

SUPPLEMENTARY MATERIAL

Pesticides and other occupational exposures are associated with airway obstruction; the LifeLines cohort study

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Supplementary tables 1-8

Additional information 1. Additional information on pesticide use in the northern Dutch provinces since 1985

Supplementary table 2. Characteristics of the included and excluded subjects from the LifeLines cohort.

	Included	Excluded	Test	p-value
N with non-missing data	11851	1450		
Males , n (%)	4878 (41)	679 (47)	Chi-square	<0.001
Age (yrs), median (min-max)	47 (18-89)	51 (22-88)	MWU	<0.001
Ever smokers , n (%)	6760 (57)	1068 (80)	Chi-square	<0.001
Packyears in ever smokers, median (25-75 th percentiles)	10 (5-19)	12 (5-22)	MWU	0.002
Lung function , mean (sd)				
FEV ₁ %predicted ^a	103 (14)	100 (16)	t-test	<0.001
FEV ₁ /FVC (%)	76 (7)	74 (8)	t-test	<0.001

^a FEV₁%predicted is FEV₁ as percentage predicted based on reference equations by Quanjer et al (1993).

Supplementary table 3. Overview of the number of workers (%) with high exposure to VGDF in the LifeLines cohort.

N	%	ISCO code	Occupation
159	11.9	6121	Dairy and livestock producers
102	7.7	8324	Heavy truck and lorry drivers
100	7.5	7124	Carpenters and joiners
77	5.8	7231	Motor vehicle mechanics and fitters
67	5.0	7212	Welders and flame cutters
64	4.8	7233	Agricultural- or industrial-machinery mechanics and fitters
63	4.7	9333	Freight handlers
57	4.3	7136	Plumbers and pipe fitters
50	3.8	6113	*Gardeners, horticultural and nursery growers
50	3.8	9313	Building construction labourers
41	3.1	7141	Painters and related workers
33	2.5	6111	*Field crop and vegetable growers
31	2.3	7411	Butchers, fishmongers and related food preparers
23	1.7	6130	*Market-oriented crop and animal producers
22	1.7	7412	Bakers, pastry-cooks and confectionery makers
22	1.7	8332	Earth-moving and related plant operators
22	1.7	9312	Construction and maintenance labourers: roads, dams and similar constructions
21	1.6	3141	Ships' engineers
20	1.5	8251	Printing-machine operators
18	1.4	3227	Veterinary assistants
18	1.4	6100	Market-oriented skilled agricultural and fishery workers: not specifically classifiable
15	1.1	9133	Hand-launderers and pressers
14	1.1	2452	Sculptors, painters and related artists
14	1.1	7123	Concrete placers, concrete finishers and related workers
219	17.2	else	else

* workers with additional high exposure to pesticides.

Supplementary table 4. Associations between exposure to various types of solvents and level of FEV₁ and FEV₁/FVC in the LifeLines cohort. Linear regression models were adjusted for sex, age, height, weight, current, ex smoking and (log) packyears. Additionally stratification by smoking status (never/ever) and gender was performed.

LifeLines										
Solvent Exposure ^a	All		Never smokers		FEV ₁ (ml)		Males		Females	
	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N
Aromatic solvents										
Non-exposed	Ref	10812	Ref	4668	Ref	6144	Ref	4012	Ref	6800
Low	-4 (-36 ; 27)	957	22 (-24 ; 69)	400	-23 (-66 ; 20)	557	-5 (-47 ; 37)	793	23 (-36 ; 81)	164
High	-36 (-136 ; 65)	82	-81 (-262 ; 101)	23	-26 (-148 ; 97)	59	-23 (-151 ; 105)	73	-12 (-259 ; 235)	9
Chlorinated solvents										
Non-exposed	Ref	10980	Ref	4757	Ref	6223	Ref	4262	Ref	6718
Low	16 (-20 ; 51)	695	70 (15 ; 125)*	268 #	-18 (-65 ; 28)	427	28 (-26 ; 81)	450	5 (-43 ; 53)	245
High	-22 (-92 ; 47)	176	27 (-81 ; 136)	66	-59 (-149 ; 31)	110	-12 (-98 ; 74)	166	-81 (-316 ; 153)	10
Other solvents										
Non-exposed	Ref	9109	Ref	3951	Ref	5158	Ref	3857	Ref	5252
Low	12 (-8 ; 32)	2531	24 (-6 ; 54)	1064	5 (-23 ; 32)	1467	26 (-13 ; 66)	947	7 (-14 ; 29)	1584
High	-19 (-82 ; 44)	211	31 (-69 ; 132)	76	-51 (-132 ; 30)	135	-22 (-150 ; 105)	74	-5 (-69 ; 59)	137
FEV₁/FVC (%)										
Solvent Exposure _a	All		Never smokers		Ever smokers		Males		Females	
	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N
Aromatic solvents										
Non-exposed	Ref	10812	Ref	4668	Ref	6144	Ref	4012	Ref	6800
Low	-0.5 (-1.0 ; -0.1)*	957	-0.1 (-0.7 ; 0.6)	400	-0.8 (-1.5 ; -0.2)**	557	-0.5 (-1.0 ; 0)	793	-0.6 (-1.6 ; 0.4)	164
High	0.4 (-1.1 ; 1.8)	82	0.7 (-1.8 ; 3.2)	23	0.1 (-1.6 ; 1.9)	59	0.6 (-1.1 ; 2.2)	73	-1.3 (-5.4 ; 2.8)	9
Chlorinated solvents										
Non-exposed	Ref	10980	Ref	4757	Ref	6223	Ref	4262	Ref	6718
Low	-0.3 (-0.8 ; 0.2)	695	0.4 (-0.3 ; 1.2)	268	-0.7 (-1.4 ; 0)*	427	-0.1 (-0.8 ; 0.6)	450	-0.5 (-1.3 ; 0.3)	245
High	0 (-1.0 ; 0.9)	176	-0.8 (-2.3 ; 0.7)	66	0.3 (-1.0 ; 1.7)	110	0.1 (-0.9 ; 1.2)	166	-2.6 (-6.5 ; 1.3)	10
Other solvents										
Non-exposed	Ref	9109	Ref	3951	Ref	5158	Ref	3857	Ref	5252
Low	-0.1 (-0.4 ; 0.1)	2531	0.1 (-0.3 ; 0.6)	1064	-0.3 (-0.7 ; 0.1)	1467	-0.2 (-0.7 ; 0.3)	947	-0.1 (-0.4 ; 0.3)	1584
High	-0.3 (-1.2 ; 0.6)	211	-0.3 (-1.7 ; 1.1)	76	-0.4 (-1.5 ; 0.8)	135	0.2 (-1.4 ; 1.9)	74	-0.6 (-1.7 ; 0.4)	137

^a Occupational exposures (no/low/high) were estimated based on job title and function using the ALOHA+ Job Exposure Matrix. Non-exposed subjects were assigned as reference category (Ref).

Significantly different for never and ever smokers (i.e. p-value for interaction < 0.05).

Table 5. Associations between occupational exposure to solvents and airway obstruction in the LifeLines and Vlagtwedde-Vlaardingen cohorts.

Solvent Exposure _a	LifeLines						Vlagtwedde-Vlaardingen					
	Mild obstruction (FEV ₁ /FVC<70%)			Moderate/severe obstruction ^b			Mild obstruction (FEV ₁ /IVC<70%)			Moderate/severe obstruction ^b		
	OR (95% CI)	N ^c	P	OR (95% CI)	N ^c	P	OR (95% CI)	N ^c	P	OR (95% CI)	N ^c	P
Aromatic solvents												
Non-exposed	Ref	1569		Ref	414		Ref	431		Ref	208	
Low	1.26 (1.04 ; 1.52)	173	0.020	0.97 (0.67 ; 1.39)	39	0.857	1.13 (0.89 ; 1.44)	199	0.320	1.25 (0.91 ; 1.73)	101	0.165
High	0.92 (0.48 ; 1.75)	12	0.798	1.28 (0.50 ; 3.30)	5	0.604	0.70 (0.30 ; 1.67)	9	0.425	0.75 (0.25 ; 2.23)	5	0.606
Chlorinated solvents												
Non-exposed	Ref	1611		Ref	422		Ref	559		Ref	279	
Low	1.09 (0.87 ; 1.36)	112	0.452	0.93 (0.61 ; 1.41)	27	0.731	0.67 (0.47 ; 0.97)	57	0.032	0.62 (0.38 ; 1.01)	26	0.054
High	1.38 (0.91 ; 2.10)	31	0.130	1.27 (0.62 ; 2.62)	9	0.513	0.53 (0.31 ; 0.89)	23	0.018	0.40 (0.18 ; 0.87)	9	0.020
Other solvents												
Non-exposed	Ref	1369		Ref	365		Ref	491		Ref	247	
Low	1.04 (0.91 ; 1.18)	357	0.608	0.90 (0.70 ; 1.15)	82	0.392	0.93 (0.73 ; 1.19)	138	0.564	0.85 (0.61 ; 1.19)	62	0.349
High	0.99 (0.65 ; 1.50)	28	0.959	1.43 (0.76 ; 2.70)	11	0.272	0.53 (0.25 ; 1.15)	10	0.107	0.51 (0.18 ; 1.42)	5	0.197

Associations between occupational exposures (no/low/high), mild (pre-bronchodilator FEV₁/FVC<70%) and moderate/severe airway obstruction using logistic regression adjusted for sex, age, height, weight, ever smoking (no/yes) and (log) packyears smoked in the LifeLines and Vlagtwedde-Vlaardingen cohorts.

^a Occupational exposures (no/low/high) were estimated based on job title and function using the ALOHA+ Job Exposure Matrix. Non-exposed subjects were assigned as reference category (Ref).

^b Moderate/severe airway obstruction = pre-bronchodilator FEV₁/FVC<70% and FEV₁<80%, without obstruction = pre-bronchodilator FEV₁/FVC≥70% and FEV₁≥80%. Subjects with mild obstruction (pre-bronchodilator FEV₁/FVC<70% and FEV₁≥80%predicted) or pre-bronchodilator FEV₁/FVC≥70% and FEV₁<80%predicted were excluded from this analysis (LifeLines n = 1517 (13%) and Vlagtwedde-Vlaardingen n = 436 (18%)). For Vlagtwedde-Vlaardingen: FEV₁/IVC instead of FEV₁/FVC.

^c Number of subjects with obstruction.

Supplementary table 6. Verification of associations between the exposures and level of FEV₁ (ml) using linear regression with adjustment for sex, age, height, weight, current, ex smoking and (log) packyears smoked in the Vlagtwedde-Vlaardingen cohort. The analyses with VGDF, gases and fumes, mineral dust and biological dust were additionally adjusted for pesticide exposure, whereas the analyses with pesticides, herbicides and insecticides were additionally adjusted for VGDF exposure. Stratification according to smoking status (never/ever) and gender is shown.

Vlagtwedde-Vlaardingen		FEV ₁ (ml)									
Exposure ^a	All		Never smokers		Ever smokers		Males		Females		N
	b (95% CI)	N (%)	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N	
VGDF											
Non-exposed	Ref	895 (38)	Ref	355	Ref	540	Ref	373	Ref	522	
Low	-77 (-123 ; -31)***	685 (29)	-87 (-154 ; -20)*	225	-73 (-133 ; -13)*	460	-128 (-211 ; -46)**	251	#	-36 (-83 ; 12)	434
High	-93 (-149 ; -37)**	784 (33)	-136 (-245 ; -27)*	180	-91 (-158 ; -24)**	604	-126 (-163 ; 56)	641	#	-53 (-163 ; 56)	143
Gases/Fumes											
Non-exposed	Ref	1021 (43)	Ref	412	Ref	609	Ref	401	Ref	620	
Low	-54 (-98 ; -11)*	1111 (47)	-71 (-140 ; -4)*	316	-50 (-106 ; 6)	795	-94 (-167 ; -21)*	647	#	-18 (-66 ; 30)	464
High	-66 (-134 ; 3)	232 (10)	-103 (-256 ; 51)	32	-61 (-141 ; 19)	200	-88 (-174 ; -3)*	217		-33 (-223 ; 156)	15
Mineral dust											
Non-exposed	Ref	1491 (63)	Ref	520	Ref	971	Ref	630	Ref	861	
Low	-28 (-80 ; 25)	375 (16)	-76 (-159 ; 7)	117	-7 (-73 ; 61)	258	-47 (-125 ; 31)	234		-26 (-93 ; 41)	141
High	-15 (-86 ; 57)	498 (21)	4 (-147 ; 155)	123	#	-21 (-105 ; 62)	375	-20 (-108 ; 67)	401	64 (-107 ; 235)	97
Biological dust											
Non-exposed	Ref	1318 (56)	Ref	423	Ref	895	Ref	726	Ref	592	
Low	-68 (-113 ; -23)**	840 (36)	-122 (-189 ; -54)***	292	-42 (-101 ; 17)	548	-113 (-194 ; -32)**	373		-37 (-84 ; 11)	467
High	-57 (-127 ; 14)	206 (9)	-152 (-282 ; -21)*	45	-26 (-111 ; 59)	161	-88 (-181 ; 5)	166		-3 (-126 ; 121)	40
All pesticides											
Non-exposed	Ref	1936 (82)	Ref	631	Ref	1305	Ref	945	Ref	991	
Low	-39 (-120 ; 41)	153 (6)	54 (-74 ; 181)	59	-78 (-182 ; 26)	94	-44 (-156 ; 67)	96		-42 (-158 ; 74)	57
High	-47 (-113 ; 19)	275 (12)	89 (-33 ; 211)	70	#	-84 (-165 ; -4)*	205	-53 (-138 ; 31)	224	25 (-96 ; 145)	51
Herbicides											
Non-exposed	Ref	2018 (85)	Ref	654	Ref	1364	Ref	1011	Ref	1007	
Low	-78 (-159 ; 5)	145 (6)	34 (-102 ; 170)	46	-122 (-225 ; -19)*	99	-124 (-235 ; -12)*	98	#	10 (-112 ; 132)	47
High	-14 (-87 ; 59)	201 (9)	81 (-43 ; 206)	60	-44 (-134 ; 47)	141	-8 (-101 ; 56)	156		-8 (-132 ; 116)	45
Insecticides											
Non-exposed	Ref	1969 (83)	Ref	636	Ref	1333	Ref	977	Ref	992	
Low	4 (-87 ; 95)	120 (5)	111 (-21 ; 244)	54	-50 (-173 ; 74)	66	25 (-110 ; 160)	64		-35 (-153 ; 82)	56
High	-38 (-104 ; 29)	275 (12)	107 (-15 ; 228)	70	#	-78 (-158 ; 2)	205	-42 (-126 ; 42)	224	27 (-94 ; 148)	51

^a Occupational exposures (no/low/high) were estimated based on job title and function using the ALOHA+ Job Exposure Matrix. Non-exposed subjects were assigned as reference category (Ref); VGDF = Vapors, Gases, Dust, Fumes; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Significantly different for never and ever smokers or males and females (i.e. p -value for interaction < 0.05).

Supplementary table 7. Verification of associations between the exposures and level of FEV₁/IVC (%) using linear regression with adjustment for sex, age, height, weight, current, ex smoking and (log) packyears smoked in the Vlagtwedde-Vlaardingen cohort. The analyses with VGDF, gases and fumes, mineral dust and biological dust were additionally adjusted for pesticide exposure, whereas the analyses with pesticides, herbicides and insecticides were additionally adjusted for VGDF exposure. Stratification according to smoking status (never/ever) and gender is shown.

Vlagtwedde-Vlaardingen										
Exposure ^a	All		Never smokers		Ever smokers		Males		Females	
	b (95% CI)	N (%)	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N
VGDF										
Non-exposed	Ref	895 (38)	Ref	355	Ref	540	Ref	373	Ref	522
Low	-0.9 (-1.6 ; -0.1)*	685 (29)	-0.7 (-1.9 ; 0.5)	225	-1.0 (-2.0 ; 0)*	460	-1.1 (-2.4 ; 0.2)	251	-0.7 (-1.7 ; 0.2)	434
High	-1.5 (-2.5 ; -0.6)*	784 (33)	-1.4 (-3.4 ; 0.5)	180	-1.7 (-2.8 ; -0.6)**	604	-1.4 (-2.6 ; -0.2)*	641	-2.8 (-5.0 ; -0.6)*	143
Gases/Fumes										
Non-exposed	Ref	1021 (43)	Ref	412	Ref	609	Ref	401	Ref	620
Low	-0.7 (-1.4 ; 0)	1111 (47)	-0.7 (-1.9 ; 0.5)	316	-0.8 (-1.7 ; 0.1)	795	-0.9 (-2.1 ; 0.2)	647	-0.6 (-1.6 ; 0.3)	464
High	-1.2 (-2.4 ; 0)*	232 (10)	-1.1 (-3.8 ; 1.7)	32	-1.3 (-2.6 ; 0)	200	-1.2 (-2.5 ; 0.1)	217	-2.1 (-5.9 ; 1.7)	15
Mineral dust										
Non-exposed	Ref	1491 (63)	Ref	520	Ref	971	Ref	630	Ref	861
Low	-0.5 (-1.4 ; 0.4)	375 (16)	-1.3 (-2.7 ; 0.2)	117	-0.2 (-1.3 ; 1.0)	258	-0.3 (-1.5 ; 0.9)	234	-0.8 (-2.1 ; 0.6)	141
High	-0.2 (-1.4 ; 1.0)	498 (21)	0.8 (-1.9 ; 3.4)	123	-0.4 (-1.8 ; 1.0)	375	-0.3 (-1.7 ; 1.0)	401	1.5 (-1.9 ; 5.0)	97
Biological dust										
Non-exposed	Ref	1318 (56)	Ref	423	Ref	895	Ref	726	Ref	592
Low	-0.9 (-1.6 ; -0.1)*	840 (36)	-1.1 (-2.3 ; 0.1)	292	-0.8 (-1.8 ; 0.2)	548	-1.0 (-2.2 ; 0.3)	373	-0.9 (-1.8 ; 0.1)	467
High	-0.7 (-1.9 ; 0.5)	206 (9)	-1.1 (-3.4 ; 1.3)	45	-0.6 (-2.0 ; 0.8)	161	-0.4 (-1.8 ; 1.1)	166	-2.2 (-4.6 ; 0.3)	40
All pesticides										
Non-exposed	Ref	1936 (82)	Ref	631	Ref	1305	Ref	945	Ref	991
Low	-0.3 (-1.7 ; 1.1)	153 (6)	0.6 (-1.7 ; 2.8)	59	-0.8 (-2.5 ; 1.0)	94	-0.3 (-2.0 ; 1.5)	96	-0.3 (-2.6 ; 2.0)	57
High	-1.3 (-2.4 ; -0.2)*	275 (12)	0.1 (-2.1 ; 2.2)	70	-1.8 (-3.1 ; -0.4)*	205	-1.8 (-3.1 ; -0.5)**	224	0.6 (-1.8 ; 3.0)	51
Herbicides										
Non-exposed	Ref	2018 (85)	Ref	654	Ref	1364	Ref	1011	Ref	1007
Low	-0.6 (-2.0 ; 0.8)	145 (6)	1.3 (-1.1 ; 3.7)	46 #	-1.5 (-3.2 ; 0.2)	99	-1.2 (-3.0 ; 0.5)	98	0.7 (-1.5 ; 3.1)	47
High	-1.3 (-2.6 ; -0.1)*	201 (9)	-0.7 (-2.9 ; 1.5)	60	-1.6 (-3.1 ; -0.1)*	141	-1.8 (-3.2 ; -0.3)*	156	0.1 (-2.4 ; 2.6)	45
Insecticides										
Non-exposed	Ref	1969 (83)	Ref	636	Ref	1333	Ref	977	Ref	992
Low	0.2 (-1.4 ; 1.7)	120 (5)	0.8 (-1.5 ; 3.2)	54	-0.3 (-2.4 ; 1.8)	66	0.6 (-1.5 ; 2.7)	64	-0.8 (-2.5 ; 2.2)	56
High	-1.2 (-2.3 ; -0.1)*	275 (12)	0.1 (-2.0 ; 2.3)	70	-1.7 (-3.0 ; -0.3)*	205	-1.7 (-3.0 ; -0.4)*	224	0.6 (-1.8 ; 3.0)	51

^a Occupational exposures (no/low/high) were estimated based on job title and function using the ALOHA+ Job Exposure Matrix. Non-exposed subjects were assigned as reference category (Ref); VGDF = Vapors, Gases, Dust, Fumes; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Significantly different for never and ever smokers (i.e. p -value for interaction < 0.05).

Supplementary table 8. Verification of associations between exposure to various types of solvents and level of FEV₁ and FEV₁/IVC in the Vlagtwedde-Vlaardingen cohort. Linear regression models were adjusted for sex, age, height, weight, current, ex smoking and (log) packyears. Additionally stratification by smoking status (never/ever) and gender is shown.

Vlagtwedde-Vlaardingen										
Solvent Exposure ^a	All		Never smokers		Ever smokers		Males		Females	
	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N	b (95% CI)	N
FEV₁ (ml)										
Aromatic solvents										
Non-exposed	Ref	1755	Ref	644	Ref	1111	Ref	731	Ref	1024
Low	-61 (-108 ; -14)*	577	-93 (-179 ; -8)*	115	-47 (-104 ; 9)	462	-58 (-117 ; 1)	505	-23 (-111 ; 65)	72
High	-32 (-192 ; 129)	32	217 (-577 ; 1012)	1	-33 (-205 ; 139)	31	-32 (-223 ; 159)	29	-28 (-444 ; 389)	3
Chlorinated solvents										
Non-exposed	Ref	2067	Ref	713	Ref	1354	Ref	1010	Ref	1057
Low	29 (-39 ; 96)	202	-53 (-194 ; 88)	34	48 (-30 ; 126)	168	35 (-50 ; 120)	165	42 (-79 ; 163)	37
High	-13 (-109 ; 83)	95	-213 (-441 ; 15)	13	19 (-89 ; 127)	82	4 (-108 ; 115)	90	-112 (-438 ; 213)	5
Other solvents										
Non-exposed	Ref	1808	Ref	637	Ref	1171	Ref	915	Ref	893
Low	-7 (-53 ; 38)	505	-85 (-166 ; -5)*	116	17 (-38 ; 73)	389	-6 (-72 ; 60)	318	13 (-46 ; 72)	187
High	6 (-122 ; 133)	51	157 (-143 ; 458)	7	-14 (-159 ; 131)	44	-27 (-209 ; 156)	32	69 (-99 ; 237)	19
FEV₁/IVC (%)										
Solvent Exposure ^a	All	N	Never smokers	N	Ever smokers	N	Males	N	Females	N
	b (95% CI)		b (95% CI)		b (95% CI)		b (95% CI)		b (95% CI)	
Aromatic solvents										
Non-exposed	Ref	1755	Ref	644	Ref	1111	Ref	731	Ref	1024
Low	-0.9 (-1.7 ; -0.1)*	577	-1.0 (-2.6 ; 0.5)	115	-0.8 (-1.8 ; 0.1)	462	-0.9 (-1.8 ; 0)	505	-0.6 (-2.3 ; 1.2)	72
High	-1.3 (-4.0 ; 1.4)	32	3.1 (-10.9 ; 17.1)	1	-1.4 (-4.3 ; 1.5)	31	-1.4 (-4.4 ; 1.6)	29	0.7 (-7.6 ; 9.1)	3
Chlorinated solvents										
Non-exposed	Ref	2067	Ref	713	Ref	1354	Ref	1010	Ref	1057
Low	0.7 (-0.4 ; 1.8)	202	0 (-2.5 ; 2.5)	34	-0.9 (-2.3 ; 0.6)	168	0.9 (-0.4 ; 2.3)	165	-0.1 (-2.5 ; 2.4)	37
High	1.7 (0.1 ; 3.3)*	95	0.9 (-3.2 ; 4.9)	13	2.5 (-2.8 ; 7.8)	82	1.9 (0.1 ; 3.6)*	90	1.0 (-5.5 ; 7.5)	5
Other solvents										
Non-exposed	Ref	1808	Ref	637	Ref	1171	Ref	915	Ref	893
Low	0.3 (-0.5 ; 1.1)	505	0.9 (-0.4 ; 2.2)	116	0.7 (-0.3 ; 1.6)	389	0.9 (-0.2 ; 1.9)	318	-0.5 (-1.7 ; 0.6)	187
High	-0.2 (-2.4 ; 1.9)	51	1.8 (0 ; 3.6)*	7	-0.6 (-3.0 ; 1.9)	44	-0.6 (-3.5 ; 2.2)	32	0.7 (-2.6 ; 4.1)	19

^a Occupational exposures (no/low/high) were estimated based on job title and function using the ALOHA+ Job Exposure Matrix. Non-exposed subjects were assigned as reference category (Ref).

Significantly different for never and ever smokers (i.e. p-value for interaction < 0.05).

Additional information 1. Pesticide use in the northern Dutch provinces since 1985

Between 1985 and today roughly 90% of agriculture in the northern Dutch provinces consisted of arable crops, on average ~30% potatoes, ~30% cereals, ~15% beets and ~15% maize (for animal feeding). The area of maize has increased since 1985, whereas cereal cultivation has decreased. There is little fruit growing, bulb cultivation or greenhouses in this area. In terms of pesticide use this means that mainly herbicides have been applied (cereals, beets, maize) and substantial fungicide use on potatoes (mainly dithiocarbamate fungicides).

- **Potatoes:** Dithiocarbamate fungicides (maneb, mancozeb), organotin-fungicides (fentin-acetate), quaternary ammonium herbicides (paraquat, diquat) and other fungicides like cymoxanil and fluazinam.
- **Cereals:** Phenoxy herbicides (MCPA, MCPP), urea herbicides (isoproturon), growth regulator chlormequat, conazole fungicides (propiconazole, prochloraz, epoxiconazole etc).
- **Beets:** Carbamate herbicides (phenmedipham, desmedipham), other herbicides like metamitron, chloridazone, ethofumesate and glyphosate.
- **Maize:** triazine herbicides (atrazine, terbutylazin), anilide herbicides (metolachloor, propachloor), other herbicides like bentazone and pyridate.

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