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Occupational exposures to solvents and metals are associated with fixed airflow obstruction ¹

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¹ *Supplementary material*

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METHODS

Quality and Calibration measures for lung function

All participant testing was performed in accredited lung function laboratories with trained staff and strictly followed ATS/ERS guidelines. Briefly, the accuracy of spirometer was checked regularly at the study site per the manufacturer's guideline with a 3L calibration syringe (15 mL volume calibration was used). The calibrated syringe was stored at the same temperature, maintained at the same humidity, kept away from sunlight and heat sources. Spirometers were also checked regularly to identify any leakages or mechanical errors.

Z-score conversion of lung function

We also calculated z-score values for post-bronchodilator FEV₁, FVC, and FEV₁/FVC from the Global Lung Initiative (GLI-2012) regression equations (1) which have been validated in an Australian population (2) and D_{LCO} from the reference equation by Thompson and colleagues (3). A z-score is the deviation from the mean predicted value, where 95% of the normally distributed population mean lies between -1.96 standard deviation (SD) to +1.96 SD. In other words, a positive z-score indicates the data point is above the population mean whereas a negative z-score indicates the data point is below the population mean. For example, if the z-score of the FEV₁ = -1.0, that signifies that the FEV₁ is less than the mean of the reference population (4). We also used pre-BD lung function to define airflow obstruction (AO) and compare the effect estimates observed with fixed nature of AO.

Definitions of confounding variables

Current asthma was defined by an affirmative response to the question “Have you, at any time in your life, suffered from attacks of asthma or wheezy breathing?” and having the last attack of asthma within last 12 months. Childhood asthma was defined as asthma reported at age 7 and 13 by an affirmative response by the parents to the question “Has he/she at any time of his/her life suffered from attacks of asthma or wheezy breathing?” Smoking status of the participants was categorized as current, past and never-smokers. Current smoker was defined as smoking status within last four weeks. Pack-years were calculated as the number of cigarettes smoked per day divided by 20 multiplied by the number of years of smoking (5). Childhood and adulthood socioeconomic status were defined using Australian census data of Socio-Economic Indexes for Areas (SEIFA indexes) (6). We used

the Index of Education and Occupation (IEO) variables that focused on the skills of the people required in different occupations. A high IEO score indicated that individuals who lived in that area had high qualifications and highly skilled jobs.

RESULTS

A comparison of non-responders to different parts of the 2002 to 2008 follow-up study is shown in Supplementary material (Supplementary Table S1). We had a higher proportion of men in our “laboratory invitees but non-attenders” group, and our “laboratory invitees but non-attenders” were also more likely to be current and heavier smokers. Current employment status (employed or not) was not significantly different between the groups. Overall, 29.4% were exposed to aromatic solvents, 23.6% exposed to metals, 21.9% exposed to chlorinated solvents and 39.6% of participants were exposed to other solvents. Men were more likely to have had any exposure and to have had greater cumulative-EU-years to both solvents and metals than women (Supplementary Table S2).

Supplementary Table S1: Comparisons of characteristics between responders and non-responders at of 2002 to 2008 follow-up study

Study characteristics	Laboratory attendees	Laboratory non-attendees	p-value*	Completed Postal survey only	p-value**
Sample size	N=1,397	N=990		N=3,350	
Sex, %			0.03		0.92
Men	684 (51.6)	509 (54.3)		1,574 (50.6)	
Women	651 (48.3)	417 (45.6)		1,558 (49.3)	
Smoking history					
Never, n (%)	586 (44.6)	323 (36.8)		1,366 (41.0)	
Past, n (%)	413 (29.6)	259 (27.3)		1,037 (30.9)	
Pack-years, median[IQR]	7.5[2-17.4]	11[2.3-22.5]	<0.001	8 [2-18.8]	0.71
Current, n (%)	392 (25.7)	395 (35.8)		933 (28.0)	
Pack-years, median[IQR]	21[9.5-30]	23.3[13.5-33.7]		19.5[10-29.4]	
Currently employed, n (%)	1,182 (87.0)	802 (84.4)	0.16	2,868 (85.9)	0.28
Ever asthma	929 (39.8)	686 (44.2)	<0.001	710 (11.7)	<0.001
Child asthma	401 (15.2)	282 (15.3)	<0.001	112 (1.3)	<0.001

Definitions of abbreviations: SD, Standard Deviation; IQR, Interquartile Range;

† The estimate prevalences were calculated using inverse-probability-of-inclusion weights to adjust for the enriched sample of the 2002 to 2008 follow-up survey

* comparing laboratory attendees to non-attendees

** compared postal survey participants to laboratory attendees

Supplementary Table S2: Descriptions of occupational exposures

Exposures	Both (n=1335)				Men (n=684)				Women (n=651)			
Aromatic solvents	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR
Not exposed	943	70.6			369	53.9			574	88.2		
Exposed	392	29.4			315	46.1			77	11.8		
Cumulative exposure			11	4.5-23			13	5-25.5			5	2-10
Chlorinated solvents												
Not exposed	1,042	78.1			446	65.2			596	91.6		
Exposed	293	21.9			238	34.8			55	8.5		
Cumulative exposure			18.5	6.5-45			23	8.5-56			8	2-13.5
Other solvents												
Not exposed	807	60.5			352	51.5			455	69.9		
Exposed	528	39.6			332	48.5			196	30.1		
Cumulative exposure			13	5-24.5			13	6-25			13	4-24.5
Metals												
Not exposed	1,020	76.4			388	56.7			632	97.1		
Exposed	315	23.6			296	43.3			19	2.9		
Cumulative exposure			17	6-42			18	6.5-46			5.5	1.5-26

Supplementary Table S3: Associations between ever exposures and lung functions (n=1335)

Exposures	N	Z-score FEV ₁				Z-score FVC				Z-score FEV ₁ /FVC				Z-score D _{lco}		
		β	95%CI	P-value		β	95%CI	P-value		β	95%CI	P-value		β	95%CI	P-value
Aromatic solvents																
Not exposed	942	Ref.				Ref.				Ref.				Ref.		
Exposed	392	0.05	-0.08 to 0.18	0.44		0.10	-0.02 to 0.22	0.09		-0.05	-0.17 to 0.08	0.47		0.02	-0.09 to 0.15	0.64
Chlorinated solvents																
Not exposed	1,041	Ref.				Ref.				Ref.				Ref.		
Exposed	293	0.02	-0.11 to 0.17	0.68		0.10	-0.02 to 0.23	0.11		-0.07	-0.21 to 0.06	0.29		-0.02	-0.15 to 0.11	0.77
Other solvents																
Not exposed	806	Ref.				Ref.				Ref.				Ref.		
Exposed	528	-0.06	-0.18 to 0.05	0.29		0.01	-0.09 to 0.12	0.79		-0.08	-0.20 to 0.03	0.12		0.02	-0.08 to 0.13	0.63
Metals																
Not exposed	1,019	Ref.				Ref.				Ref.				Ref.		
Exposed	315	-0.05	-0.20 to 0.09	0.48		0.08	-0.05 to 0.22	0.21		-0.17	-0.33 to -0.02	0.01		-0.04	-0.19 to 0.09	0.49

† Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and childhood and adulthood asthma

Supplementary Table S4: Associations between cumulative-EU-years and lung functions (n=1201)

Exposures	Z-score FEV ₁			Z-score FVC			Z-score FEV ₁ /FVC			Z-score D _{lco}		
	β	95%CI	P-value	β	95%CI	P-value	β	95%CI	P-value	β	95%CI	P-value
Aromatic solvents	-0.01	-0.06 to 0.04	0.84	0.02	-0.02 to 0.06	0.42	-0.03	-0.08 to 0.02	0.23	-0.02	-0.06 to 0.03	0.47
Chlorinated solvents	-0.01	-0.03 to 0.02	0.64	-0.01	-0.02 to 0.02	0.93	0.0	-0.02 to 0.02	0.75	-0.02	-0.04 to 0.01	0.16
Other solvents	-0.01	-0.05 to 0.03	0.71	-0.01	-0.04 to 0.03	0.74	0.0	-0.04 to 0.04	0.86	-0.02	-0.05 to 0.02	0.39
Metals	-0.01	-0.03 to 0.02	0.52	-0.00	-0.02 to 0.02	0.73	0.0	-0.02 to 0.03	0.71	-0.01	-0.04 to 0.01	0.38

Supplementary Table S5: Associations between ever exposures, and airflow obstruction using pre-BD lung function measures

Exposure	Pre-BD FEV ₁ /FVC<0.7				Pre-BD FEV ₁ /FVC<LLN			
	No 1,138	Yes 197	RR	95%CI	No 1,143	Yes 192	RR	95%CI
Aromatic solvents								
Not exposed	816	127	Ref.		819	124	Ref.	
Exposed	322	70	1.21	0.84-1.74	324	68	1.23	0.85-1.78
Chlorinated solvents								
Not exposed	896	146	Ref.		899	143	Ref.	
Exposed	242	51	1.12	0.76-1.65	244	49	1.12	0.75-1.65
Other solvents								
Not exposed	705	102	Ref.		709	98	Ref.	
Exposed	433	95	1.39	1.00-1.93	434	94	1.46	1.05-2.05
Metals								
Not exposed	886	134	Ref.		890	130	Ref.	
Exposed	252	63	1.47	1.00-2.21	253	62	1.57	1.04-2.39

† Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and childhood and adulthood asthma .

Supplementary Table S6: Association between cumulative EU-years, and airflow obstruction using pre-BD lung function measures

Cumulative EU-years	Pre-BD FEV ₁ /FVC<0.7			Pre-BD FEV ₁ /FVC<LLN		
	RR	95% CI	p-value	RR	95% CI	p-value
Aromatic solvents	1.00	0.98-1.01	0.82	1.00	0.98-1.01	0.87
Chlorinated solvents	0.99	0.98-1.00	0.31	0.99	0.99-1.00	0.59
Other solvents	0.99	0.98-1.01	0.69	0.99	0.98-1.01	0.80
Metals	0.99	0.98-1.00	0.29	0.99	0.98-1.00	0.58

† Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and childhood and adulthood asthma .

Supplementary Table S7: Associations between ever exposures, fixed airflow obstruction-GOLD and fixed airflow obstruction-LLN

stratified by sex

Exposure	Fixed AO -GOLD								Fixed AO -LLN							
	Men				Women				Men				Women			
	No 614	Yes 70	RR	95%CI	No 608	Yes 43	RR	95%CI	No 615	Yes 69	RR	95%CI	No 608	Yes 43	RR	95%CI
Aromatic solvents																
Not exposed	338	31	Ref.		535	39	Ref.		338	31	Ref.		535	39	Ref.	
Exposed	276	39	1.43	0.83-2.44	73	4	0.53	0.15-1.91	277	38	1.39	0.81-2.38	73	4	0.53	0.15-1.91
Chlorinated solvents																
Not exposed	405	41	Ref.		559	37	Ref.		405	41	Ref.		559	37	Ref.	
Exposed	209	29	1.29	0.75-2.22	49	6	2.03	0.78-5.30	210	28	1.25	0.72-2.15	49	6	2.03	0.78-5.30
Other solvents																
Not exposed	321	31	Ref.		428	27	Ref.		321	31	Ref.		428	27	Ref.	
Exposed	293	39	1.25	0.74-2.14	180	16	1.49	0.74-3.01	294	38	1.23	0.72-2.08	180	16	1.49	0.74-3.01
Metals																
Not exposed	356	32	Ref.		592	40	Ref.		356	32	Ref.		592	40	Ref.	
Exposed	258	38	1.63	0.95-2.80	16	3	1.88	0.40-8.95	259	37	1.58	0.92-2.73	16	3	1.88	0.40-8.95

Supplementary Table S8: Job distribution of number of participants exposed to chlorinated solvents

Job title description	ISCO-88	Number of participants
<i>Women exposed to chlorinated solvents</i>		
Hand-laundrers and pressers	9133	12
Sculptors, painters and related artists	2452	11
Decorators and commercial designers	3471	9
Chemist	2113	9
Hairdresser or beauticians	5141	7
Chemical and physical science technicians	3111	5
Precision, handicraft, printing and related trades workers	7300	2
	Total	55
<i>Men exposed to chlorinated solvents</i>		
Metal-, rubber- and plastic-products assemblers	8284	46
Glass, ceramics and related decorative painters	7324	38
Mechanical engineering technicians	3115	32
Electrical and electronic equipment mechanics and fitters	7240	27
Sheet metal workers	7213	27
Painters, building structure cleaners and related trades workers	7140	25
Blacksmiths, tool-makers and related trades workers	7220	18
Wood treaters, cabinet-makers and related trades workers	7420	13
Metal finishing-, plating- and coating-machine operators	8223	12
Ships' engineers	3141	6
	Total	238

REFERENCES

1. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et.al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324-1343.
2. Hall GL, Thompson BR, Stanojevic S, Abramson MJ, Beasley R, Coates A, et al. The Global Lung Initiative 2012 reference values reflect contemporary Australasian spirometry. *Respirology* 2012; 17: 1150-1151.
3. Thompson BR, Johns DP, Bailey M, Raven J, Walters EH, Abramson MJ. Prediction equations for single breath diffusing capacity (TICO) in a middle aged caucasian population. *Thorax* 2008; 63: 889-893.
4. Lambert A, Drummond MB, Wei C, Irvin C, Kaminsky D, McCormack M, et al. Diagnostic accuracy of FEV₁/forced vital capacity ratio z scores in asthmatic patients. *J Allergy Clin Immunol* 2015; 136: 649-653.
5. Alif S, Dharmage S, Benke G, Dennekamp M, Burgess JA, Perret JL, et al. Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age. *Thorax* 2017 (In press).
6. Australian Bureau of Statistics. Socio-Economic Indexes for Areas (SEIFA) Technical Paper. Canberra.:Commonwealth of Australia; 2011. ABS Catalogue no. 2033.0.55.001; 2011.