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Supplemental Material

Exposure to Bisphenol A and Bisphenol S and Incident Type 2 Diabetes: A Case–Cohort Study in the French Cohort D.E.S.I.R.

Fanny Rancière, Jérémie Botton, Rémy Slama, Marlène Z. Lacroix, Laurent Debrauwer, Marie Aline Charles, Ronan Roussel, Beverley Balkau, Dianna J. Magliano, and the D.E.S.I.R. Study Group

Table of Contents

Table S1. Baseline characteristics of D.E.S.I.R. individuals included and not included in the random subcohort after applying exclusion criteria.

Table S2. Adjusted associations between exposure to BPA and BPS and the risk of type 2 diabetes in the D.E.S.I.R. cohort (models including both BPA and BPS).

Table S3. Adjusted associations between average BPA exposure and average BPS detection and the risk of type 2 diabetes among men and women in the D.E.S.I.R. cohort.

Table S4. Adjusted associations between average BPS detection and the risk of type 2 diabetes according to baseline BMI in the D.E.S.I.R. cohort.

Figure S1. Flow chart of the case-cohort study nested in the French prospective cohort study D.E.S.I.R. when considering exposure at year 3 in relation to incident T2D.

Figure S2. Relationship between log-transformed BPA-G concentration at baseline and adjusted hazard ratio (HR) of type 2 diabetes in the D.E.S.I.R. case-cohort study fitted with restricted cubic splines (three knots placed at the 10th, 50th and 90th percentiles).

Table S1. Baseline characteristics of D.E.S.I.R. individuals included and not included in the random subcohort after applying exclusion criteria

Baseline characteristics	Participants included in the subcohort (n=600)	Participants not included in the subcohort (n=2809)	P-value ^a
Men	283 (47.2)	1382 (49.2)	0.37
Age (years)	47 (39, 56)	47 (39, 56)	0.71
Education level			
< 12 years of education	453 (76.1)	2101 (75.3)	0.66
≥ 12 years of education	142 (23.9)	690 (24.7)	
Missing	5	18	
Employment			
No	165 (27.5)	781 (27.8)	0.88
Yes	434 (72.5)	2024 (72.2)	
Missing	1	4	
Current smoker			
No	491 (82.0)	2278 (81.3)	0.69
Yes	108 (18.0)	525 (18.7)	
Missing	1	6	
Physical activity			
No	142 (23.7)	737 (26.3)	0.22
Moderate	319 (53.3)	1499 (53.4)	
Vigorous	138 (23.0)	569 (20.3)	
Missing	1	4	
Dietary intake (kcal/day)	1989 (1684, 2503)	2021 (1728, 2467)	0.39
Family history of diabetes			
No	500 (83.3)	2237 (79.7)	0.04
Yes	100 (16.7)	571 (20.3)	
Missing	0	1	
Hypertension ^b			
No	391 (65.2)	1800 (64.1)	0.62
Yes	209 (34.8)	1008 (35.9)	
Missing	0	1	
Body mass index (kg/m ²)	24.0 (22.0, 26.8)	24.2 (22.1, 26.8)	0.48

Data are n (%) for categorical variables and median (P25, P75) for continuous variables.

^aChi-squared test for qualitative variables and Kruskal-Wallis rank test for quantitative variables.

^bSystolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or ongoing blood pressure-lowering treatment.

Table S2. Adjusted associations between exposure to BPA and BPS and the risk of type 2 diabetes in the D.E.S.I.R. cohort (models including both BPA and BPS)

	Baseline	Year 3	Baseline-Year 3
	HR (95% CI)^a	HR (95% CI)^b	HR (95% CI)^b
	N=644	N=579	N=529
BPA exposure			
Groups of BPA-G concentration (ng/mL)			
<0.71	1	1	1
[0.71, 1.75)	0.79 (0.51, 1.22)	1.25 (0.58, 2.71)	2.09 (0.91, 4.79)
[1.75, 3.78)	0.91 (0.57, 1.45)	2.13 (1.03, 4.43)	1.98 (0.87, 4.53)
≥3.78	0.87 (0.54, 1.41)	0.84 (0.37, 1.89)	1.40 (0.59, 3.35)
BPS detection			
BPS-G concentration ≥LOD			
Yes vs. No	1.69 (1.10, 2.60)	2.01 (1.05, 3.85)	2.78 (1.72, 4.52)

CI: confidence interval; HR, hazard ratio; LOD, limit of detection.

Groups of BPA exposure were defined on the pooled baseline and year 3 BPA-G concentrations in subcohort members.

HRs quantify the association of BPA exposure and BPS detection with the incidence of diabetes onset (^a between baseline and year 9 or ^b between year 3 and year 9).

Cox models with age as the time-scale and stratified on smoking status were adjusted for urinary creatinine level (at baseline, at year 3, or on average), sex, and for the following variables from baseline^a (when examining diabetes incidence between baseline and year 9) or from year 3^b (when examining diabetes incidence between year 3 and year 9): education level, employment, marital status, physical activity, caloric intake, family history of diabetes, hypertension, and BMI.

Table S3. Adjusted associations between average BPA exposure and average BPS detection and the risk of type 2 diabetes among men and women in the D.E.S.I.R. cohort

BPA exposure	Men		Women		P for interaction
	n/N*	HR (95% CI)	n/N*	HR (95% CI)	
	N=304		N=319		
Average BPA-G concentration (ng/mL)					
<0.71	7/27	1	3/48	1	0.76
[0.71, 1.75)	18/83	1.59 (0.57, 4.43)	15/93	6.18 (1.21, 31.60)	
[1.75, 3.78)	22/96	1.30 (0.47, 3.59)	14/102	5.22 (1.05, 25.92)	
≥3.78	21/98	1.02 (0.36, 2.91)	8/76	2.11 (0.33, 13.50)	
BPS detection	Men		Women		P for interaction
	n/N*	HR (95% CI)	n/N*	HR (95% CI)	
	N=256		N=273		
BPS-G concentration ≥LOD at baseline and/or year 3					
No	42/184	1	19/205	1	0.09
Yes	20/72	1.76 (0.93, 3.33)	18/68	4.23 (1.69, 10.63)	

CI: confidence interval; HR, hazard ratio; LOD, limit of detection (0.3 ng/mL).

*n/N indicates the numbers of type 2 diabetes cases relatively to the total number of participants in each exposure category.

Groups of BPA exposure were defined on the pooled baseline and year 3 BPA-G concentrations in subcohort members.

HRs quantify the association between average exposure to BPA/BPS and incidence of diabetes between year 3 and year 9.

Cox models with age as the time-scale and stratified on smoking status were adjusted for average urinary creatinine level, sex, and for the following variables from year 3: education level, physical activity, caloric intake, family history of diabetes, hypertension, and BMI.

Table S4. Adjusted associations between average BPS detection and the risk of type 2 diabetes according to baseline BMI in the D.E.S.I.R. cohort

	Baseline BMI < 25 kg/m ²		Baseline BMI ≥ 25 kg/m ²		<i>P</i> for interaction
	n/N*	aHR (95% CI)	n/N*	aHR (95% CI)	
	N=290		N=239		
BPS-G concentration ≥ LOD at baseline and/or year 3					0.18
No	18/215	1	43/174	1	
Yes	11/75	1.58 (0.66, 3.81)	27/65	2.59 (1.41, 4.74)	
	Baseline age < 50 years		Baseline age ≥ 50 years		<i>P</i> for interaction
	n/N*	aHR (95% CI)	n/N*	aHR (95% CI)	
	N=298		N=231		
BPS-G concentration ≥ LOD at baseline and/or year 3					0.13
No	29/231	1	32/158	1	
Yes	18/67	3.70 (1.83, 7.50)	20/73	1.78 (0.86, 3.70)	
	No family history of diabetes		Family history of diabetes		<i>P</i> for interaction
	n/N*	aHR (95% CI)	n/N*	aHR (95% CI)	
	N=428		N=101		
BPS-G concentration ≥ LOD at baseline and/or year 3					0.04
No	47/320	1	14/69	1	
Yes	25/108	2.06 (1.17, 3.61)	13/32	41.45 (5.23, 328.37)	

CI: confidence interval; aHR, adjusted hazard ratio; LOD, limit of detection (0.3 ng/mL).

*n/N indicates the numbers of type 2 diabetes cases relatively to the total number of participants in each exposure category.

HRs quantify the association between average BPS detection and incidence of diabetes between year 3 and year 9.

Figure S1. Flow chart of the case-cohort study nested in the French prospective cohort study D.E.S.I.R. when considering exposure at year 3 in relation to incident T2D

Legend: BMI: body mass index, FPG: fasting plasma glucose, HbA_{1c}: glycosylated hemoglobin, T2D: type 2 diabetes.

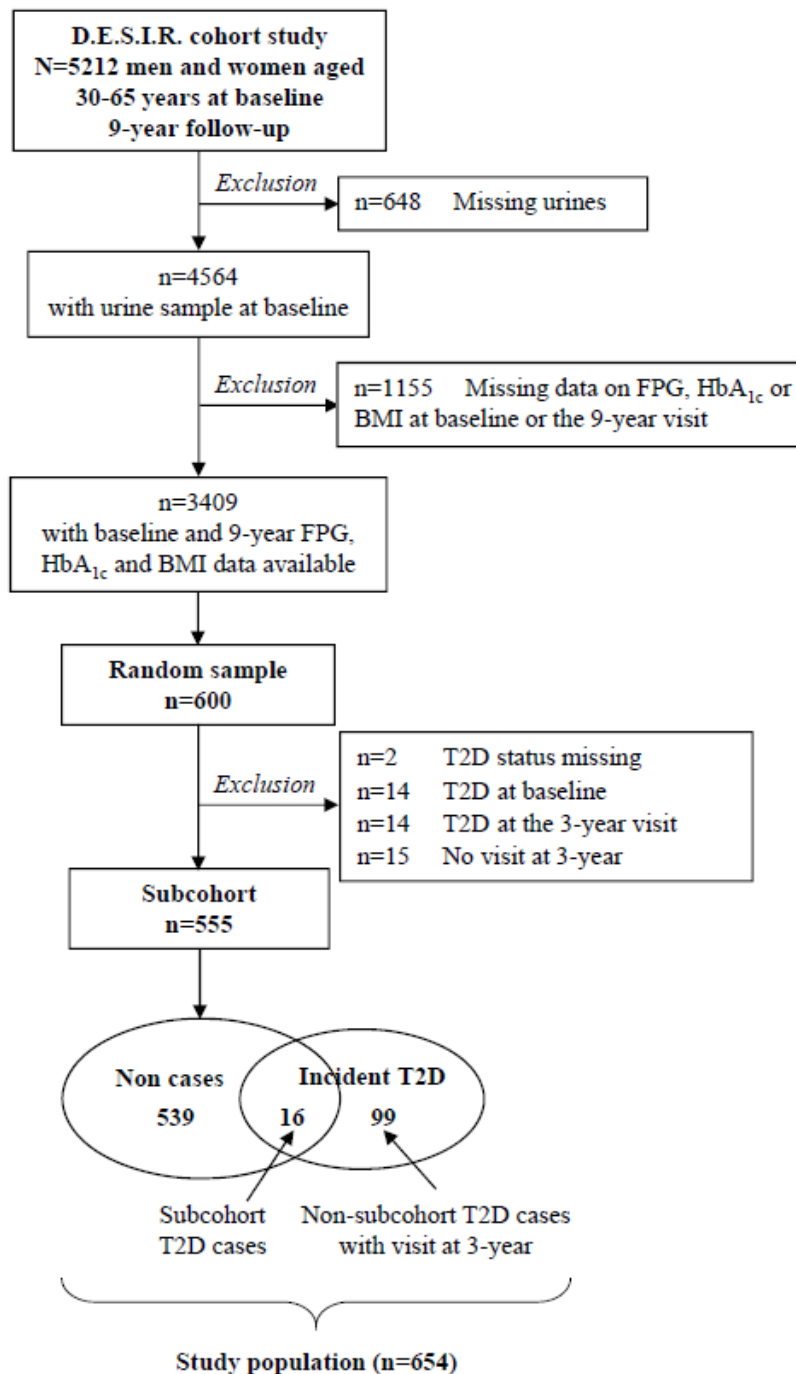


Figure S2. Relationship between log-transformed BPA-G concentration at baseline and adjusted hazard ratio (HR) of type 2 diabetes in the D.E.S.I.R. case-cohort study fitted with restricted cubic splines (three knots placed at the 10th, 50th and 90th percentiles).

Legend: Reference value for HRs is the minimum BPA-G concentration (<LOD); the solid line represent the HRs and the dashed lines the 95% confidence interval. P overall=0.05, P nonlinear=0.01. Cox model with age as the time-scale and stratified on smoking status was adjusted for urinary creatinine level, sex, education level, employment, marital status, physical activity, caloric intake, family history of diabetes, hypertension, and BMI (all variables from baseline).

