A prospective European study on persistent pollutants and pancreatic cancer risk

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COLUMBIA | MAILMAN SCHOOL OF PUBLIC HEALTH

New York,
6 November 2019

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Methodological issues and results from a prospective European study on persistent organic pollutants and pancreatic cancer risk.

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NYU Langone Health · EPIDEMIOLOGY SEMINAR SERIES · DEPARTMENT OF POPULATION HEALTH · CENTER FOR THE INVESTIGATION OF ENVIRONMENTAL HAZARDS

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Seminars at UNC, NYU, Harvard, Columbia ⇝ October and November, 2019.

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Boston,
16 October 2019

IMIM Institut de Recerca Hospital del Mar · Parc de Salut MAR Barcelona · PRBB Parc Recerca Biomèdica Barcelona · ciberesp Centro de Investigación Biomédica en red Epidemiología y Salud Pública · UAB Universitat Autònoma de Barcelona Facultat de Medicina

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UNC Chapel Hill
8 October 2019

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- What do we know about the causes of pancreatic cancer?

- Is such knowledge helpful
  - for primary prevention?
  - to understand mechanisms?
  - to ...?

Environmental Research (2019)

Methodological issues in a prospective study on plasma concentrations of persistent organic pollutants and pancreatic cancer risk within the EPIC cohort

Magda Gasull[a,b,c,1], José Pumarega[a,c,1], Hannu Kiviranta[d], Panu Rantakokko[d], Ole Raaschou-Nielsen[e], Ingvar A. Bergdahl[f,g], Torkjel Manning Sandanger[h], Fernando Goñi[c,i], Lluís Cirera[c,j], Carolina Donat-Vargas[k], Juan Alguacil[c,l], Mar Iglesias[m], Anne Tjønneland[e], Kim Overvad[n], Francesca Romana Mancini[o,p], Marie-Christine Boutron-Ruault[o,p], Gianluca Severi[o,p], Theron Johnson[q], Tilman Kühn[a], Antonia Trichopoulou[r], Anna Karakatsani[r], Eleni Peppa[r], Domenico Palli[i], Valeria Pala[u], Rosario Tumino[v], Alessio Naccarati[w], Salvatore Panico[x], Monique Verschuren[y], Roel Vermeulen[z], Charlotta Rylander[h], Therese Haugdahl Nøst[h], Miguel Rodríguez-Barranco[c,aa], Amaia Molinuevo[c,i], María-Dolores Chirlaque[c,j,ab], Eva Ardanaz[c,ac,ad], Malin Sund[ae], Tim Key[af], Weimin Ye[f,ag], Mazda Jenab[ah], Dominique Michaud[ai], Giuseppe Matullo[aj], Federico Canzian[ak], Rudolf Kaaks[q], Alexandra Nieters[al], Ute Nöthlings[am], Suzanne Jeurnink[an,ao], Veronique Chajes[ah], Marco Matejcic[ah], Marc Gunter[ah], Dagfinn Aune[ai], Elio Riboli[ai], Antoni Agudo[ap], Carlos Alberto Gonzalez[ap], Elisabete Weiderpass[h,ag,aq,ar], Bas Bueno-de-Mesquita[ai,ao,as], Eric J. Duell[ap], Paolo Vineis[w,ai], Miquel Porta[a,b,c,*]

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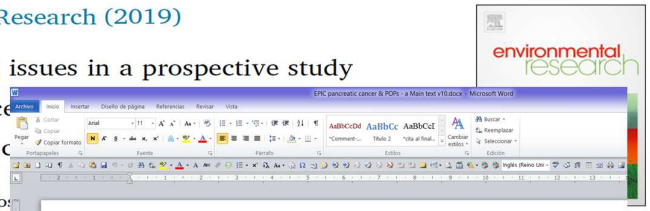
- What do we know about the causes of pancreatic cancer?

- Too little.

→ There's little we can do to prevent it.

Environmental Research (2019)

Methodological issues in a prospective study on plasma conce and pancreatic c



Magda Gasull[a,b,c,1], Jos
Ole Raaschou-Nielsen[e]
Lluís Cirera[c,j], Carolina
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Gianluca Severi[o,p], The
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Salvatore Panico[x], Mon
Therese Haugdahl Nøs
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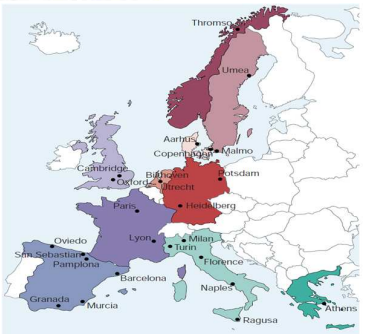
Mazda Jenab[ah], Domir
Alexandra Nieters[al], Ut
Marco Matejcic[ah], Mar
Carlos Alberto Gonzale
Eric J. Duell[ap], Paolo Vineis[w,ai], Miquel Porta[a,b,c,*]

Findings Median concentrations of the 22 POPs were similar in cases and controls. However, some, generally modest effects were seen at higher concentrations of *p,p'*-DDT, trans-nonachlor, β-HCH, and for the sum of orders of the 6 organochlorine pesticides and of the 16 POPs. The OR for the upper quartile of trans-nonachlor was 1.55 (CI: 1.06, 2.26; p for trend = 0.025). Associations were stronger in the most valid or relevant stratum of fasting (>6 hours), diagnostic basis (microscopic confirmation), BMI (normal weight), interval between blood extraction and cancer diagnosis (≥10 years), and smoking (never smokers). The OR for the upper quartile of the sum of orders of the 16 POPs among subjects with an interval ≥10 years was 3.00 (CI: 1.39, 6.46; p for trend = 0.016).

Conclusions Individually or in combination, the 22 POPs analysed did not or only modestly increased the risk of exocrine pancreatic cancer. While the study overcame some weaknesses of previous reports, several study findings and limitations warrant conducting additional, more complex research.

- → Cohort of >520,000 participants healthy when enrolled in 1992 - 2000
- → 10 European countries (23 centres): Denmark, Sweden, Germany, UK, Italy, Netherlands, Spain, Greece, France, Norway
- → More than 25 years of follow-up
- → Biobank: 4 million samples

Bingham S, Riboli E
MARCH 2004
NATURE REVIEWS | CANCER



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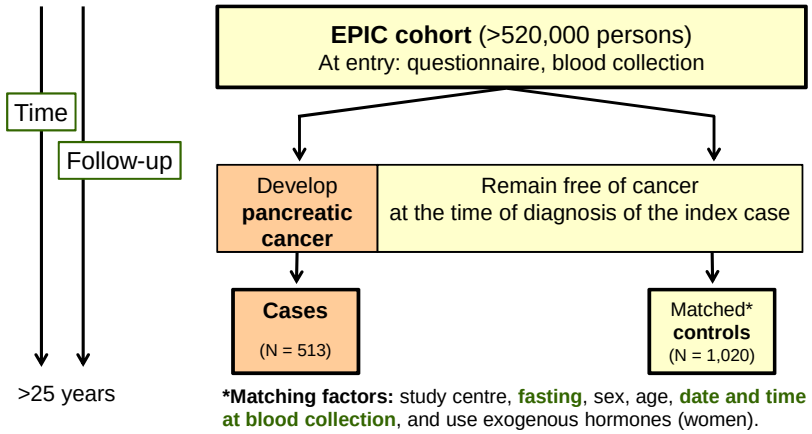
Crude concentrations expressed in pg/mL (parts per trillion, ppt).

10 polychlorinated biphenyls (PCBs):
8 non-dioxin like (congeners 74, 99, 138, 153, 170, 180, 183, and 187), and
2 dioxin like PCBs (congeners 118 and 156).

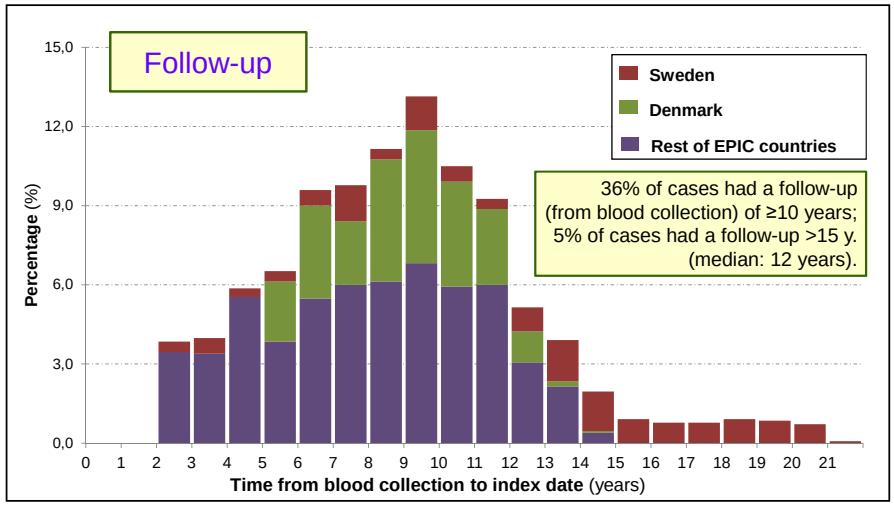
For the 6 most prevalent organochlorine (OC) pesticides (p,p'-DDT, p,p'-DDE, oxychlordane, trans-nonachlor, HCB, and β-HCH), the sum of orders was computed by categorizing each POP in quartiles and adding the category number, thus producing a value ranging between 6 and 24.

For all 16 persistent organic pollutants (POPs) (the POPs most prevalent in the study subjects, quantified in >90% of subjects), the sum of orders was computed by categorizing each POP in quartiles and then adding the category number, thus producing a value ranging between 16 and 64.

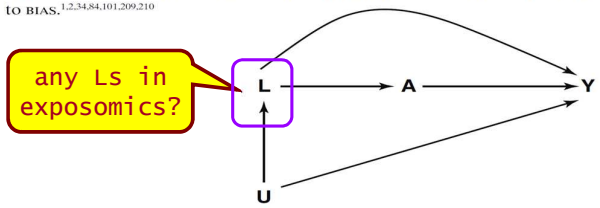
prospective, cohort-nested case-control study (N = 1,533)



***Matching factors:** study centre, **fasting**, sex, age, **date and time at blood collection**, and use exogenous hormones (women).



CAUSAL DIAGRAM (Syn: causal graph, path diagram) A graphical display of causal relations among variables, in which each variable is assigned a fixed location on the graph (called a *node*), and in which each direct causal effect of one variable on another is represented by an arrow with its tail at the cause and its head at the effect.[100] Direct noncausal associations are usually represented by lines without arrowheads. Graphs with only directed arrows (in which all direct associations are causal) are called *directed graphs*. Graphs in which no variable can affect itself (no feedback loop) are called *acyclic*. Methods have been developed to determine from causal diagrams which sets of variables are sufficient to control CONFOUNDING and for when control of variables leads to BIAS.[1,2,34,84,101,209,210]



Causal diagram representing outcome Y, exposure A, their unmeasured common cause U, and risk factor L. Graph theory can be used to show that data on L are sufficient to eliminate the confounding, caused by the presence of U, for the effect of A on Y.

Porta M++, ed. A dictionary of epidemiology. 6th. edition (2014).

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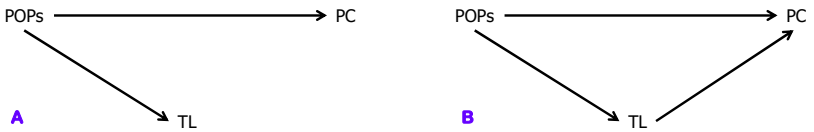
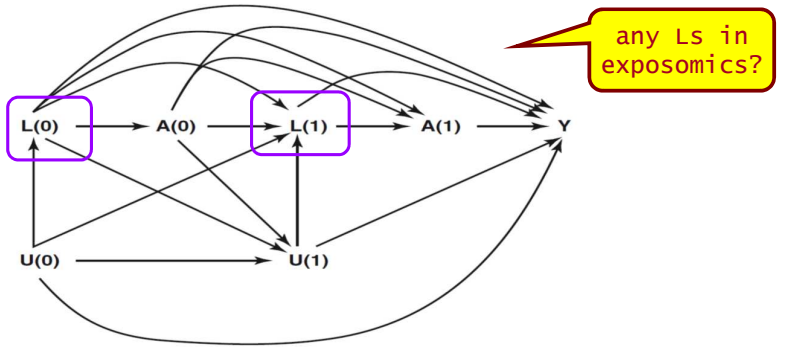


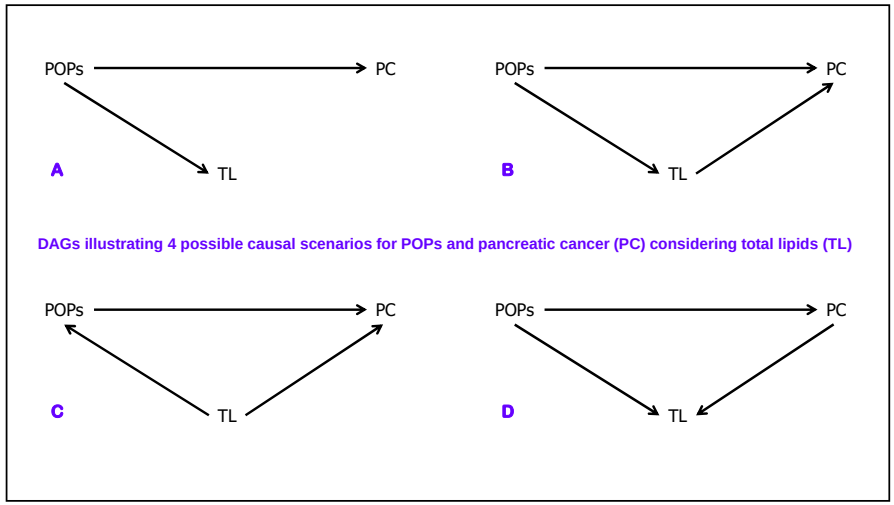
DAGs illustrating 4 possible causal scenarios for POPs and pancreatic cancer (PC) considering total lipids (TL)

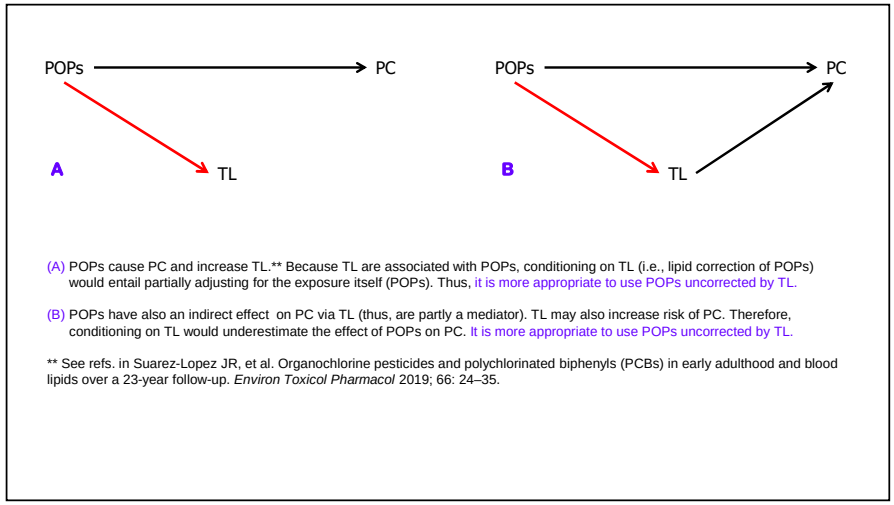
- ✓ Geneletti SG, Gallo V, Porta M, Khoury MJ, Vineis P. Assessing causal relationships in genomics: From Bradford-Hill criteria to complex gene-environment interactions and directed acyclic graphs. *Emerging Themes in Epidemiology* 2011; 8: 5. http://www.ete-online.com/content/8/1/5.
- ✓ Porta M. The deconstruction of paradoxes and a methodological revolution in clinical and epidemiological research. OUPblog (Oxford University Press Blog). 17 October 2014. http://blog.oup.com/2014/10/deconstruction-paradoxes-sociology-epidemiology/
- ✓ Porta M, Vineis P, Bolúmar F. The current deconstruction of paradoxes: One sign of the ongoing methodological "revolution". *European Journal of Epidemiology* 2015 and *European Journal of Epidemiology* 2015.
- ✓ Lee DH, Porta M, Lind L, Lind PM, Jacobs DR Jr. Neurotoxic chemicals in adipose tissue: a role in puzzling findings on obesity and dementia. *Neurology* 2018.
- ✓ Suarez-Lopez JR, et al. Organochlorine pesticides and polychlorinated biphenyls (PCBs) in early adulthood and blood lipids over a 23-year follow-up. *Environ Toxicol Pharmacol* 2019.



Causal diagram representing outcome Y and time-varying exposure A(t), their unmeasured common cause U(t), and risk factor L(t) at times t = 0 and t = 1. Graph theory can be used to show that data on L(0) and L(1) are sufficient to eliminate the confounding, caused by the presence of U(0) and U(1), for the joint effect of A(0) and A(1) on Y.

Porta M++, ed. A dictionary of epidemiology. 6th. edition (2014).

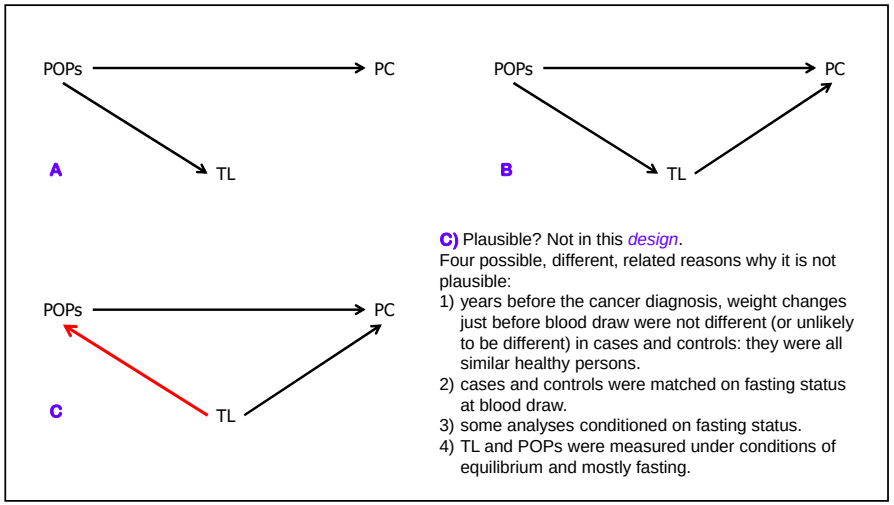




(A) POPs cause PC and increase TL.** Because TL are associated with POPs, conditioning on TL (i.e., lipid correction of POPs) would entail partially adjusting for the exposure itself (POPs). Thus, it is more appropriate to use POPs uncorrected by TL.

(B) POPs have also an indirect effect on PC via TL (thus, are partly a mediator). TL may also increase risk of PC. Therefore, conditioning on TL would underestimate the effect of POPs on PC. It is more appropriate to use POPs uncorrected by TL.

** See refs. in Suarez-Lopez JR, et al. Organochlorine pesticides and polychlorinated biphenyls (PCBs) in early adulthood and blood lipids over a 23-year follow-up. *Environ Toxicol Pharmacol* 2019; 66: 24–35.



C) Plausible? Not in this *design*.
Four possible, different, related reasons why it is not plausible:

1) years before the cancer diagnosis, weight changes just before blood draw were not different (or unlikely to be different) in cases and controls: they were all similar healthy persons.
2) cases and controls were matched on fasting status at blood draw.
3) some analyses conditioned on fasting status.
4) TL and POPs were measured under conditions of equilibrium and mostly fasting.

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Quartile cutoff points: based on the distribution of concentrations in controls.

Base models from conditional (matched) logistic regression.

Matching factors: center, sex, age at blood collection, **date and time at blood collection, fasting status**, and, for women, use of exogenous hormones.

Wald's test applied when no linear trend was apparent.
Test for linear trend (multivariate analogue of Mantel's extension test).

Level of statistical significance set at 0.05 and all tests were two tailed.
"Both the magnitude of effects and their statistical significance were autonomously assessed." →Amrhein V, Greenland S, McShane B, et al. Scientists rise up against statistical significance. *Nature* 2019; 567: 305–7.

Plasma concentrations of persistent organic pollutants (POPs) among cases and controls.

Compounds	Cases (N = 513)	Controls (N = 1020)	P[a]
***p,p'*-DDT**	90.9 (49.7 - 160.5)	82.2 (46.5 - 170.2)	0.219
***p,p'*-DDE**	3590.3 (1870.2 - 6914.2)	3255.6 (1695.9 - 6623.6)	0.126
Oxychlordane	55.7 (38.9 - 85.2)	55.0 (36.8 - 81.4)	0.199
Trans-nonachlor	77.0 (50.1 - 125.2)	72.1 (46.6 - 118.9)	0.080
Hexachlorobenze	405.2 (263.5 - 746.3)	389.1 (247.5 - 807.1)	0.535
β-hexachlorocyclohexane	373.7 (200.7 - 689.3)	332.9 (200.5 - 658.6)	0.361
PCB 99	73.7 (46.0 - 110.9)	69.6 (45.9 - 105.8)	0.387
PCB 138	641.8 (438.3 - 945.0)	632.3 (424.5 - 924.9)	0.450
PCB 183	77.5 (51.4 - 115.8)	75.1 (48.7 - 111.9)	0.424
Sum of all 10 PCBs[b]	3631.6 (2485.2 - 5011.5)	3571.0 (2496.6 - 4946.1)	0.711
Sum of 4 PCBs[c]	2676.5 (1851.0 - 3720.1)	2645.0 (1835.1 - 3698.1)	0.709
Sum of orders, 6 OC pesticides[d]	16 (12 - 19)	15 (11 - 19)	0.105
Sum of orders, 16 POPs[d]	41 (31 - 51)	40 (29 - 51)	0.380
Number of POPs at high concentr.	3 (0 - 7)	2 (0 - 7)	0.363

Crude concentrations expressed in median (and percentile 25 - percentile 75), pg/mL (parts per trillion, ppt).

Baseline characteristics of cases and controls, 1.

Characteristics	Cases (N = 513)	Controls (N = 1,020)	p-value[1]
Sex (%)			
Men	48.7	48.6	Matched
Women	51.3	51.4	
Age at blood collection (years)			
Median	57.6	57.7	Matched
Body mass index (kg/m²) (%)			
Normal weight	39.3	41.2	0.773
Overweight	43.7	42.6	
Obese	16.2	15.4	

[1] Fisher's exact test (two-tailed).

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Baseline characteristics of cases and controls, 2.

Characteristics (%)	Cases (N = 513)	Controls (N = 1,020)	p-value[1]
Smoking			
Never	40.8	**43.8**	<0.001
Former	26.7	33.3	
Current	**32.5**	22.9	
Alcohol intake at recruitment			
Never and former drinkers	8.8	9.4	0.930
0 – 6 g alcohol/day	38.6	39.6	
6 – 18 g alcohol/day	24.5	23.4	
More than 18 g alcohol/day	28.2	27.5	
Physical activity			
Active	7.1	8.4	0.884
Moderately active	47.3	46.1	
Moderately inactive	28.5	28.6	
Inactive	17.1	16.9	
Diabetes mellitus			
No	93.7	96.7	0.011
Yes	**6.3**	**3.3**	

[1] Fisher's exact test (two-tailed).

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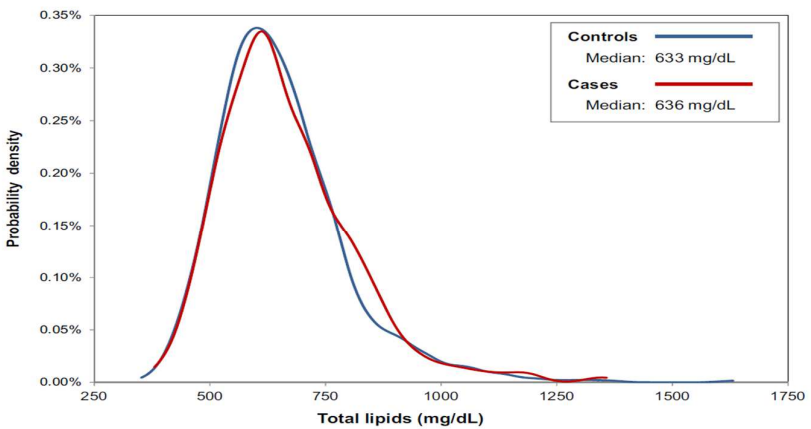

Fig. 2. Distribution of plasma concentrations of total lipids (mg/dL) by case-control status (N = 1533).

Methodological issues in a prospective study on plasma concentrations of persistent organic pollutants and pancreatic cancer risk within the EPIC cohort

Environmental Research 169 (2019)

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Background: The use of biomarkers of environmental exposure to explore new risk factors for pancreatic cancer presents clinical, logistic, and methodological challenges that are also relevant in research on other complex diseases.

Methods: Study subjects were 1533 participants (513 cases and 1020 controls matched by study centre, sex, age at blood collection, date and time of blood collection, and fasting status) enrolled between 1992 and 2000. Plasma concentrations of 22 POPs were measured by gas chromatography - triple quadrupole mass spectrometry

Diagnostic basis and **diagnostic certainty:**
Microscopic confirmation vs. **Clinical** diagnosis

Microscopic confirmation
was significantly less likely with increasing age
more likely with increasing education (statistically non-significant).

No differences in diagnostic basis
by sex, BMI, smoking, alcohol intake, and physical activity (adjusted models).

No differences in POP and TL concentrations by diagnostic basis.

Remember that **misclassification of disease status is often differential**;
e.g., related to confounders and exposures of interest.

- Porta M et al. Integrative research, '-omics' research ... J Clin Epidemiol 2007.
- Porta M. In: Von Hoff DD, et al, eds. *Pancreatic cancer.* Boston: Jones & Bartlett, 2005.

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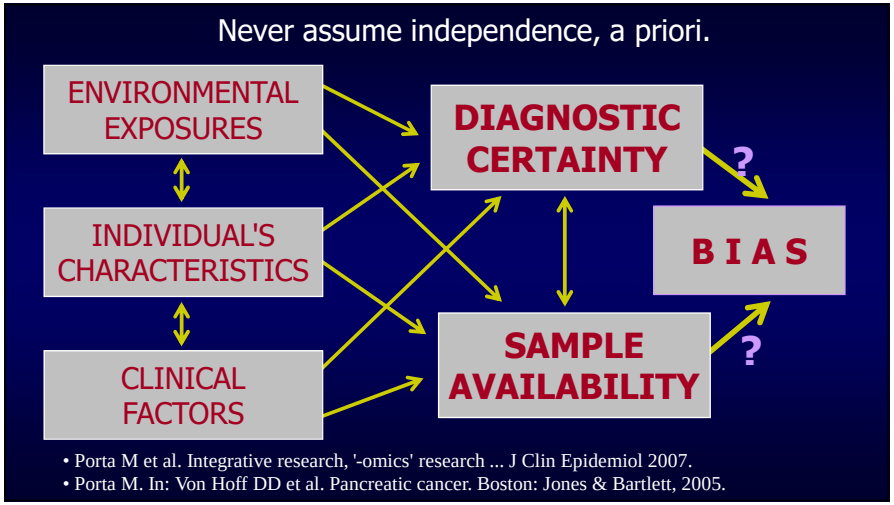
There were **differences among countries / study centers:**

for **subjects' characteristics**
(as age, gender, smoking, lipid and POP concentrations),
and
for **study characteristics** (as time from blood collection to index date, year of last follow-up, length of follow-up, basis of cancer diagnosis, fasting status).

→ Should the relationship between subjects' and study center characteristics more often be addressed (and published) in multicenter studies?



Fasting status at blood collection at entry into the cohort

Fasting >6 hours (30% of cases and controls)
– more likely when sample was collected in early morning.
– differences by study center; e.g., in Sweden >93% had fastened >6 hours.

Fasting 3-6 h: (20%). Non-fasting: 50%.

No differences by sex, age, BMI, smoking, alcohol intake, and physical activity in adjusted models.

No differences by case-control status (matching factor).

Fasting <6 hours was related to higher concentrations of triglycerides & total lipids.
participants with <3 hours of fasting: TL (aGM): 654 mg/dL
participants with >6 hours of fasting: TL (aGM): 616 mg/dL.
Fasting was not associated with total cholesterol.

Participants' characteristics → Total lipids

Age, BMI, country, smoking, and fasting were → related to Total Lipids.

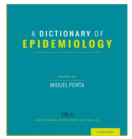
No differences in TL by sex, alcohol intake, and physical activity.

No differences in TL by case-control status (also in adjusted models).

Remember: fasting was a matching factor.

DISEASE PROGRESSION BIAS

2. In etiologic studies, biases that occur when disease progression entails metabolic or other pathophysiologic changes that alter the characteristics or concentrations (e.g., in blood, adipose tissue, target organs, peritumoral tissue) of the study exposure BIOMARKERS. Biomarkers of exposure collected during subclinical or overt disease will then not reflect exposures of true etiologic significance that took place in more distant time windows, and may hence cause REVERSE CAUSATION; e.g., lower blood concentrations of certain vitamins may not actually increase the risk of a disease, but be a consequence of the (subclinical) disease. Similarly, during the progression of some cancers, long before clinical diagnosis, blood concentrations of lipophilic substances of putative etiologic interest (e.g., lipophilic vitamins, organochlorine compounds) may be increased or decreased due to pathophysiologic changes associated with cancer-induced weight loss, cholestasis, or lipid mobilization.[146] See also PATHOPHYSIOLOGY.



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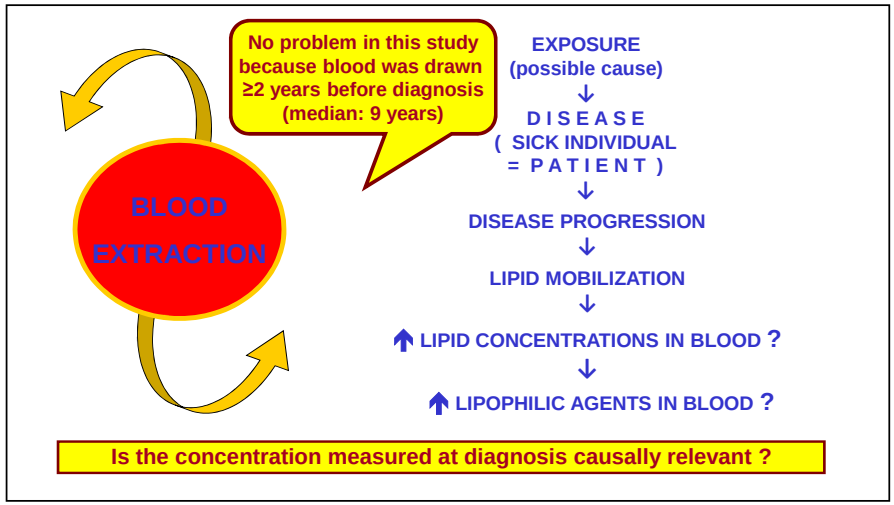
Rationale

- Tumor-induced lipid mobilization, weight loss and metabolic changes can be profound before diagnosis.

→ Do the POP concentrations in blood (at diagnosis or close to diagnosis) partly result from such pathophysiologic changes?

→ The [POP] that we measure at diagnosis, are a cause or a consequence of the cancer?

Porta M et al. Epidemiology 2001, Eur J Epidem 2007, J Clin Epidemiol 2008, Cancer Causes & Control 2009...



We assessed the possible occurrence of disease progression bias (DPB) in 8 situations defined by

1) concentrations of lipids and 2) POPs at baseline, on one hand,

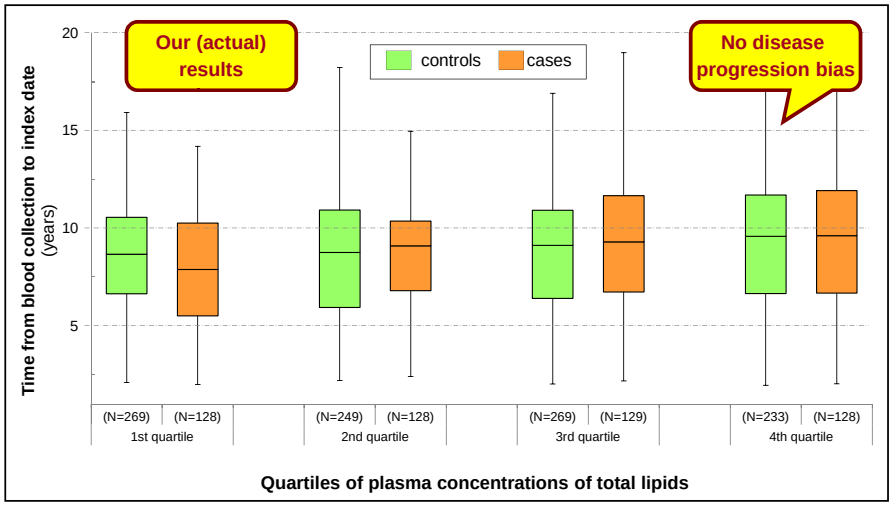
and by 4 factors:

– interval from blood draw to index date,

– tumour site, – tumour stage, and – grade of differentiation.

In 7 of the 8 situations results argued against the occurrence of DPB.
In 0 of the 8 situations results argued in favor of the occurrence of DPB.
One was inconclusive.

Further details also in Gasull M et al. *Environmental Research* 2019.



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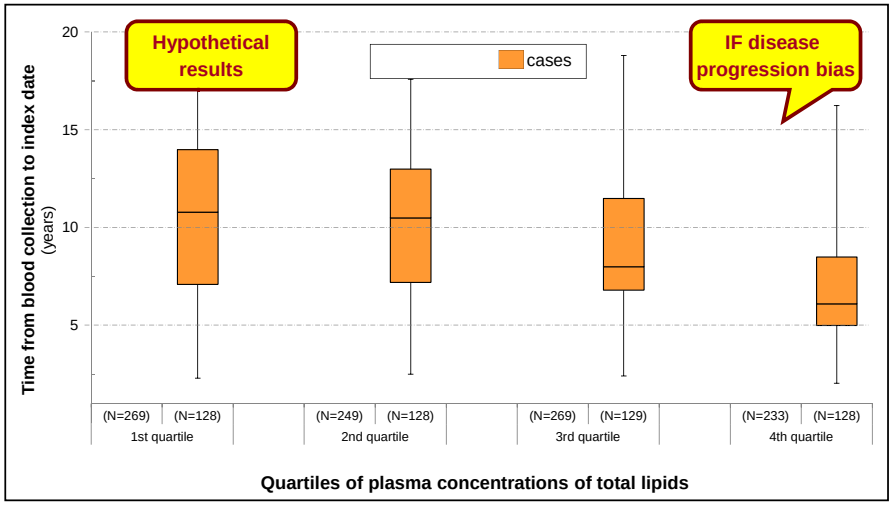

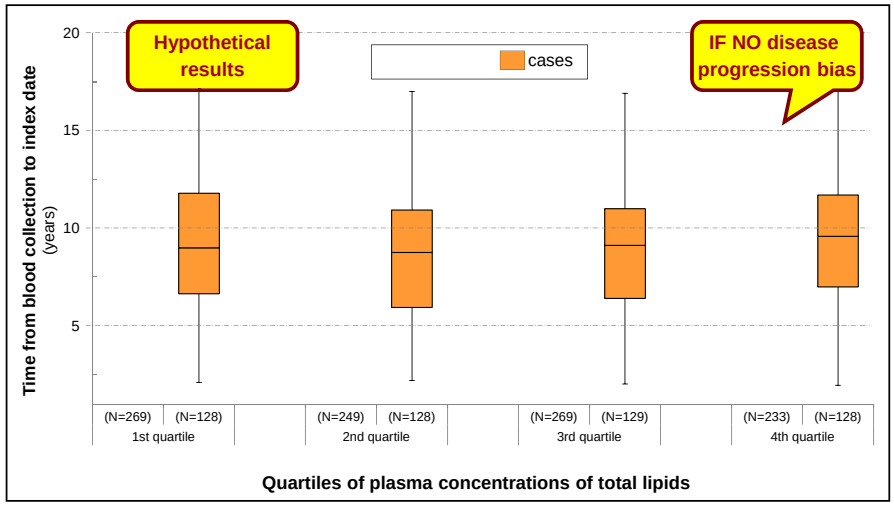

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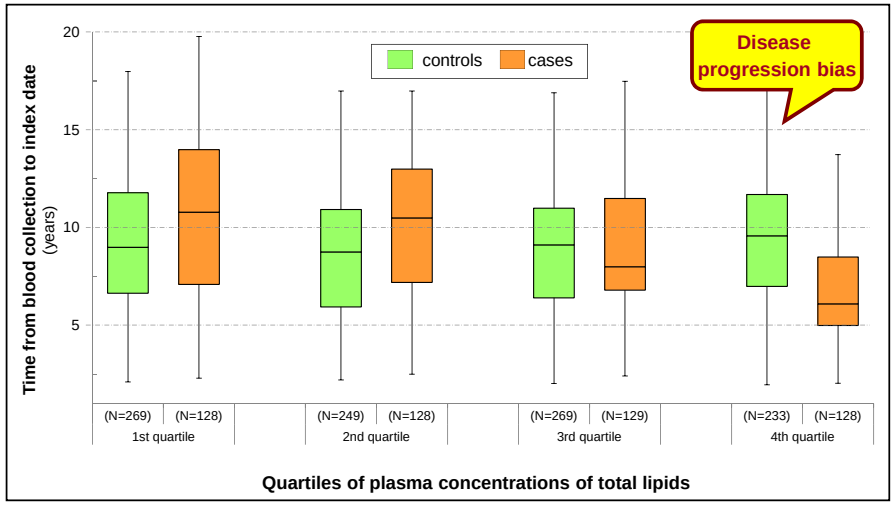

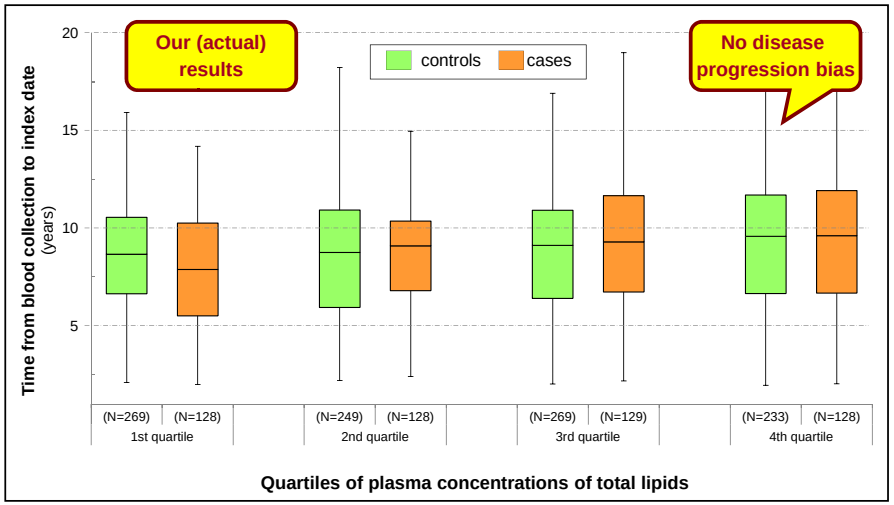

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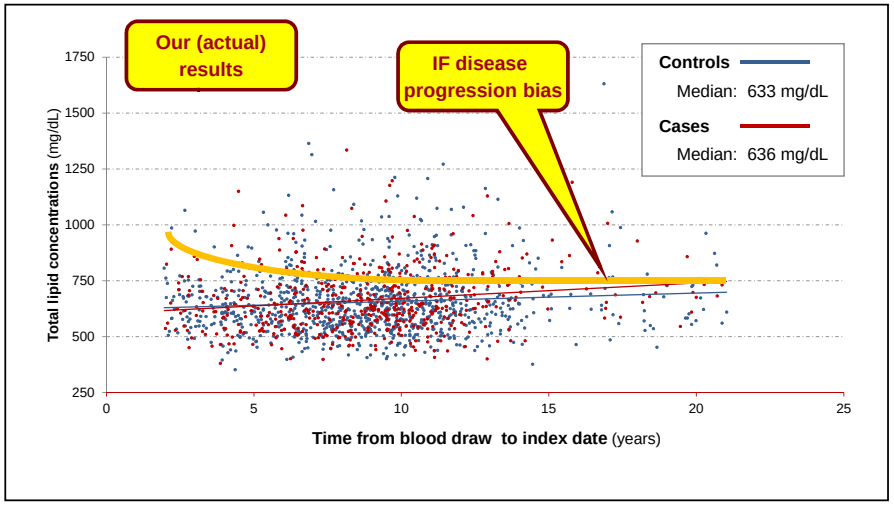

Association between total lipid concentrations of pancreatic cancer cases and time from blood collection to cancer diagnosis (years)

		Time from blood draw to diagnosis		
	%	aGM	(95% CI)	*p*-value
Total lipids (mg/dL)				
<565.0	25.5	7.4	(6.8-8.0)	
565.0-635.7	24.8	8.3	(7.7-8.9)	0.036
635.8-733.0	25.5	8.6	(8.0-9.3)	0.005
≥733.0	24.2	8.5	(7.9-9.2)	0.012

aGM: Geometric mean of the time from blood collection to the diagnosis of pancreatic cancer adjusted for age, sex, body mass index, smoking, centre and fasting status.

No disease progression bias

Detection and quantification of all POPs analyzed (N = 1,533)

→ **We detected all 22 POPs analyzed.**

→ **16 of the 22 POPs were detected in >90% of subjects.**

→ **No individual was free from POPs :**
smallest number of POPs detected in one person = 15 .

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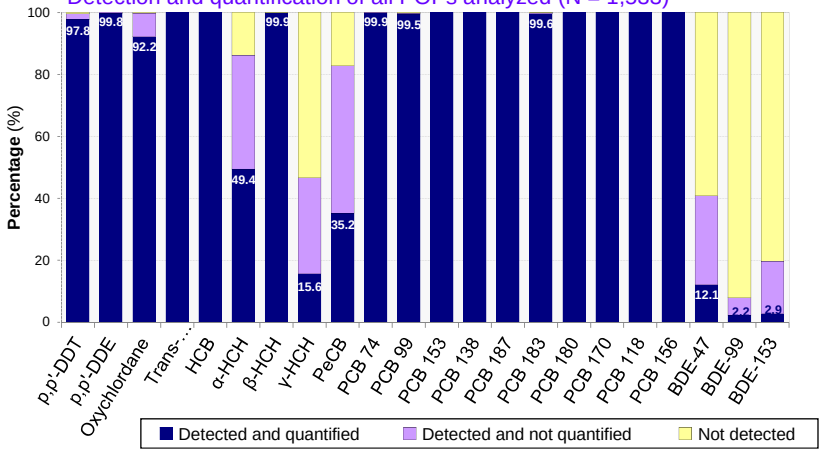
Guidelines and Guidance

STrengthening the Reporting of OBservational studies in Epidemiology – Molecular Epidemiology (STROBE-ME): An Extension of the STROBE Statement

Valentina Gallo[1,2*], Matthias Egger[3], Valerie McCormack[4], Peter B. Farmer[5], John P. A. Ioannidis[6,7], Micheline Kirsch-Volders[8], Giuseppe Matullo[9,10], David H. Phillips[11], Bernadette Schoket[12], Ulf Stromberg[13], Roel Vermeulen[14], Christopher Wild[4], Miquel Porta[15], Paolo Vineis[9,16]

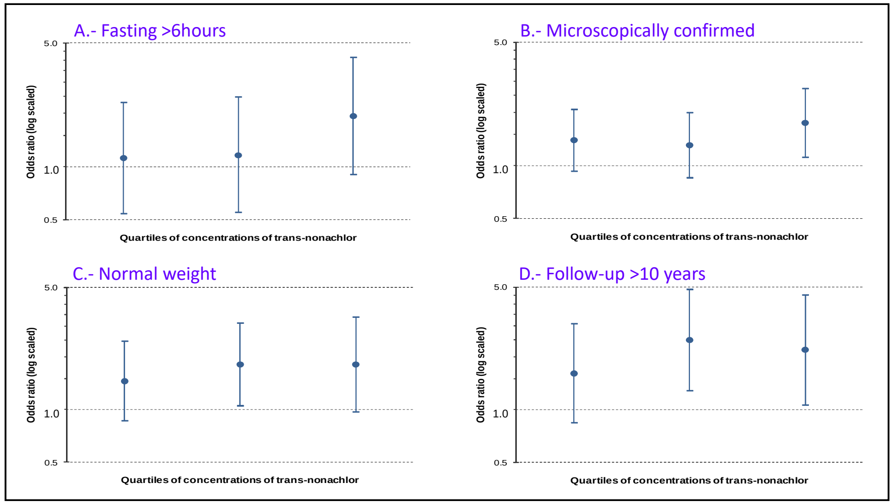
- Specific additions relate to the collection, handling and storage of biological samples; laboratory methods, validity and reliability of biomarkers; specificities of study design; and ethical considerations.
- A checklist to help authors in reporting biomarker studies is published as supporting information (Table S1).

Detection and quantification of all POPs analyzed (N = 1,533)



Detection and quantification of all POPs analyzed (N = 1,533)

- The highest concentrations were found for p,p'-DDE, PCBs 153 & 180: median = 3371, 1023, and 810 pg/mL, respectively.
- Differences in [POP] were found by age, sex, and body mass index.
  - Higher [POP] with increasing age
  - Women: higher concentrations of HCB and β-HCH
    Men: higher concentrations of trans-nonachlor and PCBs
  - Higher [POP] with increasing BMI, except for PCBs
- Subjects from some countries had higher concentrations of some compounds (e.g., DDT, HCB, β-HCH and PCBs 183 or 187) than subjects from other countries.



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Risk of pancreatic cancer according to quartiles of POP concentrations.*

	Model 1 OR (95% CI)	Model 1 P[a]	Model 2 OR (95% CI)	Model 2 P[a]	Model 3 OR (95% CI)	Model 3 P[a]
p,p'-DDT						
1st quartile	1.00	0.029	1.00	0.037	1.00	0.909
2nd quartile	1.11 (0.80-1.53)		1.06 (0.77-1.48)		1.09 (0.79-1.52)	
3rd quartile	1.57 (1.12-2.19)		1.46 (1.04-2.06)		1.14 (0.80-1.62)	
4th quartile	1.12 (0.74-1.70)		0.97 (0.62-1.50)		1.09 (0.69-1.73)	
Trans-nonachlor						
1st quartile	1.00	0.025[b]	1.00	0.038[b]	1.00	0.110[b]
2nd quartile	1.27 (0.91-1.76)		1.32 (0.94-1.85)		1.12 (0.80-1.58)	

Model 1: crude POP concentrations. N = 1533 (513 cases, 1020 controls).
Model 2: crude POP concentrations; further adjusted for BMI. N = 1493 (501 cases, 992 controls).
Model 3: POP concentrations individually corrected by total lipids; further adjusted for BMI and smoking. N = 1464 (493, 971).

	Model 1 OR (95% CI)	Model 1 P[a]	Model 2 OR (95% CI)	Model 2 P[a]	Model 3 OR (95% CI)	Model 3 P[a]
Sum of orders, 6 OC pesticides						
1st quartile	1.00	0.045[b]	1.00	0.110[b]	1.00	0.680
2nd quartile	1.29 (0.92-1.79)		1.21 (0.86-1.70)		1.19 (0.87-1.64)	
3rd quartile	1.56 (1.08-2.27)		1.47 (1.00-2.16)		1.09 (0.75-1.58)	
4th quartile	1.48 (1.00-2.20)		1.37 (0.91-2.07)		1.20 (0.81-1.78)	
Sum of orders, 16 POPs						
1st quartile	1.00	0.034	1.00	0.031	1.00	0.254
2nd quartile	1.49 (1.06-2.09)		1.49 (1.05-2.11)		1.38 (0.98-1.93)	

Model 1: crude POP concentrations. N = 1533 (513 cases, 1020 controls).
Model 2: crude POP concentrations; further adjusted for BMI. N = 1493 (501 cases, 992 controls).
Model 3: POP concentrations individually corrected by total lipids; further adjusted for BMI and smoking. N = 1464 (493, 971).

	Fasting >6 hours[1,a]			Microscopic confirmation[1,b]		
	OR	(95% CI)	P[e]	OR	(95% CI)	P[e]
p,p'-DDT						
1st quartile	1.00		0.204	1.00		0.074
2nd quartile	1.06	(0.55-2.03)		1.15	(0.80-1.67)	
3rd quartile	1.81	(0.93-3.53)		1.57	(1.06-2.33)	
4th quartile	1.23	(0.52-2.91)		1.04	(0.62-1.73)	
p,p'-DDE						
1st quartile	1.00		0.012[f]	1.00		0.177[f]
2nd quartile	0.98	(0.46-2.07)		1.05	(0.73-1.51)	
3rd quartile	1.85	(0.94-3.63)		1.22	(0.84-1.79)	
4th quartile	2.23	(1.02-4.88)		1.31	(0.84-2.03)	
Oxychlordane						
1st quartile	1.00		0.072	1.00		0.192
2nd quartile	1.51	(0.77-2.94)		1.37	(0.94-1.99)	
3rd quartile	0.88	(0.41-1.87)		1.14	(0.76-1.71)	
4th quartile	1.78	(0.84-3.81)		1.50	(0.97-2.31)	

Crude POP concentrations.

[1] Conditional logistic regression and further adjusted for BMI.

Matching factors: study centre, fasting, sex, age, date and time at blood collection, and exogenous hormones (women).

[a] N = 430 (150 cases-280 controls).

[b] N = 1110 (372 cases-738 controls).

	Normal weight[2,c]			Interval ≥10 years[1,d]		
	OR	(95% CI)	P[e]	OR	(95% CI)	P[e]
p,p'-DDT						
1st quartile	1.00		0.180	1.00		0.026
2nd quartile	1.45	(0.91-2.32)		1.22	(0.70-2.14)	
3rd quartile	1.57	(0.94-2.61)		1.94	(1.10-3.42)	
4th quartile	0.98	(0.46-2.11)		0.93	(0.44-1.99)	
p,p'-DDE						
1st quartile	1.00		0.012[f]	1.00		0.088[f]
2nd quartile	1.32	(0.81-2.14)		1.23	(0.70-2.15)	
3rd quartile	2.04	(1.23-3.39)		1.44	(0.81-2.56)	
4th quartile	1.79	(0.95-3.37)		1.71	(0.90-3.26)	
Oxychlordane						
1st quartile	1.00		0.111[f]	1.00		0.242
2nd quartile	1.04	(0.63-1.74)		1.52	(0.84-2.73)	
3rd quartile	1.31	(0.76-2.24)		1.81	(0.99-3.31)	
4th quartile	1.58	(0.85-2.94)		1.34	(0.69-2.63)	
Trans-nonachlor						
1st quartile	1.00		0.041[f]	1.00		0.026[f]

Crude POP concentrations.

[1] Conditional logistic regression and further adjusted for BMI.

Matching factors: study centre, fasting, sex, age, date and time at blood collection, and exogenous hormones (women).

[2] Unconditional logistic regression, adjusting for all matching factors.

[c] N = 611 (197 cases-414 controls).

[d] N = 532 (179 cases-353 controls).

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	Fasting >6 hours[1,a]			Microscopic confirmation[1,b]		
	OR	(95% CI)	P[e]	OR	(95% CI)	P[e]
PCB 138						
1st quartile	1.00		0.319	1.00		0.749
2nd quartile	0.87	(0.41-1.82)		0.95	(0.63-1.43)	
3rd quartile	1.20	(0.56-2.59)		0.96	(0.63-1.47)	
4th quartile	1.56	(0.70-3.44)		1.13	(0.73-1.76)	
PCB 183						
1st quartile	1.00		0.072[f]	1.00		0.369[f]
2nd quartile	1.38	(0.57-3.33)		1.10	(0.74-1.64)	
3rd quartile	1.41	(0.59-3.38)		1.15	(0.76-1.75)	
4th quartile	2.12	(0.86-5.21)		1.22	(0.79-1.90)	
Sum of orders, 16 POPs						
1st quartile	1.00		0.080[f]	1.00		0.053
2nd quartile	1.77	(0.79-3.97)		1.41	(0.95-2.10)	
3rd quartile	2.17	(0.98-4.78)		1.80	(1.18-2.73)	
4th quartile	2.19	(0.97-4.92)		1.42	(0.92-2.20)	
Number of POPs at high						

Crude POP concentrations.

[1] Conditional logistic regression and further adjusted for BMI.

Matching factors: study centre, fasting, sex, age, date and time at blood collection, and exogenous hormones (women).

[a] N = 430 (150 cases-280 controls).

[b] N = 1110 (372 cases-738 controls).

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	Normal weight[2,c]			Interval ≥10 years[1,d]		
	OR	(95% CI)	P[e]	OR	(95% CI)	P[e]
PCB 138						
1st quartile	1.00		0.035[f]	1.00		0.024[f]
2nd quartile	1.97	(1.13-3.41)		1.30	(0.65-2.61)	
3rd quartile	1.64	(0.90-3.00)		1.85	(0.90-3.79)	
4th quartile	2.32	(1.23-4.36)		2.13	(1.01-4.51)	
PCB 183						
1st quartile	1.00		0.027[f]	1.00		0.023[f]
2nd quartile	1.55	(0.90-2.65)		2.21	(1.15-4.25)	
3rd quartile	1.57	(0.90-2.73)		2.46	(1.20-5.05)	
4th quartile	2.10	(1.14-3.88)		2.76	(1.31-5.80)	
Sum of orders, 16 POPs						
1st quartile	1.00		0.047[f]	1.00		0.016[f]
2nd quartile	1.57	(0.92-2.67)		2.41	(1.20-4.83)	
3rd quartile	1.75	(1.03-3.00)		3.02	(1.45-6.29)	
4th quartile	1.83	(1.00-3.35)		3.00	(1.39-6.46)	

Crude POP concentrations.

[1] Conditional logistic regression and further adjusted for BMI.

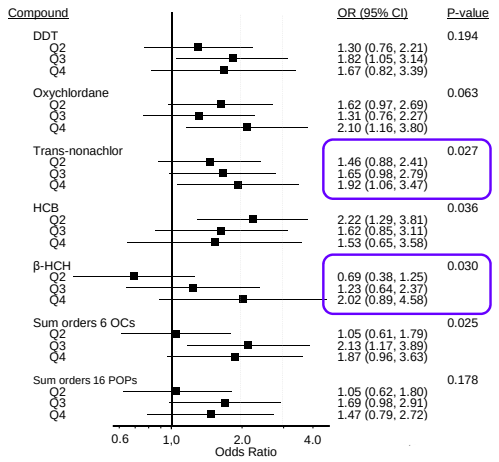
Matching factors: study centre, fasting, sex, age, date and time at blood collection, and exogenous hormones (women).

[2] Unconditional logistic regression, adjusting for all matching factors.

[c] N = 611 (197 cases-414 controls).

[d] N = 532 (179 cases-353 controls).

Risk of pancreatic cancer according to quartiles of POP concentrations **in never smokers.**



Strengths and limitations, 1.

- Small number of contaminants analyzed, given
  – available knowledge on adverse pancreatic effects of other compounds, and
  – number of compounds / mixtures contaminating humans.

- High correlation between [POPs] we measured and [other contaminants], such as trace elements, dioxins and furans, phthalates, other polybrominated diphenyl ethers (PBDEs), phenols, per- and polyfluorinated alkyl substances (PFAS) and ++.

- Today few Western populations worldwide have mean POP concentrations above the POP quartiles where the present study observed effects.
  – But subgroups with high [POPs].
  – Other pancreatic toxicants may be increasing in humans.

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Strengths and limitations, 2.

- Large number of associations tested without changing the level of statistical significance. Autonomous assessment of statistical significance and magnitude OR.

- Median length of follow-up ~12 years: fine. But risks after longer periods?

- Although POPs have long half-lives, one single measure of [POP] in adulthood is more limited than ≥2 measures to assess the intensity and duration of POP body burden in puberty / youth / adulthood / old age.

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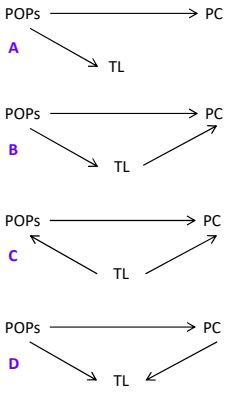
Strengths and limitations, and 3.

- First study that measured POPs long before pancreatic cancer occurred: similar concentrations of lipids and BMI among cases and controls; best assesment of disease progression bias.

- Included a higher number of subjects and contaminants than previous studies. See Gasull M et al. 2019.

- More complex studies are necessary: to measure at several points during the lifecourse and with different latency periods the possible effects on pancreatic cancer risk of a higher variety of chemical mixtures, as well as their interactions with other biological, clinical, and environmental factors; eg, interactions with changes in BMI and with endocrine, metabolic, and inflammatory disorders.



DAGs illustrating 4 possible causal scenarios for POPs and pancreatic cancer (PC) considering total lipids (TL).

(A) POPs cause PC and increase TL. Because TL are associated with POPs, conditioning on TL (i.e., lipid correction of POPs) would be equivalent to partially adjusting for the exposure itself (POPs). Thus, it is more appropriate to use POPs uncorrected by TL.

(B) POPs have also an indirect effect on PC via TL (thus, are partly a mediator). TL may also increase risk of PC. Therefore, conditioning on TL would underestimate the effect of POPs on PC. It is more appropriate to use POPs uncorrected by TL.

(C) POPs and PC are (unconditionally) associated when we do not adjust for TL. Using POPs uncorrected by TL would fail to address the confounding by TL. It is more appropriate to use POPs corrected by TL. Even so, using POPs corrected by TL may be insufficient to account for the confounding effects of TL over time. The influence of TL on POPs is only plausible in study designs that measure TL and POPs under conditions of non-equilibrium or non-fasting (e.g., when a number subjects experienced weight changes or were not fasting). 1) Years before the cancer diagnosis, weight changes just before blood draw were not different in cases than controls, they were all healthy persons. 2) Ccases and controls were matched on fasting status at blood draw. 3) Some analyses conditioned on fasting status. 4) TL and POPs were measured under conditions of equilibrium and mostly fasting. Thus, causal scenario C does not seem to apply to the present study design.

(D) TL are a common effect of POPs and PC (TL are a collider). Adjusting for a collider creates a spurious association between POPs and PC. The influence of PC on TL is only plausible in study designs that measure TL at the time of PC diagnosis or shortly before. This is not the case of the present study. Causal scenario D does not apply to the present study.

Causal scenarios

Based on causal scenarios A and B, we built conditional logistic regression models (ie, adjusting for matching factors), essentially using crude concentrations of POPs. Precedence should be given to the mentioned models.

There were no differences between cases and controls in total lipids and its components (ie, as in the scenario A), nor in BMI.

While smoking was more frequent among cases than controls, it was not associated with POPs. These facts argue against the need to condition on TL, BMI, or smoking.

Nevertheless, to explore alternative scenarios, in some instances we also used lipid-corrected POPs, or further conditioned on BMI or smoking.

Further comments

- By study centre, POP estimates were only consistently increased in Sweden. Compared to participants from the other countries, more participants from Sweden had been fasting for more than six hours, were younger at blood collection, had a lower BMI, had a longer follow-up, and higher concentrations of total lipids. These factors did not explain the stronger associations in Sweden.

- We did not yet adjust the effects of POPs on pancreatic cancer by dietary factors because diet is a common source of POPs. Different questions.
a) The influence of diet, other lifestyle and anthropometric factors on [POP] in cases and controls: future report. We'll also assess:
b) the joint and separate impact of POPs, dietary patterns, and anthropometric factors on pancreatic cancer risk;
c) the possible mediating role of type 2 diabetes in the association between POPs and pancreatic cancer risk; and
d) the possible mediating role of POPs in the association between type 2 diabetes and pancreatic cancer risk.

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Conclusions

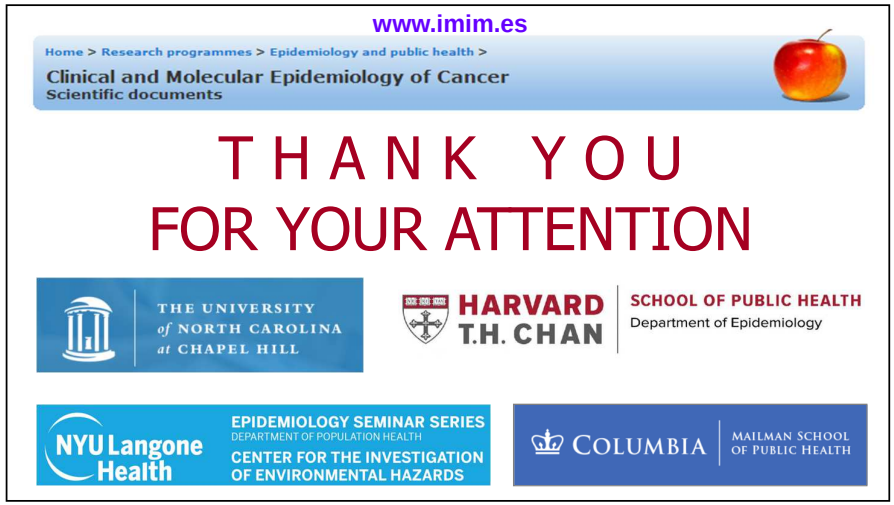
- Individually or in combination, the 22 POPs analysed did not generally increase risk of exocrine pancreatic cancer.

- A few modestly increased risks of exocrine pancreatic cancer were apparent for the crude concentrations of some POPs, sometimes with a dose-response relation.

- Risks were weaker or not consistently increased when analysing most lipid-corrected POP concentrations.

- As compared to estimates for all subjects, associations were stronger in the most valid or relevant stratum of fasting (>6 hours), diagnostic basis (microscopic confirmation), BMI (normal weight), interval between blood extraction and index date (≥10 years), and smoking (never smokers).

- While the study overcame some weaknesses of previous reports, several study findings and limitations warrant conducting additional, more complex research.



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