 29% (22 to 36%), and for overall pesticides of 27% (18 to 37%).

279

280 **Metaregressions**

281 Hexachlorocyclohexane increased the risk of MetS in comparison to most other pesticides.
282 Simultaneous exposure to several pesticides showed no higher risk of MetS in comparison to
283 single exposure of pesticide, but there was only one study reporting multi-pesticides exposure.
284 The risk of MetS following pesticides exposure increased for most recent studies (Coefficient
285 0.28, 95CI 0.20 to 0.37, $p < 0.001$, by year). Higher BMI and waist circumference decreased
286 the risk of MetS following pesticides exposure (-0.28, -0.38 to -0.18; and -0.11, -0.23 to -0.00,
287 respectively). The risk of MetS following pesticides exposure was lower in men (-0.14, -0.19
288 to -0.10, per %men) (Figure 6).

289

290 **Discussion**

291 The main finding was that pesticides exposure increases the risk of MetS, with data mainly for
292 organochlorine pesticides. The risk has increased in recent years. More recent studies have shown
293 an increased risk of MetS following pesticides exposure. Physiologically, the inverse relationship
294 with BMI may signify a stockage of pesticides in fat tissue.

295

296 **Pesticides exposure as a major risk of MetS**

297 The exposure to pesticides has been proven to increase the risk for multiple cardiovascular and
298 metabolic pathologies⁶ such as myocardial infarction,⁷ diabetes⁸ and obesity.⁹ MetS is considered
299 a prediabetic stage and is also a major risk of cardiovascular diseases.⁵²⁻⁵⁵ The onset of MetS is
300 linked to visceral adiposity, which is itself linked to an excess of fast fat and sugar, and sedentary
301 lifestyle. This visceral adiposity is responsible for activating the inflammatory pathways mediated
302 by cytokines.⁵⁶ This mechanism leads to the production of nitric oxide and insulin resistance. The
303 last two lead to a vasodilation defect and thus an alteration of the endothelium implicated in the
304 cardiovascular complications of the MetS.⁵⁷ Major meta-analyses demonstrated the increased risk
305 of T2DM, obesity and cardiovascular diseases following exposure to pesticides.⁷⁻⁹ We
306 demonstrated that pesticides exposure increases the risk for MetS which is closely related to
307 cardiovascular and metabolic diseases.⁵⁰ Mechanistically, MetS is closely related to dysregulation
308 of adipose tissue, i.e. visceral adiposity.⁵⁸ The increased risk of MetS following pesticides
309 exposure may be directly linked to their effects on adipose tissue. Some pesticides, like DDE may
310 enhance proliferative capacity of preadipocytes and thus the development of adipose tissue.⁵⁹
311 Others, like OCP, may disturb the function of estrogen receptors that play a role in adipogenesis.⁶⁰
312 In addition to pesticides exposure, their contaminants also increased the risk of MetS. PCDF and
313 PCDD are produced during pesticides manufacturing, burning of waste, and automobile
314 emissions.^{61,62} Their abundance in the environment may explain our findings as other pesticides
315 are mainly used in agriculture. Despite OCP and PCB being banned since 1970s,⁶³ they are still a
316 major risk of MetS which can be explained by their persistence in the environment.^{5,64,65} For
317 example, the unfortunately famous Chlordecone was an organochlorine used in the 1980s in the
318 French West Indies. Despite its hazardous effect on humans, it was used until 1993 against a

319 banana pest. Considered as one of the worst persistent organic pollutants (POP), for centuries
320 chlordecone because of its very long remanence will continue to pollute Martinican rivers.⁶⁶

321

322 **Risk of MetS and types of pesticide**

323 Organochlorines are the main types of pesticides explored in our study. Among organochlorines,
324 hexachlorocyclohexane has the most important risk as it is found in soil, water and air; and as
325 other organochlorine, it has a prolonged remanence.⁴⁹ It is produced in many countries and
326 exported to countries that do not produce it anymore.⁴⁹ Although mechanism of pathological
327 effects are not totally known, studies in animals showed alteration in cytochrome P450,
328 glutathione-S-transferase and glucose-6-phosphate dehydrogenase activities indicating its
329 implication in oxidative dysregulation.⁶⁷ Oxidative stress is now known to be increased in
330 metabolic syndrome as it's associated with adiposity and insulin resistance.⁶⁸ Heptachlor-epoxide
331 use is now restricted to control fire ants in power transformers.⁶⁹ We failed to show that
332 heptachlor-epoxide increased a risk for MetS, which can be explained by its fast elimination from
333 the organism,⁷⁰ and undetectable levels in population.^{71,72} Several studies showed that
334 transnonchlor and oxychlordan exposure increased the risk of diabetes and induced alteration of
335 the metabolic profile,⁷³ and therefore our results on the risk of MetS is in line with the literature. A
336 study on effects of oxychlordan in female rats showed a cluster of vacuolated hepatocytes
337 between the hepatic triad and central vein.⁷⁴ These same changes are seen in nonalcoholic fatty
338 liver disease⁷⁵ which is now known to have a close relation with MetS both pathophysiologically
339 and by cardiovascular risk prediction.⁷⁶ Hexachlorobenzene is known to have pathological effects
340 on the skin, liver and thyroid.⁷⁷ Despite a limited number of studies assessing its effects on the
341 metabolic profile, we showed its risks on MetS. Dichlorodiphenyldichloroethylene (DDE) and
342 Dichlorodiphenyltrichloroethane (DDT) are related pesticides.⁷⁷ Even if DDE and DDT are
343 mainly known for their side effects on liver and reproductive function,⁷⁷ we also demonstrated

344 their potential to increase the risk of MetS. Surprisingly, mirex had an inverse relationship with
345 the risk of MetS but scarcity of data prevailed as shown using the GRADE certainty of evidence.
346 Although, no data are known on how it affects human health, studies on animals showed liver and
347 kidney effects.⁷⁸ Apart from organochlorines, results of our meta-analysis showed a lack of data
348 for other types of pesticides (organophosphates, carbamates, pyrethroids, and triazines). Such data
349 should be strongly needed considering their global use.⁷⁷ We also showed that the risk was the
350 highest for hexachlorocyclohexane and transnonchlor whatever the statistical model used,
351 highlighting their side effect on the risk of MetS.

352

353 **Unique and multiple exposures in a time-effect manner**

354 Multiple pesticides exposure is the most common exposure of populations, worldwide.^{57,69}
355 Literature showed that simultaneous exposure to pesticides and their contaminants increased the
356 risk of variable pathologies more than single exposure.^{13,40,41,79} We did not find such relation for
357 the risk of MetS as most included studies examined only single pesticide exposure. Toxicological
358 effects of low-dose pesticides mixture on human health are largely unknown and anticipating these
359 effects is often difficult to prove, however synergism and potentiation in pesticides effects have
360 been demonstrated in laboratory animals.⁸⁰ Nonetheless, we demonstrated that even unique
361 exposures increased the risk of MetS. Therefore, preventive strategy should also focus on handling
362 single exposure as this may prevent multiple exposure.^{15,62} We demonstrated an increased risk
363 with time as recent studies showed more important risk of MetS due to pesticides exposure. This
364 may be explained by the increase production and use of pesticides worldwide to meet the growing
365 global food demand,^{14,15} but also by the persistence of banned pesticides in the environment.^{4,5}
366 Furthermore, pesticides like other pollutants are well known to accumulate all along the food
367 chain, with transfer across areas and over borders; they even have been identified in areas where
368 they have never been used.^{81,82} Our findings should trigger an alarm regarding limitations in the

369 steps taken to restrict the production of pesticides and development of better technologies for
370 agriculture, food, and pesticide industries.⁶²

371

372 **Anthropometric and sociodemographic effects**

373 MetS is closely related to visceral adiposity,⁵⁶ where pesticides mainly accumulate because of
374 their lipophilic nature.¹⁶ However, we demonstrated an inverse relationship between BMI or
375 waist circumference, and the risk of MetS following pesticides exposure. Similarly as
376 exposure to other lipophilic agents, such as POP for example, the adipose tissue may capture
377 the pesticides and store them without provoking major detrimental effects. Sequestration of
378 pesticide in adipose tissue, like other POPs, decrease their concentration in blood, limiting
379 their availability to other tissues where they may have damaging effects.⁸³ This may add a
380 protective function to adipose tissue regarding pesticides.⁸⁴ And paradoxically, lean
381 individuals with few adipose tissues will have higher detrimental effects of POP because they
382 will not be stored in the adipose tissue. Even if not all pesticides are POPs, they are lipophile,
383 and thus the protective effect of adipose tissue should be similar. Despite the very strong
384 inverse relationship between BMI and the risk of MetS following exposure to pesticides, two
385 limitations should be noted. First, pesticides are present in higher concentration in adipose
386 tissue than in blood,¹⁶ but all included studies in our meta-analysis assessed blood pesticides
387 levels and none assessed levels of pesticides within adipose tissue. However, assessing
388 pesticides levels in adipose tissue need biopsies which is practically impossible to achieve on
389 a large population scale. Second, a recent review of 17 studies showed significant increased
390 blood levels of pesticides after weight-loss interventions such as hypocaloric diet, medications
391 and bariatric surgery.⁸⁵ Studies included in our meta-analyses should have reported weight
392 variation history of participants ahead of inclusion. The main other influencing variable is
393 gender. While being a man is a risk factors for MetS,^{18,86} we demonstrated that women were

394 more at risk of MetS following pesticides exposure. Our findings may be explained by
395 differences in characteristics of adipose tissue and lifestyle patterns between men and
396 women.⁸⁷⁻⁹² Even if most included studies enrolled more women than men, the unbalanced
397 sex ratio should not have affected our results as we controlled this parameter in our analysis.
398 Lastly, despite smoking and alcohol⁹³⁻⁹⁵ are known to increase the risk of MetS, we showed
399 that they have no modification on the risk of MetS following exposure to pesticides.

400

401 **Limitations**

402 Our study has some limitations. Only 11 studies were included in which some case-control studies
403 had a limited number of participants,^{36,39,45} and some studies included targeted population that did
404 not represent the general population.^{36,40-42,44,45,47} However, we included a large sample size of
405 6789 individuals, in which 1708 were included in case control studies of all ages and categories
406 promoting the generalizability of our results. We also computed sensitivity analyses by excluding
407 studies with the oldest individuals to limit age-related cofounders. Most studies had cross-
408 sectional or case-control designs, and prospective studies had also a short follow-up period,
409 limiting the possibility to detect causality between pesticides exposure and MetS. All studies were
410 in high-income and developed countries except one in India, where the use and exposure to
411 pesticides is of greater concern. Having significant risk in developing countries where exposure to
412 pesticides is of less concern in comparison to undeveloped countries may upgrade the quality of
413 evidence of this meta-analysis. No study reported the duration of exposure allowing the analysis
414 of a dose-effect relationship. However, the importance of duration of exposure has been illustrated
415 in several pathologies including diabetes.^{6,8,96-100} Some studies evaluated the association between
416 pesticides exposure and MetS as a secondary aim which required extra statistical tests that might
417 generate false-positive associations.^{40,41,45,46} In all studies, exposure was assessed by measuring
418 pesticides plasma or serum levels using gas chromatography/isotope and high-resolution mass

419 spectrometry using the isotope dilution method, except one study that assessed exposure using a
420 questionnaire.⁴³ Although, not all studies offered details of measurement protocols, all
421 measurements were done in laboratories attached to research facilities. We believe that differences
422 in protocols could be negligible and would not affect the overall comparability across studies.
423 Even though the major site of accumulation of pesticides is adipose tissue, blood pesticides levels
424 are the only realistic large-scale assessments.⁴⁰ Most included studies did not adjust for lipid
425 levels, even if such normalization is controversial.¹² There could be selection bias as one study
426 used capillary blood instead of venous blood to define hyperglycemia.⁴⁶ There could also be an
427 observation bias as only some selected pesticides were evaluated. However, our meta-analysis
428 covered most common environmental pesticides. The fact that risk of MetS following pesticides
429 exposure was less salient when using a fully adjusted model, could be related to differences across
430 studies in their adjustment criteria, included populations, and observational designs. However,
431 results were still significant for overall pesticides and contaminants, and for
432 hexachlorocyclohexane and transnonchlor. All studies did not report characteristics of non-
433 participants. Most included studies did not report lifestyle behavior such as pesticides using
434 behavior, dietary habits, or physical activity. However, all included studies adjusted their risk
435 measurement on anthropometric and sociodemographic variables such as age, sex, smoking,
436 alcohol, education, or obesity. Overall, our meta-analysis inherited the limitations of the 11
437 individual studies of which it was composed and therefore was subjected to the bias of included
438 studies such as bias of selection and bias of outcome assessment.

439

440 **Conclusion**

441 We demonstrated that pesticides exposure is a major risk of metabolic syndrome, increasing the
442 risk by 42%. There were data mainly for organochlorine pesticides that globally increased the risk
443 of MetS, as well as for most types of organochlorines, with a high level of proof for

444 hexachlorocyclohexane and transnonchlor. Besides organochlorine exposure, data are lacking for
445 other types of pesticides. The risk increased in more recent studies which may be due to the
446 increase of the worldwide use of pesticides. We also demonstrated an inverse relationship with
447 body mass index, that may be linked with a storage of pesticides in fat tissue. Authorities should
448 enforce measurements to limit the use and production of pesticides.

449

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452 **Competing Interests**

453 No conflicting relationship exists for any author.

454 **Author contributions**

455 Conceived and designed the study: FD. Conducted the systematic literature search: HL, SM. Final
456 approval of eligible articles: all authors. Analyzed the data: FD. Wrote the first draft of the article:
457 HL, FD. Critical revision of the article: all authors. Integrity of the data analysis: HL, FD.

458 **Data availability statement**

459 All relevant data are within the paper.

460

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- 700

Table 1. Characteristics of included studies

*: not included in the meta-analysis. ATP3: National cholesterol education program, adult treatment panel III; BMI: Body mass index; IDF: International Diabetes Federation; OR: Odds ratio; PR: prevalence risk; RR: relative risk.

Study	Country	Period	Design	Population				Metabolic syndrome			Other variables listed
				Total (n)	Men (%)	Age	Type	Definition	Risk	Adjustment	
Aminov 2020*	USA	2016	cross-sectional	601	37.27	18-84	Local community	ATP3	β	Age, gender, smoking, BMI, serum total lipids	-
Dusanov 2018	Norway	2005-2010	cross-sectional	431	37.4	18-78	Clinic patients	ATP3	OR	Age, sex, BMI, smoking, alcohol, total cholesterol	CRP, ALAT
Gasull 2018	Spain	2002	cross-sectional	860	43.6	-	General population	ATP3 / IDF	PR	Age, sex, BMI, smoking, alcohol, physical activity	Social class, education, physical activity, CRP, HOMA-IR
Ha 2018	South Korea	2016	nested case-control	100	18.0	-	Targeted population	ATP3	OR	Smoking, family history of diabetes, HOMA-IR.	Total fat mass, lean mass, visceral fat mass, physical activity, family history of diabetes, fasting insulin
Kim 2019	South Korea	2005-2008	cohort	1162	56.6	39-72	Farmer	ATP3	RR	Age, smoking, alcohol, regular exercise, education, marital status	Marital status
Lee 2007	USA	1999-2002	cross-sectional	721	-	≥20	General population	ATP3	OR	Age, sex, race, poverty income ratio, smoking, serum cotinine, alcohol, exercise, BMI	-
Lee 2014	South Korea	2006-2010	nested case-control	246	32.9	≥40	Local community	ATP3	OR	Age, sex, smoking, alcohol, exercise, triglycerides, total cholesterol, BMI	Physically inactive, total cholesterol
Lind 2013	Sweden	2011	cross-sectional	1016	-	70	General population	ATP3	OR	Fatty acids, fatty acid factor, sex.	Myocardial infarction, stroke, diabetes, statin treatment, alcohol intake
Lind 2017	Sweden	2006-2017	cohort	452	50.0	70	General population	ATP3	OR	Lipid levels	Education, exercise habits, energy intake, fat intake, hypertension treatment, LDL, alcohol intake
Park 2010	South Korea	2006	nested case-control	100	28.0	≥40	General population	ATP3	OR	Age, sex, alcohol, smoking, BMI	Race, education, marital status, family history of diabetes / heart disease, liver disease, total lipids
Rosenbaum 2017	USA	2005-2007	cross-sectional	548	32.0	>18	General population	ATP3	OR	Age, family of heart disease/diabetes, liver disease, sex, race, alcohol, smoking, marital status, education, BMI, total lipids	Fasting insulin
Tomar 2013	India	2013	case-control	100	-	-	Clinic patients	ATP3	OR	Age, sex, smoking, alcohol	-

Figures Legend

Figure 1. Search strategy.

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for the search strategy.

Figure 2. Risk of bias assessment – Newcastle Ottawa scale

We used the Newcastle Ottawa scale (NOS) criteria to assess the methodological quality of the included articles, both for case-control and cohort studies (9 items) and cross-sectional studies (10 items), with the dedicated evaluation grids. We presented an overall quality score based on three dimensions: selection, comparability, and exposure for case-control studies; and selection, comparability and outcome for cohort and cross-sectional studies.

Figure 3. Meta-analysis stratified by type of pesticides (using all risks)

Each overall summary of a meta-analysis is represented in the graph by a lozenge on a horizontal line and each stratification by a dot. Dots represent risk of MetS after exposure by individual pesticides or individual contaminants, grey lozenges represent risks by types of pesticides, blue lozenges for the overall pesticides and the overall contaminants, and the red lozenge for the overall combination of pesticides and contaminants. The lozenges / dots represent the overall pooled-effect estimate of individual meta-analyses (pooled effect size - ES), and the length of each horizontal line around the dots represent their 95% confidence interval (95CI). Shorter lines represent a narrower 95CI thus higher precision around pooled-ES. Conversely, longer lines represent a wider 95CI and less precision around pooled-ES. The black solid vertical line represents the null estimate (with a value of 1). Horizontal lines that cross the null vertical line represent a non-significant overall summary of the meta-analysis, for each efficacy outcome.

n studies (subgroups): number of studies and subgroups included for each meta-analysis; I-squared (%): percentage of heterogeneity between studies for each meta-analysis; Weight (%): Weight of each stratification (meta-analysis) in the overall meta-analysis.

Figure 4. Metafunnels

Each dot represents a single study, with its corresponding effect size (x axis) and its associated standard error of the effect estimate (y-axis). Large high-powered studies are placed towards the top, and smaller low-powered studies towards the bottom. The plot should ideally resemble a pyramid or inverted funnel, with scatter due to sampling variation. Studies outside funnel plot are likely to present bias.¹⁰¹

Figure 5. Sensitivity analysis: meta-analysis using crude odds ratio and fully adjusted model (see details in Supplementary Figure 1 and 2)

Each overall summary of a meta-analysis is represented in the graph by a lozenge on a horizontal line and each stratification by a dot. Dots represent risk of MetS after exposure by individual pesticides or individual contaminants, grey lozenges represent risks by types of pesticides, blue lozenges for the overall pesticides and the overall contaminants, and the red lozenge for the overall combination of pesticides and contaminants. The lozenges / dots represent the overall pooled-effect estimate of individual meta-analyses (pooled effect size - ES), and the length of each horizontal line around the dots represent their 95% confidence interval (95CI). The black solid vertical line represents the null estimate (with a value of 1). Horizontal lines that cross the null vertical line represent a non-significant overall summary of the meta-analysis, for each efficacy outcome.

Figure 6. Meta-regression i.e. factors influencing the risk of MetS following pesticides exposure

The effect of each variable on the outcome is represented in the forest-plot by a dot on a horizontal line. The 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 represent non-significant variables on the outcome.

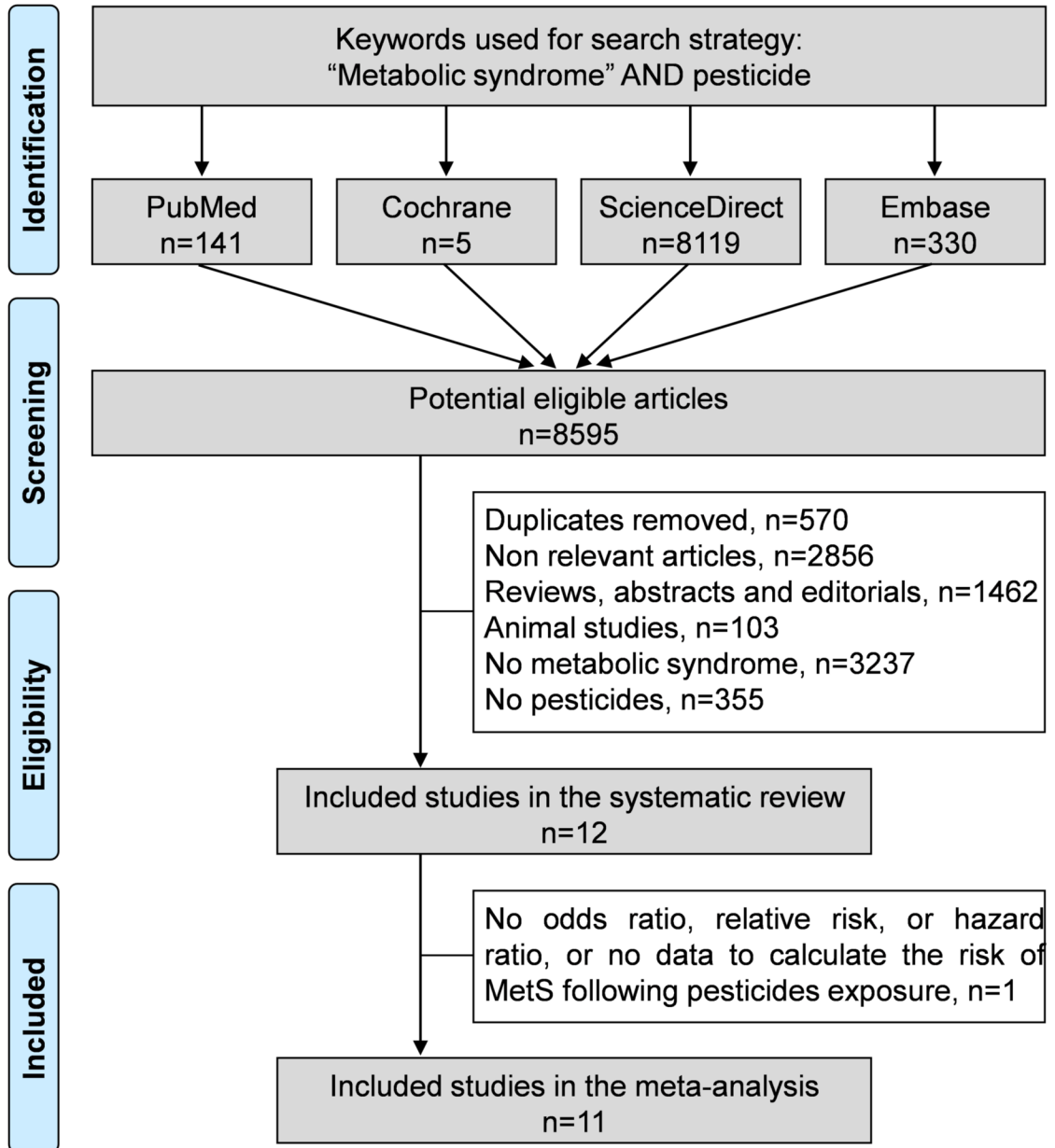
Supplementary materials

Supplementary Figure 1. Meta-analysis stratified by type of pesticide (crude model)

Supplementary Figure 2. Meta-analysis stratified by type of pesticide (fully adjusted model)

Appendix 1. Details for the search strategy used within each database

Appendix 2. Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) instrument



Case-control studies

Ha 2018
Kim 2019
Lee2014
Park 2010
Tomar 2013

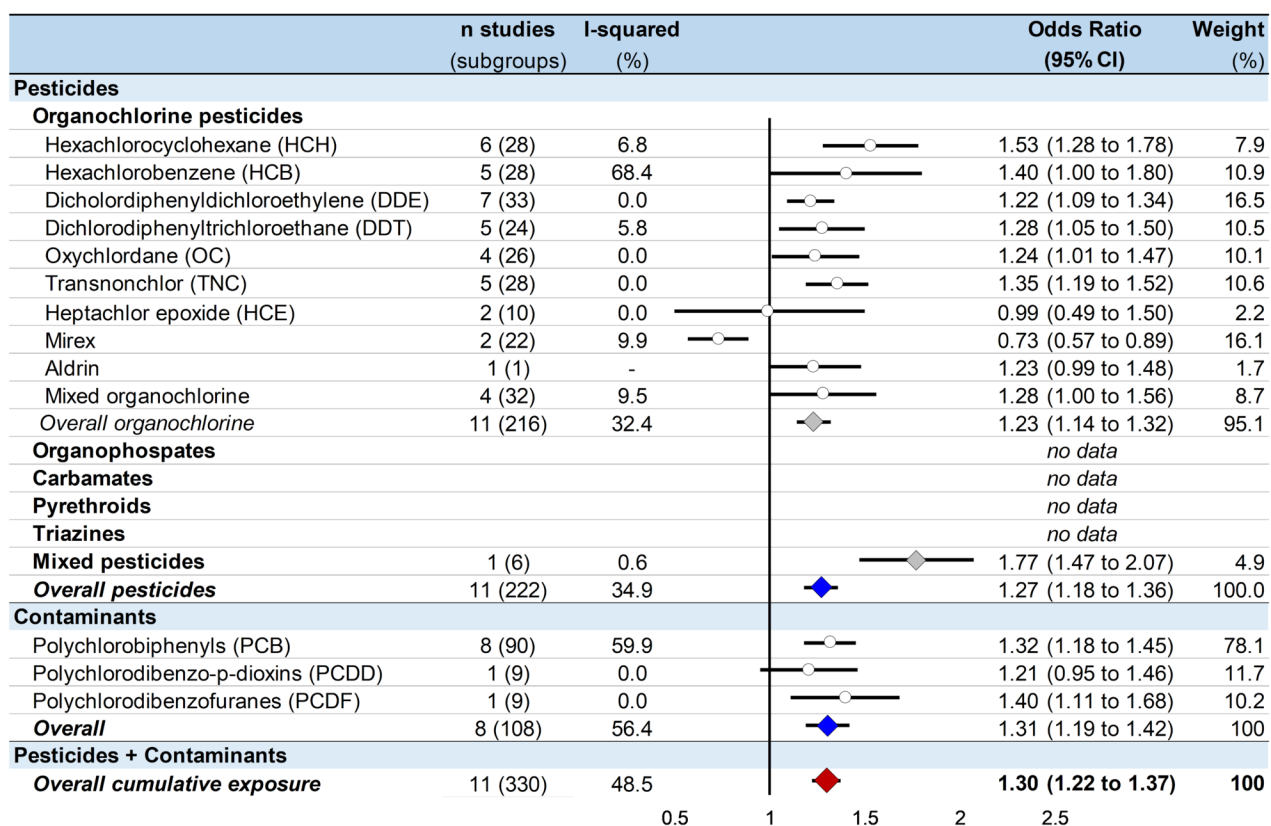
	Selection bias			Comparability bias		Exposure bias				
	Is the case definition adequate ?	Representativeness of the cases	Selection of controls	Definition of controls	Study controls for the most important factor	Study controls for any important factor	Ascertainment of exposure	Same ascertainment method for cases & controls	Non response rate	
Ha 2018	+	-	-	+	+	+	+	+	-	*****
Kim 2019	-	-	+	+	+	+	-	+	-	*****
Lee2014	+	+	+	+	+	+	+	+	-	*****
Park 2010	+	+	+	+	+	+	+	+	-	*****
Tomar 2013	+	-	-	+	+	+	+	+	-	*****

Cross-sectional & Cohort studies

Aminov 2020
Dusanov 2018
Gasull 2018
Lee 2007
Lind 2013
Lind 2017
Rosenbaum 2017

	Selection bias			Comparability bias		Outcome bias				
	Representativeness of the exposed cohort/ sample	Selection of the non exposed cohort/ sample size	Outcome not present at baseline/ Non-respondents	Ascertainment of exposure	Control of the most important factor	Controlling for any important factor	Assessment of outcome	Follow-up long enough	Adequacy of follow up/ statistics	
Aminov 2020	+	+	-	+	+	+	+	NA	+	*****
Dusanov 2018	-	+	-	+	+	+	+	NA	+	*****
Gasull 2018	-	+	-	+	+	+	+	NA	+	*****
Lee 2007	+	+	-	+	+	+	+	NA	+	*****
Lind 2013	+	+	-	+	+	+	+	NA	+	*****
Lind 2017	+	+	+	+	+	+	+	+	-	*****
Rosenbaum 2017	+	+	-	+	+	+	+	NA	+	*****

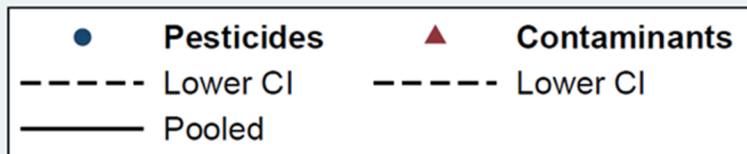
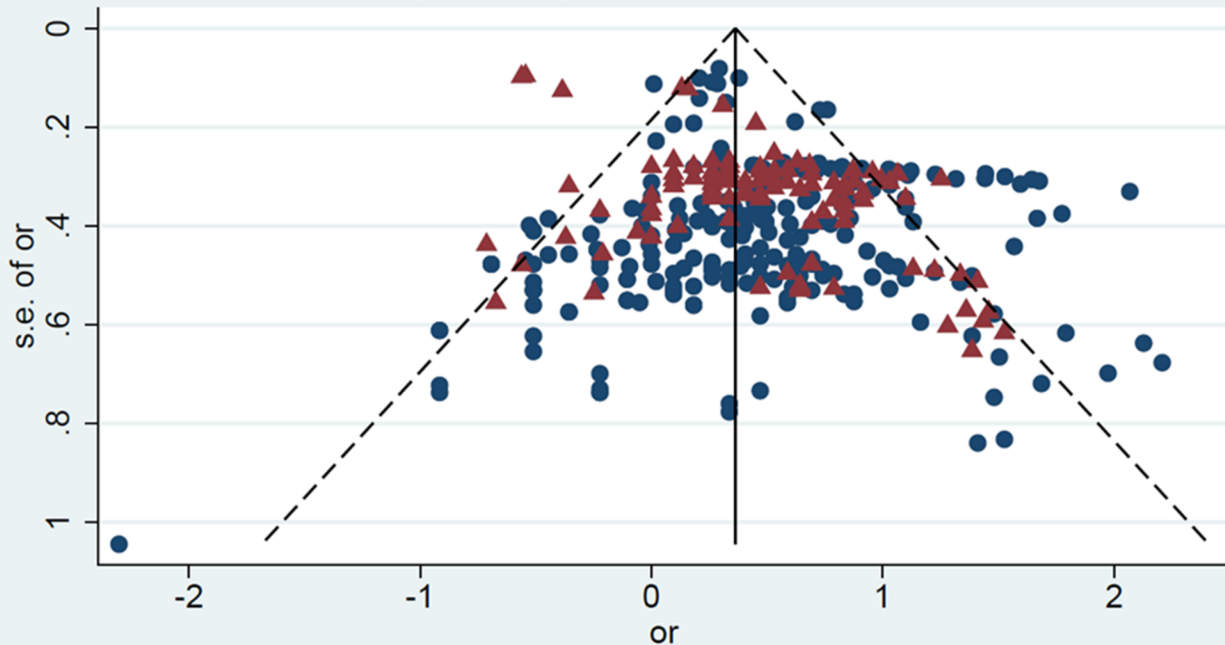
Overall quality



0.5 1 1.5 2 2.5

Overall exposure

Funnel plot with pseudo 95% confidence limits



Sensitivity analysis

Crude odds ratio

Fully-adjusted model

Pesticides

Organochlorine pesticides

Hexachlorocyclohexane (HCH)

Hexachlorobenzene (HCB)

Dichlorodiphenyldichloroethylene (DDE)

Dichlorodiphenyltrichloroethane (DDT)

Oxychlorane (OC)

Transnonchlor (TNC)

Heptachlor epoxide (HCE)

Mirex

Aldrin

Mixed organochlorine

Overall organochlorine

Organophosphates

Carbamates

Pyrethroids

Triazines

Mixed pesticides

Overall pesticides

Contaminants

Polychlorobiphenyls (PCB)

Polychlorodibenzo-p-dioxins (PCDD)

Polychlorodibenzofuranes (PCDF)

Overall contaminants

Pesticides + Contaminants

Overall cumulative exposure

