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1 Exposure to persistent organic pollutants and the risk of type 2 diabetes: a
2 case-cohort study

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72

73 ABSTRACT

74 *Aims.* - To explore exposure to 22 persistent organic pollutants (POPs) and incident type 2
75 diabetes in a population-based, prospective cohort.

76 *Methods.* - This case-cohort study on 753 participants without type 2 diabetes at baseline, was
77 followed-up over nine years, as part of the French D.E.S.I.R. cohort. We measured 22 POPs in
78 fasting serum at baseline. The associations between baseline POP concentrations, pre-adjusted
79 for lipids, BMI, age and sex, with incident type 2 diabetes, were assessed using Prentice-
80 weighted Cox regression models (time scale: age), adjusted for traditional confounding factors.
81 POPs were also modelled summed in functional groups: polychlorinated biphenyls (Σ PCB) and
82 organochlorines (Σ OC) and also individually, after log-transformation, in adjusted Cox models.

83 *Results.* - There were 200 incident diabetes cases over nine years. Pre-adjusted POP
84 concentrations were not related to diabetes risk for any of the 22 POPs examined. For the PCBs,
85 hazard ratios (HRs) per interquartile range of the pre-adjusted POPs, ranged from 0.87 (95% CI:
86 0.64,1.19) to 1.22 (0.93,1.59,). For (*p*, *p'*-DDE) and (*p*, *p'*-DDT), the HRs were 1.09 (0.83,1.43)
87 and 0.89 (0.70,1.13), respectively. The HRs for PeCB, HCB, β -HCH, γ -HCH, Oxychlorane,
88 Trans-nonachlor were 0.98 (0.85,1.13), 1.06 (0.84,1.33), 1.22 (0.93,1.59), 1.13 (0.89,1.42), 1.00
89 (0.76,1.31), 0.86 (0.66,1.43), respectively. HRs for Σ PCB and Σ OC did not differ significantly
90 from one.

91 *Conclusion.* - We did not observe any relations between exposure to POPs and diabetes in this
92 population-based cohort. These results do not support causal inferences reported in previous
93 studies linking serum POP concentrations and diabetes risk.

94 **KEY WORDS:**

95 Diabetes mellitus, Incidence, Organochlorine insecticides, Pesticides, Persistent organic
96 pollutants, Polybrominated biphenyls

97

98 **Introduction**

99 Diabetes is one of the most challenging health problems of the 20th century, with large and
100 rapid increases in prevalence observed across almost all developed and developing countries [1].
101 Traditional risk factors (obesity, unhealthy diet and lack of physical activity) are likely to be key
102 contributors, however, they are unlikely to be the sole reasons for increases in diabetes
103 prevalence [2]. In recent years, there has been increased attention on environmental risk factors
104 which may be contributing to the epidemic. Endocrine and metabolic disruptors are a broad
105 group of compounds which have been implicated in the development of type 2 diabetes [3]. One
106 class of these compounds is the persistent organic pollutants (POPs) which are ubiquitous in our
107 environment, due to their lipophily. Some POPs are intentionally made and others are by-
108 products; they comprise a group of diverse substances and include organochlorine insecticides
109 such as dieldrin, dichlorodiphenyltrichloroethane (*p, p'* DDT) and its main metabolite in humans,
110 dichlorodipenyldichloroethylene (*p, p'* DDE), as well as several industrial chemical products or
111 by-products including polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins
112 (PCDDs, *e.g.*, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, or TCDD), hexachlorobenzene (HCB),
113 polybrominated biphenyls (PBBs), polybrominated diphenylethers (PBDEs) [4]. These
114 compounds are resistant to biodegradation and persist in the environment for long periods of
115 time. Humans are predominantly exposed through the consumption of contaminated food,
116 mainly meat, fish, and dairy products even at low doses, although some exposure also exists
117 through air and water [4].

118 Most of the studies linking POPs to diabetes in humans are cross-sectional in design. A few
119 cohort studies have measured exposure to POPs and diabetes in a prospective setting, but only a
120 few of these are population-based and many have small numbers of diabetes cases (a few tens).
121 Furthermore, the results from these studies are mixed and no single POP predicts diabetes
122 consistently. The only study which has large numbers, is the Nurses' Health study (NHS). Using
123 two independent, nested case-control studies from within the NHS, Wu et al. showed that after
124 multivariable adjustment, plasma HCB concentration was positively associated with incident
125 type 2 diabetes [pooled OR 3.59 (95% CI 1.49,8.64), comparing the third terile with the first
126 tertile [5]. Further work published more recently, using a more contemporary sample within the
127 NHS population and with new measurements of a broader set of POPs, showed that a score,

128 summing the concentrations of five dioxin-like PCBs congeners (DL-PCBs), was an independent
129 risk factor for diabetes with an OR of 1.78 [1.14,2.76], comparing the third tertile with the first
130 tertile [6]. POPs have been linked to diabetes in two studies from Sweden. In a case-control
131 study of women aged 50–59 years, after a follow-up of 6 years, (*p*, *p*'-DDE) was related to an
132 increasing risk of diabetes [4th quartile versus 1st, OR 5.5 (1.2,25)] [7]. In a more recent study,
133 the prospective investigation of the Vasculature in Uppsala Seniors (PIVUS) study, the ORs for
134 type 2 diabetes according to quintiles of a sum of ranks of PCB measures (vs. the lowest quintile)
135 were 4.5 (0.9,23.5), 5.1 (1.0,26.0), 8.8 (1.8,42.7) and 7.5 (1.4,38.8) ($p_{trend} < 0.01$) after adjustment
136 for known risk factors [8]. There were also significant relationships with the organochlorines.
137 However, with only 36 cases of diabetes, the confidence intervals around the odds ratios was
138 large, leading to some uncertainty relating to the effect size [8].

139 POPs are strongly associated with lipids and obesity [9]. Disentangling the mediating and
140 potentially confounding effects of lipids and body mass index (BMI) in regard to lipophilic
141 environmental compounds has presented some challenges [10, 11]. While the ideal methodology
142 would be to assess POPs in fat tissue rather than serum, this is difficult to do in large numbers
143 within the general population. Recently, new statistical methods have been developed which may
144 overcome some of these challenges [10, 12, 13]. These include an approach [10, 12] which pre-
145 adjusts the environmental compounds for factors such as lipids, BMI, age, sex, followed by
146 modelling with confounding factors. Here, we examine the prospective relationship between
147 POP concentrations with incident type 2 diabetes, in a population-based cohort in France, using
148 this novel approach, coupled with conventional analytic approaches, to investigate the
149 relationship between POPs and incident type 2 diabetes over 9 years of follow-up.

150

151 **Material and methods**

152 *Source population*

153 D.E.S.I.R. is a prospective, population-based cohort study that aimed to explore the
154 development of the insulin resistance syndrome and type 2 diabetes [14]. Between 1994 and
155 1996, the D.E.S.I.R. study recruited 5212 men and women aged 30–65 years, from volunteers
156 who were offered four free health examinations over nine years, by the French Health Insurance
157 System in 10 health examination centers in central-western France. Participants attended a

158 baseline visit and a range of biological and clinical tests were conducted. These examinations
159 were repeated at 3-, 6-, and 9-year visits. The procedures and methods undertaken at each
160 follow-up have been previously published [14]. The study protocol was approved by French
161 Ethics Committees and written informed consent was obtained from all participants.

162

163 *Study population*

164 We conducted a case-cohort study nested within the French D.E.S.I.R. cohort. Participants
165 were recruited between 1994-1996 and followed for 9 years. All participants with blood glucose
166 and BMI data at baseline and 9-year visits were eligible for this study (n=3409). We randomly
167 selected 600 (11.5%) participants at baseline from all participants, consistent with sampling
168 fractions of other case-cohort studies [15]. We refer to this as the subcohort hereafter. Incident
169 type 2 diabetes was defined by treatment with glucose-lowering agents or by a fasting plasma
170 glucose above 7.0 mM or by HbA_{1c} above 6.5% at any of the three 3-yearly health examinations
171 after inclusion in the study. After excluding participants with prevalent type 2 diabetes or
172 uncertain diabetes status at baseline, and one missing serum for assays, the final study population
173 included 583 subcohort members and 200 incident cases of type 2 diabetes, 30 of whom were in
174 the subcohort. The sampling strategy is shown in Fig. 1.

175

176 *Covariates*

177 Blood samples were collected after at least 12 h of fasting at each of the four examinations.
178 All samples were stored at -80 °C. Blood samples were analyzed for glucose and lipids as
179 previously described and weight, height and waist circumference were measured [14]. Blood
180 pressure was measured in duplicate using a mercury sphygmomanometer in a supine position,
181 and mean values were calculated. Information on family history of diabetes, treatment for
182 diabetes, hypertension, elevated lipids was collected during an interview with a physician.
183 Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90
184 mmHg or ongoing blood pressure-lowering treatment. A self-administered questionnaire
185 provided data on education level, living with a partner, smoking status, diet, and physical activity
186 (at home, at work and during sporting activities). Physical activity was categorized as: sedentary,
187 moderately active and active based on the frequency of participation in active sporting activities

188 (never, <1 once a week, 1–2 times a week, >2 times a week) and the intensity of usual physical
189 activity at home and at work (low, moderate, important, intensive). The dietary intake (in Kcal
190 per day) was calculated using the NAQA food consumption questionnaire, [16] describing usual
191 food consumption, based on the composition of meals and snacks and the frequency of
192 consumption of meat, fish, fried foods, butter, cheese, dairy products, bread, sugary desserts,
193 sugar, soft drinks and alcoholic beverages.

194

195 *Chemical analysis of persistent organic pollutants*

196 We used the literature to guide us in the choice of POPs to study, according to their presence
197 in appropriate concentrations in similar populations and whether they have been used
198 historically, worldwide.

199 The methods used for the laboratory analysis of 22 POP in serum samples has been
200 described previously[13, 17] and we provide the same detail below. The POP compounds
201 measured were ten PCBs (PCBs -74, -99, -118, -138, -153, -156, -170, -180, -183, -187); nine
202 pesticides or pesticide metabolites (pentachlorobenzene (PeCB), hexachlorobenzene (HCB),
203 alpha-hexachlorocyclohexane (α -HCH), beta-hexachlorocyclohexane (β -HCH), gamma-
204 hexachlorocyclohexane (γ -HCH), oxychlorane, *trans*-nonachlor, (*p*, *p'*-DDT), (*p*, *p'*-DDE)).
205 Three brominated diphenyl ethers (BDE-47, BDE-99, BDE-153) were also measured.

206 Pretreatment of the serum samples was as follows: ethanol and ^{13}C -labelled internal
207 standards of each compound in toluene were added to samples (200 μL) in test tubes and mixed
208 to precipitate the proteins and equilibrate internal standards. Dichloromethane-hexane (1:4) was
209 added for extraction followed by activated silica to bind the sample water, ethanol, and
210 precipitate. Samples were mixed, and layers were allowed to separate. The upper
211 dichloromethane-hexane layer was poured to a solid phase extraction cartridge (SPE cartridge)
212 containing from bottom to top 10% AgNO_3 impregnated silica and a mixture of Na_2SO_4 and
213 silica. Elution of SPE-cartridges was performed with dichloromethane-hexane, and the eluate
214 was concentrated to 15-20 μL for gas chromatography - triple quadrupole mass spectrometry
215 (GC-MS/MS) analysis. The instrument used was an Agilent 7010 GC-MS/MS system
216 (Wilmington, DE, USA), GC column DB-5MS UI (J&W Scientific, 20 m, ID 0.18 mm, 0.18

217 μm). Limits of quantification (LOQ) ranged from 5 pg/mL for PCB congeners and trans-
218 nonachlor to 40 pg/mL for *p, p'*-DDE. Two blank samples and two control samples (NIST SRM
219 1958) were included in each batch of samples. Measured concentrations of POPs in SRM 1958
220 were 80–105% of the certified/reference concentrations. The coefficient of variation (CV-%)
221 from SRM 1958 ($n = 18$) was below 3.6% for all compounds. The THL laboratory participates
222 three times a year in AMAP interlaboratory comparisons (Ring Test for Persistent Organic
223 Pollutants in human serum, National Institute of Public Health, Quebec, Canada). In AMAP ring
224 tests for POPs, laboratory's results varied from 83 to 132% of the assigned values, depending on
225 the compound.

226 Machine values were used in the analyses, including for POP concentrations below the level
227 of quantification (LOQ). POPs that had more than 70% of values below the LOQ were not
228 analyzed (α -HCH, BDE-49, BDE-99 and BD-153).

229 *Statistical analysis*

230 Descriptive data are presented as n (%), mean (standard deviation), median (25th and 75th
231 percentiles), and comparisons tested by χ^2 or Student-t tests.

232
233 Hazards ratios for incident diabetes were modeled in age-adjusted (crude) and multivariable
234 Prentice-weighted Cox regression models, adapted to the case-cohort design [18], allowing
235 estimation of adjusted hazard ratios (HRs) associated with POPs for incident type 2 diabetes,
236 with their 95% confidence intervals (CI).

237
238 Three analytical approaches were used to define the variables representing POP concentrations in
239 serum.

240 241 Approach 1: Lipid, BMI, age, sex-adjusted POP levels

242 POPs are lipophilic compounds, and lipids, age, BMI and sex have been shown to be related
243 to POPs [12, 13], and also to incident diabetes. It has been argued that it is difficult to
244 disentangle the possible causal effects of lipophilic substances such as POPs with incident
245 diabetes, independently of the concomitant confounding and mediating effects. Adjusting for
246 lipids may not adequately remove the effect of confounding. To address this, alternative

247 methodological approaches have been developed, using ‘pre-adjusted residuals’. Indeed,
248 residuals of the linear regression model where a POP is explained by a set of variables
249 correspond theoretically, if the model is correct, to the part of the POP’s variability unexplained
250 by these variables. Linear regression was used in the subcohort sample to model log-transformed
251 POP concentrations with predictors: LDL-cholesterol, triglycerides (log-transformed), BMI, age,
252 sex where all were assessed at baseline. Two-way interaction terms between all covariates were
253 also included to model exposure at best, using a multiplicative variable. Residuals were
254 estimated for the subcohort and then calculated for the cases, applying the model (with identical
255 parameters) derived from the subcohort. We refer to these as ‘pre-adjusted residuals’ [12].

256 To allow easier interpretation of the results, the residuals were divided by the
257 interquartile range (IQR) and the results are reported per one unit increase in the IQR of the
258 residual, for each of the POPs. These pre-adjusted POP levels can be interpreted as those
259 expected at baseline, if all study participants had the same LDL-cholesterol and triglyceride
260 levels, BMI, age and sex.

261

262 Approach 2: Sum of PCBs, sum of organochlorine chemicals

263 Since populations are exposed to a variety of organic pollutants at the same time we also
264 modelled POPs in functional groups according to the literature [19]. Modelling composite
265 variables also decreases the number of separate analyses undertaken thereby reducing the
266 potential for false positives.

267 POPs were grouped and summed according to two functional classes [19]:

268 a) the sum of PCBs (\sum PCBs) for each participant, adding concentrations of all ten PCBs as
269 previously described [20];

270 b) the sum of organochlorine chemicals (OCs), (\sum OCs) adding concentrations of eight
271 chemicals: PeCB, HCB, β - and γ -HCH, oxychlorane, *trans*-nonachlor, (*p*, *p*'-DDT) and (*p*, *p*'-
272 DDE).

273 Both summed variables (units, ng/L) were log-transformed and modelled as continuous
274 variables.

275

276 Approach 3: POPs as continuous variables without pre-adjustment

277 The logarithms of the POP were modelled per IQR.

278

279 The pre-adjusted POP residuals, the summed POPs and the log-transformed POP
280 concentrations - all per IQR - were modeled in age-adjusted (crude) and multivariable Prentice-
281 weighted Cox regression models, adapted to the case-cohort design [18]. We estimated the date
282 of diabetes onset as the midpoint between the last visit without diabetes and the first visit with
283 diabetes. Age was used as the timescale. Participants were followed-up until the earliest of
284 diabetes onset, death or nine years after entry into the study. The proportional-hazards
285 assumption was checked using Schoenfeld residuals and the assumption was not violated.

286 Multivariable models were adjusted for potential diabetes risk factors: sex (men/women),
287 waist circumference (continuous), family history of diabetes (yes/no), smoking (Never,
288 exsmoker, current), physical activity (sedentary, moderately active or active), education (no or
289 partial primary school, secondary school, post secondary school), living with a partner (yes/no),
290 HDL-cholesterol (continuous), triglycerides (continuous), hypertension (yes/no) and calorie intake
291 (continuous).

292 Multiple fractional polynomials were used to determine the functional form, for each POP,
293 with incident diabetes; none of the POPs significantly deviated from a linear relation.

294 As relationships between POPs and diabetes have been reported to vary by sex [21], we
295 compared the likelihood of models with and without the sex interaction term; a P value of 0.2
296 was considered as suggestive of an interaction. Spearman correlation coefficients were
297 calculated between the pre-adjusted POP residuals in the subcohort. All analyses used Stata/SE
298 version 15.1. We adhered to reporting guidelines of case-cohort studies as per recommendations
299 by Sharp et al. [15].

300 **Results**

301 *Study population*

302 Baseline characteristics of subcohort members, without the cases of incident diabetes, and
303 all cases of incident type 2 diabetes, are presented in Table 1. In the subcohort without diabetes,
304 the mean age (\pm SD) at inclusion was 48 ± 10 years and 54% were women. Sociodemographic
305 characteristics (sex, age, education level) of individuals from the random subcohort did not differ
306 substantially from those of other participants included in the D.E.S.I.R. cohort (data not shown).
307 The mean age (SD) when type 2 diabetes was diagnosed was 52 ± 9 years. The incidence rate
308 (95% CI) of type 2 diabetes was 5.5 (4.8–6.3) per 1000 person-years in the entire cohort.
309 Compared to the subcohort without the diabetes cases, the incident cases of diabetes were
310 significantly more likely to be men, smoke, have a family history of diabetes, have hypertension,
311 be less likely to engage in intensive physical activity at baseline. They were also significantly
312 older, had a higher mean BMI and waist circumference, lower mean HDL and higher median
313 triglycerides levels, and consumed more calories than members of the subcohort without diabetes
314 (Table 1).

315 *Concentration of persistent organic pollutants*

316 As more than 90% of the concentrations of α -HCB, BDE-47, BDE-99 and BDE-153 were
317 below the LOQ, they were excluded from the analyses (data not shown in Table 2). For the
318 people in the subcohort, the highest concentrations were found for (*p*, *p'*-DDE), PCB-153 and
319 PCB-180 (median concentrations: 1962, 1480 and 1191 ng/mL, respectively) (Table 2). Among
320 the PCBs, the median concentrations ranged from 139 ng/mL for PCB99 to 1480 ng/mL for
321 PCB-153. The concentration of the remaining organochlorine pesticides ranged from 78 ng/mL
322 for oxychlordan to 562 ng/mL for β -HCH. The medians of HCB, β -HCH, γ -HCH, oxychlordan,
323 *trans*-nonachlor, (*p*, *p'*-DDE), (*p*, *p'*-DDT), PCB-99, PCB-118, PCB-138 and PCB-187 were
324 significantly higher in the incident cases of diabetes versus the subcohort without cases. The
325 Spearman correlation coefficients (*rho*) of the pre-adjusted POP are shown in Table S1
326 (Supplementary analyses).

327

328 *Associations of persistent organic pollutant exposure with incident diabetes*

329 The associations between POP exposure and the risk of developing type 2 diabetes using
330 approaches 1, 2 and 3 are presented respectively, in Tables 3, 4 and 5.

331 *Approach 1 pre-adjusted POP concentrations*

332 In analyses where the POP were pre-adjusted for lipids, BMI, age and sex and then the
333 residuals modelled by Cox regression, PCB180 was the only chemical associated with diabetes
334 risk, with a hazards ratio of 0.77 (0.61,0.98). After additionally adjusted for confounding factors,
335 no statistically significant relationships were observed (Table 3). There were no significant
336 interactions with sex (data not shown).

337 *Approach 2: Summed POP concentrations*

338 In multivariable-adjusted analyses, the HRs for summed OCs was 1.00 (0.72,1.41) and 0.66
339 (0.35,1.23) for summed PCBs (Table 4). There were no significant interactions with sex (data
340 not shown).

341 *Approach 3 (modelling of log- transformed POP)*

342 In age-adjusted analyses, HCB, β -HCH, γ - HCH, oxychlordan, *trans*-nonachlor and (*p*, *p*'-
343 DD, were significantly associated with incident diabetes (Table 2). All of these relationships
344 were attenuated and became non-significant after adjustment in the Cox models for diabetes risk
345 factors (Table 5). There were no significant interactions with sex (data not shown).

346 Discussion

347 Using a population-based study from France, we observed that exposure to the 18 different
348 POPs measured (with quantifiable serum levels) at baseline, did not independently increase or
349 decrease the risk of incident diabetes over nine years, using three analytic approaches.

350 We observed the largest effect sizes in relation to diabetes risk with hexachlorobenzene, β -
351 HCH and some PCBs although none of these were significant. This is broadly consistent with the
352 literature. In the Nurses' Health study (NHS), both HCB and total PCBs were associated with
353 incident type 2 diabetes, in agreement with a meta-analysis of prospective studies [5]; they are
354 also consistent with a later study in the same NHS population [6]. In this study, Zong et al. [6]
355 showed significant positive findings with HCB, β -HCH, p , p' -DDE and dioxin-like PCBS (DL-
356 PCBs) and incident diabetes, in models with similar covariate adjustment to ours. In the PIVUS
357 study, POPs were shown to independently predict diabetes risk for type 2 diabetes: the ORs
358 (95% CI) according to quintiles of a sum of ranks of PCB measures (vs. the lowest quintile) were
359 4.5 (0.9,23.5), 5.1 (1.0,26.0), 8.8 (1.8,42.7) and 7.5 (1.4,38.8) ($p_{trend} < 0.01$) after adjustment for
360 known risk factors [8]. In a very recently published hospital based case- control study from
361 China, OC exposure was positively associated with the prevalence of type 2 diabetes β -HCH
362 and (p , p' -DDE) were associated with higher levels of fasting plasma glucose, even among those
363 without diabetes.[22] It is noteworthy that this study modelled log transformed POPs as
364 continuous variables expressed per wet-weight of lipids and the models, unlike ours, were
365 minimally adjusted for age BMI and sex [22].

366 Inconsistencies in previous studies regarding congener-specific findings are well known in
367 the POPs and diabetes literature. There are many possible factors at play which may explain
368 these differences. These include small numbers of diabetes cases, use of different study designs,
369 insufficient adjustment for confounding factors, differential background exposure status, lack of
370 or inadequate lipid adjustment and differences in other population characteristics, that may affect
371 POP retention in the body [4]. We employed a newly developed statistical approach to analyse
372 the POPs which take into account that POP concentrations are related to obesity, lipids and other
373 covariates [10, 13, 23]. It has been reported that pre-adjusting the POPs before modelling leads
374 to more conservative relationships, which is consistent to what we observe. However, we do not
375 fully attribute our null findings to this methodology as we employed two additional methods and

376 the results across the three methods were consistent with each other: all three methods failed to
377 detect significant associations of POPs with incident diabetes, after adjustment for covariates.

378

379 *Strengths and weaknesses*

380 A key strength of our study is the use of a population-based, longitudinal sample with
381 carefully collected covariate data, dedicated to the study of diabetes determinants. In addition,
382 our thorough analytical approach, performing three methods, represents another strength. There
383 are several reasons why we may have failed to show more significant findings, if such
384 associations exist. The most compelling of these is statistical power. In the D.E.S.I.R study, as
385 there were only 200 incident cases of diabetes accrued over the 9 years, we cannot exclude the
386 possibility that we were underpowered to observe significant effects. We can however exclude
387 the possibility of low exposure levels as the reason for lack of significance, as the concentrations
388 detected for the POPs in the D.E.S.I.R. study are broadly similar, if not slightly higher, to those
389 reported in other European countries, as reported in the EPIC study [13]. Of note, the same
390 laboratory was used to test the POP in both studies. In particular, concentrations measured in
391 D.E.S.I.R. are closest to the concentrations observed in Denmark in 2007. Another key limitation
392 of these analyses is that our finances only allowed us to assay POPs at baseline and we
393 acknowledge that the measurement of POPs at other time points would have been very useful in
394 understanding the relationship between POPs and diabetes risk over time. This is because serum
395 concentrations of POPs are directly affected by weight changes, which are becoming more
396 common in modern societies[4].

397 Given that the cost of assaying POPs is prohibitive, we chose to use a case-cohort design to
398 test our hypothesis that POPs exposure increases the risk of diabetes. This design is an efficient
399 and cost effective method for risk assessment, as sample testing is only performed for the
400 subcohort and the cases, rather than for the full cohort. Further, statistical efficiency is
401 comparable for the case-cohort and the full cohort analyses [18].

402

403 *The link between POP exposure and diabetes*

404 The mechanisms linking POPs (organochlorine pesticides and PCBs) exposure to diabetes
405 have not been fully elucidated, but several mechanistic pathways have been postulated. POPs
406 have been shown to bind to several receptors, including the aryl hydrocarbon receptor and
407 several nuclear receptors such as the estrogen receptors alpha and beta or PPARs, that regulate
408 glucose and lipid homeostasis [4]. POPs are known to have endocrine disrupting properties
409 similar to that of bisphenol A and thus binding to such sites that rapidly activate different
410 signaling cascades, alter the regulation of glucose and lipid metabolisms [3]. Less is known
411 about whether POPs increase diabetes risk via damage to β cells or by increasing insulin
412 resistance. In animal studies, POPs have been related to both increased insulin resistance and
413 reduced insulin secretion,[24] although the human studies are less clear than the animal work in
414 this area. For human studies, the evidence is more consistent with high serum concentrations of
415 POPs being associated with decreased insulin secretion rather than increased insulin resistance
416 [25]. It is also apparent that POPs can be associated with reduced insulin secretion at low
417 concentrations (in the range of pmol/L) [26]. The reason why human studies do not support the
418 observation that high serum POPs increase insulin resistance as shown in animal studies is
419 puzzling, and could be because the high level of insulin seen in type 2 diabetes may mask any
420 measurable effect of POPs on insulin resistance [27].

421
422 *Conclusion*

423 In this cohort of middle-aged men and women, overall, we did not observe associations
424 between serum POP concentrations and incident diabetes, independently of traditional
425 confounding factors, with any one of the three methods of statistical analysis used.

426
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428 Group for their contributions.

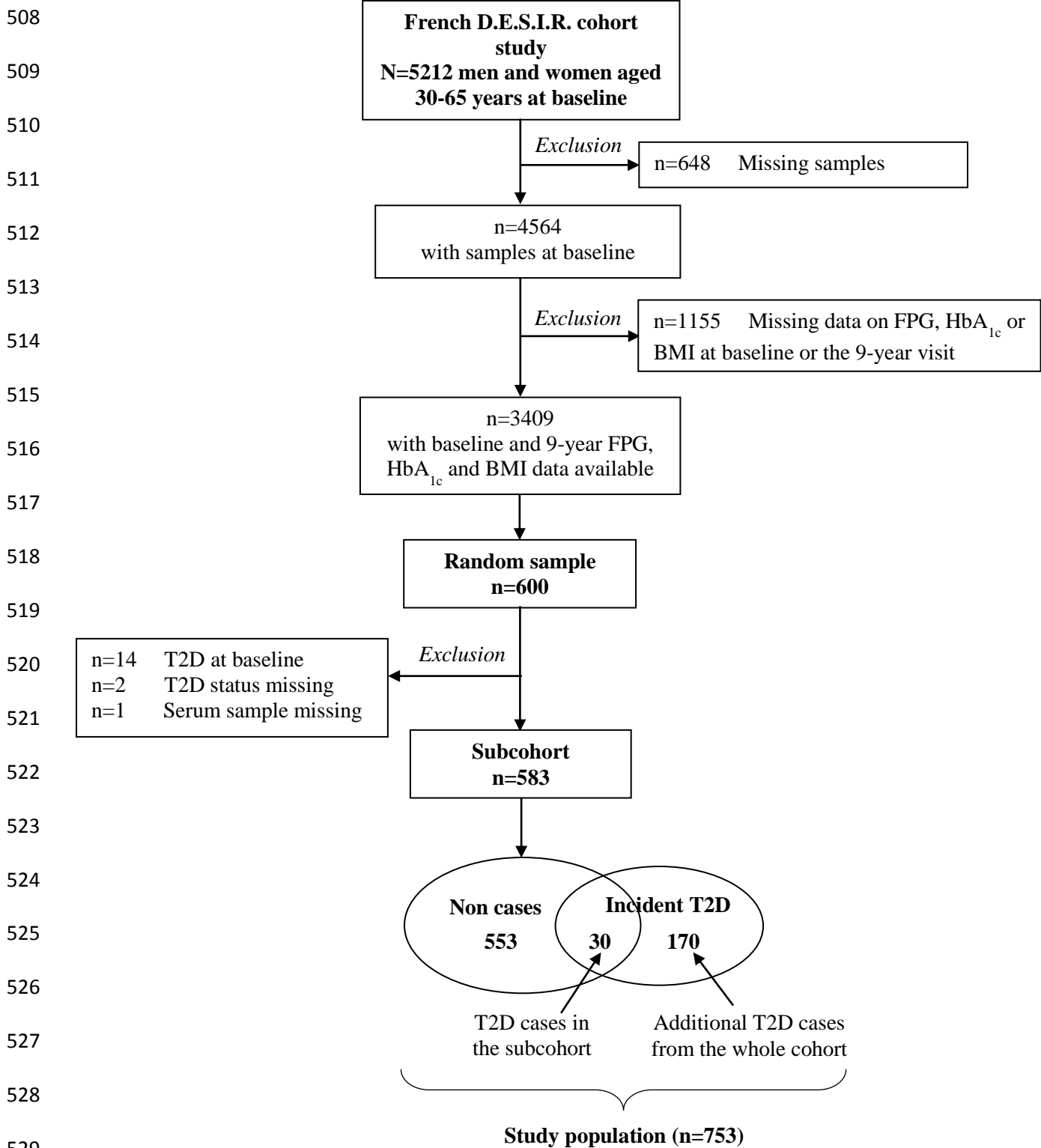
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506

507 **Fig. 1.** The sampling strategy of the study



531 **Table 1**

532 Baseline characteristics of the French D.E.S.I.R. cohort, according to the case-cohort design

533 (n=753)

	Subcohort, not including incident diabetes cases n=553	All incident diabetes cases n=200	<i>P</i> value
Age (years)	48 ± 10	51 ± 9	<0.001
Women	297 (54)	72 (36)	<0.001
Body mass index (Kg/m ²)	24.3 ± 3.2	27.3 ± 4.6	<0.001
Waist circumference (cm)			
Men	89 ± 9	97 ± 10	<0.001
Women	75 ± 8	88 ± 12	<0.001
Physical activity			0.002
Sedentary	122 (22)	73 (37)	
Moderately active	297 (54)	98 (49)	
Active	133 (23)	29 (15)	
Smoking			<0.001
Never	298 (54)	82 (41)	
Former	162 (29)	60 (30)	
Current	93 (17)	58 (29)	
Education			0.963
No or partial primary school	80 (15)	30 (15)	
Secondary school	358 (64)	130 (65)	
Post-secondary school	115 (21)	40 (20)	
Diabetes in family	90 (16)	51 (26)	<0.001
Daily calorie intake (Kcal)	2101 ± 504	2250 ± 565	<0.001
Living with a partner	457 (83)	159 (80)	0.324
HDL cholesterol (mmol/l)	1.7 ± 0.4	1.5 ± 0.4	<0.001
Triglycerides (mmol/l)	0.9 (0.6, 1.3)	1.3 (1.0, 2.0)	<0.001
Hypertension	185 (33)	121 (61)	<0.001

534 Data are n (%), mean ± SD, median (25th, 75th percentile).

535 *Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg

536 or treatment for hypertension.

537 **Table 2**
 538 Concentrations of persistent organic pesticides (POPs) (ng/l) using medians (25th, 75th percentiles).
 539 The French D.E.S.I.R. study.

Persistent organic pollutants	All cases of incident diabetes n=200	Subcohort with diabetes cases n=583	Subcohort without diabetes cases n=553	Percentage < limit of quantification
PeCB	9.80 (7.46, 10.3)	10.1 (7.46, 13.3)	10.2 (7.57, 13.2)	49
HCB	354 (237, 545)	283 (197, 413)	272 (194, 403)*	0
β -HCH	811 (459, 1176)	562 (315, 879)	513 (301, 837)*	0
γ -HCH	18.4 (12.2, 30.5)	14.6 (9.81, 25.7)	14.7 (9.71, 25.7)*	61
Oxychlorane	89.6 (69.1, 130)	78.1 (58.7, 104)	76.8 (52.3, 104)*	0.9
<i>Trans</i> -nonachlor	72.0 (52.5, 95.0)	59.1 (42.1, 81.2)	57.4 (41.1, 79.6)*	0
<i>p, p'</i> -DDT	90.7 (65.6, 131)	78.0 (51.9, 116)	74.6 (49.7, 112)*	0.4
<i>p, p'</i> -DDE	2612 (1572, 4452)	1962 (1225, 3408)	1903 (1204, 3139)*	0.4
PCB-74	180 (118, 270)	158 (101, 237)	155 (104, 234)	0
PCB-99	167 (115, 228)	139 (90.4, 195)	133 (90.4, 191)*	0
PCB-118	410 (265, 554)	305 (201, 458)	300 (200, 445)*	0
PCB-138	991 (757, 1238)	871 (693, 1136)	859 (683, 1124)*	0
PCB-153	1563 (1271, 1992)	1480 (1174, 1905)	1481 (1148, 1898)	0
PCB-156	192 (148, 247)	178 (137, 232)	181 (136, 231)	0
PCB-183	160 (125, 211)	149 (111, 195)	149 (109, 193)	0
PCB-187	323 (250, 442)	295 (211, 394)	290 (207, 390)*	0
PCB-170	528 (413, 670)	515 (405, 667)	518 (405, 663)	0
PCB-180	1187 (932, 1511)	1191 (921, 1478)	1198 (926, 1480)	0

540 Notes:
 541 **P*-value below 5%, comparing median values between all cases of incident diabetes vs. subcohort
 542 without cases of incident diabetes
 543 α -HCB, BDE-47, BDE-99, BDE-153 were also measured but, as more than 90% of samples were lower
 544 than the limit of quantification (LOQ), these compounds were excluded from further analyses.
 545

546 **Table 3**
 547 Hazard ratios (95% confidence intervals) for the relationship between pre-
 548 adjusted persistent organic pesticides (POPs) and 9 year incident diabetes
 549 (per one interquartile range (IQR) in the pre-adjusted (BMI, lipids, age and
 550 sex residuals of log of POPs). The French D.E.S.I.R study (n=753).

Persistent organic pollutants	Age-adjusted hazard ratios (95% CI)	Fully adjusted hazard ratios* (95% CI)
PeCB	0.95 (0.84, 1.08)	0.98 (0.85, 1.13)
HCB	0.96 (0.80, 1.16)	1.06 (0.84, 1.33)
β -HCH	1.17 (0.95, 1.43)	1.22 (0.93, 1.59)
γ -HCH	1.19 (0.98, 1.45)	1.13 (0.89, 1.42)
Oxychlorane	0.95 (0.77, 1.18)	1.00 (0.76, 1.31)
<i>Trans</i> -nonachlor	0.83 (0.66, 1.04)	0.86 (0.66, 1.13)
<i>p, p'</i> -DDT	0.93 (0.77, 1.12)	0.89 (0.70, 1.13)
<i>p, p'</i> -DDE	1.06 (0.85, 1.32)	1.09 (0.83, 1.43)
PCB-74	0.94 (0.77, 1.15)	0.89 (0.70, 1.13)
PCB-99	1.04 (0.86, 1.26)	1.09 (0.83, 1.43)
PCB-118	0.99 (0.82, 1.19)	1.02 (0.80, 1.29)
PCB-138	0.96 (0.79, 1.17)	1.06 (0.85, 1.33)
PCB-153	0.90 (0.73, 1.11)	1.09 (0.88, 1.35)
PCB-156	0.84 (0.68, 1.05)	1.02 (0.80, 1.31)
PCB-170	0.80 (0.63, 1.01)	0.98 (0.75, 1.27)
PCB-180	0.77 (0.61, 0.98)	0.94 (0.71, 1.24)
PCB-183	0.93 (0.77, 1.13)	0.90 (0.66, 1.23)
PCB-187	0.83 (0.64, 1.06)	0.87 (0.64, 1.19)

551 Notes:
 552 *Fully adjusted models were adjusted for age (time scale), sex, waist circumference, family
 553 history of diabetes, smoking, physical activity, education, living with a partner, HDL-
 554 cholesterol, triglycerides, hypertension and calorie intake.
 555

Table 4

Hazard ratios (95% confidence intervals) for the relationship between summed persistent organic pesticides (POPs) and 9 year incident diabetes. The French D.E.S.I.R study (n=753).

Persistent organic pollutants	Adjusted hazard ratios (95% CI) for the summed POPs	
	Total Population n=753	
Sum of PCBs* (per log)	0.66 (0.35 –1.23)	
Sum of OC POPs† (per log)	1.00 (0.72–1.41)	

Notes:

Models adjusted for age (time scale), sex, waist circumference, family history of diabetes, smoking, physical activity, education, living with a partner, HDL-cholesterol, triglycerides, hypertension and calorie intake.

* Sum of PCB74, 99, 118, 138, 153, 156, 170, 180, 183, 187 concentrations.

† Sum of PeCB, HCB, β -HCH, γ -HCH, Trans-nonachlor, Oxychlorane, (*p*, *p*'-DDT) and (*p*, *p*'-DDE) concentrations.

Table 5

Hazard ratios (95% confidence intervals) for the relationship between persistent organic pollutants (POPs) (per interquartile range (IQR) in log-transformed POPs) and 9 year incident diabetes. The French D.E.S.I.R study (n=753).

Persistent organic pollutants	Age-adjusted hazard ratios (95% CI)		Multi-adjusted hazard ratios (95% CI)	
PeCB	0.93	(0.84, 1.04)	0.96	(0.85, 1.10)
HCB	1.66	(1.28, 2.14)	1.07	(0.75, 1.52)
β -HCH	1.25	(1.03, 1.53)	1.13	(0.88, 1.46)
γ -HCH	1.45	(1.16, 1.81)	0.88	(0.65, 1.19)
Oxychlordane	1.45	(1.14, 1.84)	0.74	(0.52, 1.04)
<i>Trans</i> -nonachlor	1.22	(1.02, 1.45)	0.94	(0.74, 1.19)
<i>p, p'</i> -DDT	1.25	(1.00, 1.56)	1.01	(0.76, 1.34)
<i>p, p'</i> -DDE	0.93	(0.74, 1.17)	0.83	(0.62, 1.11)
PCB-74	1.22	(0.97, 1.52)	0.93	(0.72, 1.20)
PCB-99	1.21	(0.94, 1.56)	0.94	(0.69, 1.27)
PCB-118	1.12	(0.91, 1.38)	0.88	(0.68, 1.13)
PCB-138	0.98	(0.78, 1.24)	0.82	(0.62, 1.10)
PCB-153	0.86	(0.66, 1.11)	0.76	(0.55, 1.06)
PCB-156	0.89	(0.69, 1.15)	0.76	(0.53, 1.10)
PCB-170	0.81	(0.63, 1.05)	0.75	(0.52, 1.08)
PCB-180	1.11	(0.89, 1.38)	0.92	(0.71, 1.21)
PCB-183	1.10	(0.85, 1.43)	0.87	(0.64, 1.18)
PCB-187	0.93	(0.84, 1.04)	0.96	(0.85, 1.10)

Notes: Models adjusted for age (time scale), sex, waist circumference, family history of diabetes, smoking, physical activity education, living with a partner, HDL- cholesterol, triglycerides, hypertension and calorie intake.

Supplementary Table S1

Spearman correlations coefficients between pre-adjusted Persistent organic pollutants in the subcohort population, n=583: the French D.E.S.I.R. Study. Statistically significant correlation coefficients are shown in bold text.

	PeCB	HCB	β -HCH	γ -HCH	Oxychlordane	Trans nonachlor	p, p'		PCB										
							DDT	DDE	74	99	118	153	138	156	187	183	180		
PeCB	1																		
HCB	0.39	1																	
β -HCH	0.27	0.71	1																
γ -HCH	0.31	0.04	0.18	1															
Oxychlordane	0.29	0.68	0.69	0.08	1														
Trans-nonachlor	0.24	0.53	0.52	0.05	0.79	1													
p, p' -DDT	0.28	0.31	0.27	0.16	0.22	0.32	1												
p, p' -DDE	0.24	0.44	0.42	0.08	0.33	0.38	0.60	1											
PCB-74	0.28	0.61	0.57	0.07	0.58	0.47	0.28	0.41	1										
PCB-99	0.25	0.46	0.41	0.06	0.44	0.44	0.37	0.61	0.67	1									
PCB-118	0.24	0.48	0.45	0.03	0.43	0.44	0.33	0.43	0.76	0.72	1								
PCB-153	0.27	0.55	0.50	0.04	0.59	0.59	0.30	0.54	0.64	0.79	0.65	1							
PCB-138	0.25	0.53	0.50	0.04	0.56	0.56	0.34	0.60	0.64	0.88	0.68	0.96	1						
PCB-156	0.30	0.56	0.53	0.04	0.65	0.57	0.16	0.29	0.62	0.54	0.52	0.86	0.77	1					
PCB-187	0.22	0.42	0.35	0.04	0.43	0.57	0.30	0.41	0.49	0.61	0.53	0.83	0.79	0.75	1.				
PCB-183	0.24	0.49	0.41	0.04	0.46	0.51	0.36	0.59	0.54	0.82	0.58	0.88	0.90	0.63	0.79	1.			
PCB-180	0.22	0.45	0.42	0.04	0.55	0.54	0.16	0.29	0.46	0.47	0.41	0.86	0.75	0.88	0.79	0.71	1		
PCB-170	0.23	0.49	0.45	0.05	0.58	0.55	0.18	0.29	0.49	0.49	0.42	0.86	0.76	0.90	0.80	0.74	0.98		