

SUPPLEMENTAL MATERIAL
for

Interaction between GAD65 antibodies and dietary fish intake or plasma phospholipid n-3 polyunsaturated fatty acids on incident adult onset diabetes: The EPIC-InterAct Study

Authors

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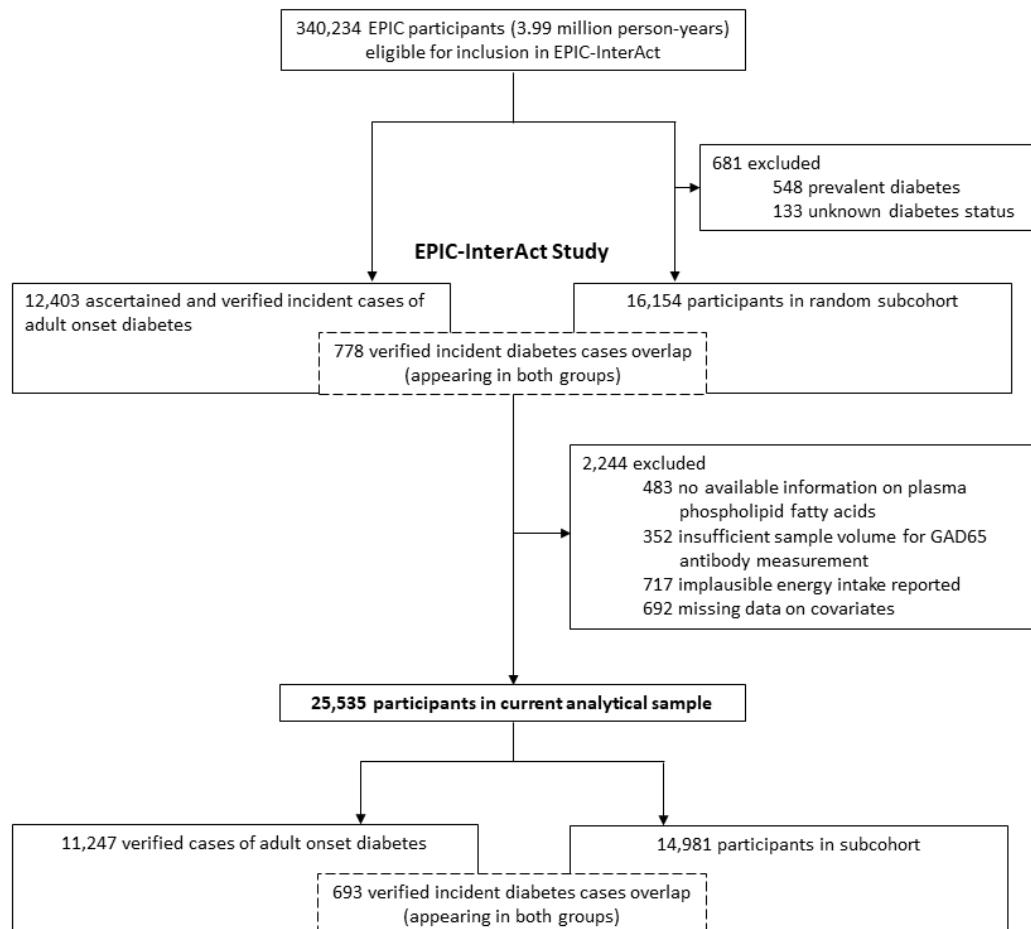
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Supplemental Figure 1. EPIC-InterAct case-cohort study design and flowchart of study participants.



Supplemental Table 1. Number of subcohort participants and incident cases in the EPIC-InterAct Study. Numbers refer to the analytical sample of the study.

	France	Italy	Spain	United Kingdom	Netherlands	Germany	Sweden	Denmark	Total
Subcohort participants, <i>n</i>	518	1,910	3,407	1,158	1,337	1,998	2,618	2,035	14,981
of which GAD65 antibody positive, <i>n</i> (%)	6 (1.2)	38 (2.0)	76 (2.2)	25 (2.2)	26 (1.9)	31 (1.6)	56 (2.1)	41 (2.0)	299 (2.0)
Incident diabetes cases, <i>n</i>	247	1,309	2,422	888	726	1,523	2,194	1,938	11,247
of which GAD65 antibody positive, <i>n</i> (%)	9 (3.6)	59 (4.5)	66 (2.7)	43 (4.8)	38 (5.2)	30 (2.0)	87 (4.0)	60 (3.1)	392 (3.5)

Supplemental Table 2. Spearman rank correlation matrix for the different types of plasma phospholipid n-3 PUFAs and fish intakes in the subcohort. The EPIC-InterAct Study.

Variable	Total n-3 PUFA (mol%)	EPA (mol%)	DPA (mol%)	DHA (mol%)	Total fish (g/d)	Fatty fish (g/d)	Lean fish (g/d)
Total n-3 PUFA (mol%)	1	0.82	0.50	0.91	0.26	0.26	0.15
EPA (mol%)	0.82	1	0.56	0.57	0.15	0.16	0.06
DPA (mol%)	0.50	0.56	1	0.26	-0.17	-0.07	-0.18
DHA (mol%)	0.91	0.57	0.26	1	0.35	0.31	0.23
Total fish (g/d)	0.26	0.15	-0.17	0.35	1	0.71	0.84
Fatty fish (g/d)	0.26	0.16	-0.07	0.31	0.71	1	0.33
Lean fish (g/d)	0.15	0.06	-0.18	0.23	0.84	0.33	1

Supplemental Table 3. Median (IQR) relative concentration of plasma phospholipid n-3 PUFAs and dietary fish intake by tertile of intake of fatty fish and lean fish in the full study sample. The EPIC-InterAct Study.

Exposure, median (IQR)	Fatty fish intake			Lean fish intake*		
	Low	Moderate	High	Low	Moderate	High
n	8,368	8,512	8,655	7,148	7,448	7,477
Total plasma phospholipid n-3 PUFA, mol%	5.97 (5.07, 7.11)	6.36 (5.33, 7.62)	7.11 (5.88, 8.57)	6.38 (5.23, 7.68)	6.37 (5.31, 7.75)	6.94 (5.82, 8.28)
Plasma phospholipid EPA, mol%	0.99 (0.72, 1.35)	1.05 (0.72, 1.53)	1.24 (0.82, 1.84)	1.07 (0.74, 1.54)	1.06 (0.72, 1.59)	1.16 (0.77, 1.69)
Plasma phospholipid DHA, mol%	3.75 (3.06, 4.53)	4.08 (3.38, 4.92)	4.66 (3.86, 5.53)	4.01 (3.21, 4.92)	4.09 (3.39, 4.96)	4.64 (3.88, 5.45)
Total fish intake*, g/wk	12.3 (0, 112.7)	96.9 (49.2, 175.9)	284.0 (191.1, 435.0)	22.7 (3.8, 69.7)	125.1 (75.7, 183.3)	335.4 (239.6, 490.7)
Fatty fish intake, g/wk	0 (0, 4.1)	42.4 (26.9, 57.5)	137.4 (103.7, 213.0)	19.8 (2.3, 65.9)	56.4 (23.9, 103.6)	92.7 (36.0, 166.2)
Lean fish intake*, g/wk	6.8 (0, 112.7)	52.2 (4.1, 125.5)	121.6 (42.5, 223.5)	0 (0, 0)	67.6 (38.2, 93.9)	213.1 (162.0, 334.7)

* Germany (n=3,462) was excluded as these centers had no data on lean fish intake.

Supplemental Table 4. Adjusted HR (95% CI) of incident diabetes for combinations of GAD65 antibody status and categories of plasma phospholipid n-3 PUFAs or dietary fish intake.

Exposure	GAD65 antibody negative		GAD65 antibody positive		AP*	<i>p</i> †
	Cases	HR (95% CI)	Cases	Low HR (95% CI)	High HR (95% CI)	
Total plasma phospholipid n-3 PUFA						
High	3,798	1.00 (ref)	57	1.18 (0.75-1.87)	51	2.32 (1.50-3.59)
Moderate	3,666	0.98 (0.91-1.06)	49	1.07 (0.68-1.67)	41	2.64 (1.71-4.07)
Low	3,391	0.98 (0.90-1.08)	61	1.37 (0.82-2.32)	55	4.26 (2.70-6.72)
					0.46 (0.12-0.80)	0.33
Plasma phospholipid EPA						
High	4,159	1.00 (ref)	56	0.98 (0.62-1.55)	76	2.42 (1.60-3.67)
Moderate	3,670	0.94 (0.87-1.02)	52	1.11 (0.66-1.87)	79	2.58 (1.67-4.00)
Low	3,026	0.87 (0.79-0.95)	59	1.42 (0.93-2.16)	70	3.71 (2.30-5.98)
					0.38 (-0.01-0.78)	0.20
Plasma phospholipid DHA						
High	3,491	1.00 (ref)	56	1.18 (0.75-1.86)	61	2.39 (1.51-3.80)
Moderate	3,872	1.06 (0.98-1.15)	48	1.30 (0.84-2.00)	71	2.72 (1.72-4.28)
Low	3,492	1.08 (0.99-1.17)	63	1.34 (0.80-2.23)	93	4.30 (2.86-6.47)
					0.43 (0.08-0.77)	0.51
Total fish intake						
High	3,400	1.00 (ref)	49	1.01 (0.64-1.60)	52	2.54 (1.57-4.11)
Moderate	3,198	0.95 (0.87-1.04)	56	1.11 (0.67-1.84)	73	2.31 (1.52-3.51)
Low	2,764	0.95 (0.85-1.06)	49	1.71 (1.01-2.91)	83	3.50 (2.14-5.73)
					0.29 (-0.20-0.78)	0.34
Fatty fish intake						
High	3,821	1.00 (ref)	61	0.87 (0.56-1.36)	65	2.16 (1.38-3.39)
Moderate	3,509	0.91 (0.84-0.99)	61	1.42 (0.91-2.22)	80	3.23 (2.13-4.90)
Low	3,525	1.03 (0.94-1.13)	45	1.66 (1.04-2.66)	80	3.42 (2.14-5.47)
					0.36 (-0.05-0.77)	0.12
Lean fish intake						
High	3,371	1.00 (ref)	44	0.98 (0.60-1.60)	58	2.56 (1.64-4.00)
Moderate	3,025	0.92 (0.84-1.00)	56	1.59 (1.06-2.38)	71	2.05 (1.35-3.11)
Low	2,966	0.97 (0.87-1.08)	54	1.12 (0.64-1.96)	79	4.12 (2.40-7.08)
					0.39 (-0.04-0.81)	0.13

* AP is calculated for the combination of high GAD65 antibody level and low plasma n-3 PUFA/fish intake.

† *p* for the multiplicative interaction term between GAD65 antibody level and categories of plasma n-3 PUFA/fish intake.

Supplemental Table 5. Adjusted HR (95% CI) of incident diabetes in relation to tertiles (based on subcohort distribution) of relative plasma phospholipid n-3 PUFA concentration and dietary fish intake among GAD65 antibody positive participants in the EPIC-InterAct Study.

Exposure	No. of cases	HR* (95% CI)
Total plasma phospholipid n-3 PUFA		
Low	143	1.00 (ref)
Moderate	120	0.75 (0.49-1.15)
High	129	0.82 (0.53-1.28)
Plasma phospholipid EPA		
Low	129	1.00 (ref)
Moderate	131	0.85 (0.55-1.31)
High	132	0.84 (0.54-1.31)
Plasma phospholipid DHA		
Low	156	1.00 (ref)
Moderate	119	0.92 (0.62-1.37)
High	117	0.82 (0.53-1.27)
Total fish intake		
Low	132	1.00 (ref)
Moderate	129	0.54 (0.33-0.88)
High	101	0.61 (0.35-1.07)
Fatty fish intake		
Low	125	1.00 (ref)
Moderate	141	0.64 (0.41-1.00)
High	126	0.46 (0.29-0.74)
Lean fish intake		
Low	133	1.00 (ref)
Moderate	127	0.68 (0.41-1.12)
High	102	0.77 (0.44-1.35)

* HRs adjusted for age (underlying timescale), center, sex, education level, smoking status, physical activity, BMI, total energy intake, and intake of alcohol, fruit and vegetables.