Supplementary Material

Title: Occupational exposure to solvents is associated with lung function decline: population-based Tasmanian Longitudinal Health Study

Authors

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Justification for assessing effect modifications

Tobacco smoking remains the predominant risk factor for airflow obstruction and lung function decline universally, and it is now well established that smoking modifies the effect of other risk factors for airflow obstruction and lung function decline.(1, 2) Despite the effect of smoking, several cross-sectional studies have suggested that prevlence of airflow obstruction is higher in women, but the reason for this increase prevalence was not known.(3, 4) Some have suggested that effect modification could be present between sex and occupational exposures,(5) while others have suggested that differential prevalences of occupational exposures might explain the differential effects in men and women.(6) Based on this evidence from previous studies (5-7) and official statements from the American Thoracic Society,(1, 8) we hypothesised that sex could act as an effect modifier.

There is increasing evidence that asthma modifies the effect of other risk factors including one study from our group.(2) However, most of the previous cross-sectional studies that have assessed occupational exposure and lung function decline using JEM have not taken asthma into account as a confounder.(9, 10) Some of them have excluded asthmatics altogether (10, 11) and others have performed sensitivity analyses to observe any changes in effect estimates.(12, 13) We have cross-sectionally investigated asthma as an effect modifier in our previous paper.(9) However, none of the previous longitudinal studies on occupational exposures have investigated effect modification with asthma, sex and smoking, so we are the first to do this.

Statistical analysis

We included 767 participants with complete lung function and work history calendar data in ever exposure analysis, but the participants with missing work history calendar (n=44) were excluded in cumulative EU-years analysis. We performed two-stages multiple imputation by imputing the missing confounding variables into our final adjusted models (Table E3). We have missing variables ranged from 1-3% for packyears smoked, adult asthma, child asthma, smoking status, and socioeconomic status. Assuming ignorability held, they were considered missing completely at random. In the first model, the missing values were imputed by using chained equations ("mi impute chained" command) for 20 imputations in Stata. In the second phase, regression analyses were conducted using the imputed data on all confounding variables. The variables included in the imputation models were the same as those used in the complete case analysis models to ensure compatibility between imputed and the complete case analysis model. We additionally added childhood lung function (FEV_1) and baseline pre-bronchodilator

lung function (FEV_1) as auxiliary variables in the imputed models (Table E7). Finally, imputed models were compared to the complete case analyses.

Results

Table E1: Distribution of occupational exposures (n=767)

Exposures	Not exposed n (%)	Exposed n (%)	Cumulative EU- years median (Q1, Q3)
Biological dust	350 (47.1)	417 (52.8)	16 (6, 29.5)
Mineral dust	379 (49.9)	388 (50.1)	17.5 (6, 44)
Gases/fumes	223 (29.4)	544 (70.5)	19 (8, 33)
Fungicides	646 (86.0)	121 (13.9)	16 (6, 31.5)
Herbicides	665 (87.9)	102 (12.0)	10 (4, 24)
Insecticides	672 (89.0)	95 (10.9)	16 (6, 33.5)
Aromatic solvents	550 (71.5)	217 (28.5)	10.5(4.5, 23)
Chlorinated solvents	616 (79.5)	151 (20.4)	19.5 (7.5, 52)
Other solvents	471 (61.2)	296 (38.7)	14(5, 26)
Metals	606 (78.1)	161 (21.8)	19 (6, 48.5)

Q1, 25th percentile; Q3, 75th percentile

Table E2: Mean changes of lung function parameter in relation to occupational exposures (n=767)

Exposures	n	ΔFEV$_1$ (mL/year) Mean (SE)	ΔFVC (mL/year) Mean (SE)	ΔFEV$_1$/FVC (%/year) Mean (SE)
Biological dust				
Not exposed	350	-26.9 (2.9)	-26.2 (4.7)	-0.7 (0.05)
Exposed	417	-28.4 (2.3)	-39.4 (3.5)	-0.6 (0.04)
Mineral dust				
Not exposed	379	-25.4 (2.6)	-31.5 (3.6)	-0.6 (0.04)
Exposed	388	-30.1 (2.5)	-35.2 (4.4)	-0.6 (0.05)
Gases/fumes				
Not exposed	223	-19.5 (3.7)	-26.0 (4.8)	-0.6 (0.1)
Exposed	544	-31.2 (2.04)	-36.4 (3.5)	-0.6 (0.04)
Fungicides				
Not exposed	654	-27.3 (1.9)	-32.3 (3.1)	-0.6 (0.04)
Exposed	113	-30.5 (4.6)	-39.7 (8.3)	-0.6 (0.1)
Herbicides				
Not exposed	665	-27.0 (1.9)	-31.9 (3.0)	-0.7 (0.03)
Exposed	102	-32.9 (5.2)	-42.6 (9.4)	-0.5 (0.1)
Insecticides				
Not exposed	672	-27.2 (1.9)	-32.1 (3.01)	-0.6 (0.03)
Exposed	95	-31.6 (4.9)	-42.5 (9.2)	-0.5 (0.1)
Aromatic solvents				
Not exposed	550	-23.9 (2.0)	-29.1 (3.1)	-0.6 (0.04)
Exposed	217	-37.6 (3.7)	-44.3 (6.3)	-0.6 (0.06)
Chlorinated solvents				
Not exposed	616	-25.6 (2.0)	-32.2 (3.0)	-0.6 (0.03)
Exposed	151	-36.5 (4.4)	-38.2 (8.1)	-0.7 (0.1)
Other solvents				
Not exposed	471	-24.5 (2.3)	-27.5 (3.3)	-0.6 (0.04)
Exposed	296	-33.0 (2.9)	-42.8 (5.3)	-0.6 (0.05)
Metals				
Not exposed	606	-25.6 (1.9)	-29.6 (2.9)	-0.6 (0.03)
Exposed	161	-35.9 (4.5)	-47.8 (8.4)	-0.6 (0.1)

*SE; standard error

Table E3: Sensitivity analysis between ever exposures to solvents and lung function decline (n=767)

Exposures	ΔFEV$_1$ (mL/year) β (95%CI)		ΔFVC (mL/year) β (95%CI)	
	Main analysis †	**Sensitivity analysis ***	**Main analysis †**	**Sensitivity analysis ***
Aromatic solvents	**-15.5 (-24.8, -6.3)**	**-15.1 (-26.8, -3.5)**	**-14.1 (-28.8, -0.7)**	-11.4 (-29.9, 7.2)
Chlorinated solvents	**-11.6 (-21.5,-1.6)**	-5.5 (-17.3, 6.3)	-3.8 (-19.6, 12.1)	7.8 (-10.9, 26.6)
Other solvents	-6.1 (-14.6, 2.4)	3.6 (-6.9, 13.9)	**-13.2 (-26.6, -0.2)**	-10.6 (-27.1, 6.0)

† Adjusted for sex, height, smoking, pack-years, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weights; the models with solvents and metals were additionally adjusted for both all type of pesticides and VGDF

*Model with aromatic solvents were additionally adjusted for chlorinated and other solvents, model with chlorinated solvents were additionally adjusted for aromatic and other solvents and model with other solvents were additionally adjusted for aromatic and chlorinated solvents

Table E4: Sensitivity analysis between ever exposures and decline in lung function additionally adjusted for baseline pre-bronchodilator lung function (N=767)

Exposures	ΔFEV$_1$ (mL/year) β (95%CI) †		ΔFVC (mL/year) β (95%CI) †		ΔFEV$_1$/FVC (%/year) β (95%CI) †	
	Main analysis †	**Sensitivity analysis ***	**Main analysis †**	**Sensitivity analysis ***	**Main analysis †**	**Sensitivity analysis ***
Biological dust	0.5 (-7.7, 8.7)	-0.49 (-8.0, 8.0)	-9.3 (-22.2, 3.6)	-9.6 (-22.5, 3.3)	0.05 (-0.1, 0.2)	0.05 (-0.1, 0.2)
Mineral dust	-4.6 (-13.1, 4.0)	-4.5 (-12.9, 3.7)	3.7 (-9.7, 17.2)	3.7 (-9.7, 11.8)	**-0.2 (-0.3, -0.02)**	**-0.2 (-0.3, -0.01)**
Gases/fumes	**-11.4 (-20.0, -2.9)**	**-12.3 (-20.7, -3.9)**	-4.9 (-18.6, 8.6)	-5.5 (-19.1, 8.0)	**-0.2 (-0.4, -0.1)**	**-0.2 (-0.4, -0.5)**
Fungicides	-2.4 (-13.3,8.4)	-0.72 (-11.3, 9.9)	-3.0 (-20.1,14.1)	-1.9 (-18.9, 15.1)	0.04 (-0.2, 0.2)	0.03 (-0.2, 0.2)
Herbicides	-4.9 (-16.0,6.3)	-2.7 (-13.6, 8.2)	-6.5 (24.1,11.1)	-5.2 (-22.8, 12.4)	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)
Insecticides	-2.8 (-14.3,8.6)	-1.1 (-12.3, 10.1)	-6.5 (-24.6, 11.6)	-5.5 (-23.5, 12.6)	0.2 (-0.1, 0.4)	0.1 (-0.1, 0.4)
Aromatic solvents	**-15.5 (-24.8, -6.3)**	**-14.2 (-23.2, -5.1)**	**-14.1 (-28.8, -0.7)**	-13.3 (-27.9, 1.4)	-0.05 (-0.2, 0.1)	-0.05 (-0.2, 0.1)
Chlorinated solvents	**-11.6 (-21.5,-1.6)**	**-9.8 (-19.6, -0.02)**	-3.8 (-19.6, 12.1)	-2.7 (-18.5, 13.1)	-0.1 (-0.3, 0.04)	-0.1 (-0.3, 0.04)
Other solvents	-6.1 (-14.6, 2.4)	-6.4 (-14.7, 1.9)	**-13.2 (-26.6, -0.2)**	**-13.4 (-26.8, -0.1)**	0.02 (-0.1, 0.2)	0.02 (-0.1, 0.2)
Metals	**-11.3 (-21.9, -0.7)**	**-11.7 (-22.1, -1.3)**	**-17.5 (-34.3, -0.8)**	**-17.7 (-34.5, -1.0)**	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)

† Adjusted for sex, height, smoking, pack-years, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weights; the models with exposures to biological dust, mineral dust, gases/fumes and VGDF were additionally adjusted for all type of pesticides, the models with exposures to fungicides, herbicides and insecticides additionally adjusted for VGDF, and the models with exposures to solvents and metals were additionally adjusted for both all type of pesticides and VGDF

*Models additionally adjusted for baseline (2002 to 2008 follow-up) raw lung function (FEV$_1$)

Table E5: Associations between ever exposures and decline in lung function using multiple linear regression and random-effect linear regression (N=767)

Exposures	**ΔFEV$_1$** (mL/year)		**ΔFVC** (mL/year)		**ΔFEV$_1$/FVC** (%/year)	
	β (95%CI) †		**β (95%CI) †**		**β (95%CI) †**	
	Multiple linear regression	**Random-effect linear regression**	**Multiple linear regression**	**Random-effect linear regression**	**Multiple linear regression**	**Random-effect linear regression**
Biological dust	0.5 (-7.7, 8.7)	-0.5 (-7.6, 8.6)	-9.3 (-22.2, 3.6)	-9.3 (-22.1, 3.5)	0.05 (-0.1, 0.2)	0.05 (-0.1, 0.2)
Mineral dust	-4.6 (-13.1, 4.0)	-4.5 (-12.9, 3.9)	3.7 (-9.7, 17.2)	3.8 (-9.6, 17.1)	**-0.2 (-0.3, -0.02)**	**-0.2 (-0.3, -0.02)**
Gases/fumes	**-11.4 (-20.0, -2.9)**	**-11.4 (-19.9, -2.9)**	-4.9 (-18.6, 8.6)	-4.9 (-18.4, 8.5)	**-0.2 (-0.4, -0.1)**	**-0.2 (-0.4, -0.1)**
Fungicides	-2.4 (-13.3,8.4)	-2.4 (-13.1, 8.3)	-3.0 (-20.1,14.1)	-2.9 (-19.9, 13.9)	0.04 (-0.2, 0.2)	0.04 (-0.2, 0.2)
Herbicides	-4.9 (-16.0,6.3)	-4.9 (-15.9, 6.2)	-6.5 (24.1,11.1)	-6.5 (-23.9, 10.9)	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)
Insecticides	-2.8 (-14.3,8.6)	-2.9 (-14.1, 8.5)	-6.5 (-24.6, 11.6)	-6.5 (-24.4, 11.4)	0.2 (-0.1, 0.4)	0.2 (-0.1, 0.4)
Aromatic solvents	**-15.5 (-24.8, -6.3)**	**-15.5 (-24.7, -6.4)**	**-14.1 (-28.8, -0.7)**	**-14.1 (-28.6, -0.5)**	-0.05 (-0.2, 0.1)	-0.05 (-0.2, 0.1)
Chlorinated solvents	**-11.6 (-21.5,-1.6)**	**-11.6 (-21.4, -1.7)**	-3.8 (-19.6, 12.1)	-3.8 (-19.4, 11.9)	-0.1 (-0.3, 0.04)	-0.1 (-0.3, 0.04)
Other solvents	-6.1 (-14.6, 2.4)	-6.1 (-14.5, 2.3)	**-13.2 (-26.6, -0.2)**	**-13.2 (-26.5, -0.2)**	0.02 (-0.1, 0.2)	0.02 (-0.1, 0.2)
Metals	**-11.3 (-21.9, -0.7)**	**-11.3 (-21.8, -0.9)**	**-17.5 (-34.3, -0.8)**	**-17.5 (-34.1, -0.9)**	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)

† Adjusted for sex, height, smoking, pack-years, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weights; the models with exposures to biological dust, mineral dust, gases/fumes and VGDF were additionally adjusted for all type of pesticides, the models with exposures to fungicides, herbicides and insecticides additionally adjusted for VGDF, and the models with exposures to solvents and metals were additionally adjusted for both all type of pesticides and VGDF

Table E6: Multivariable association between cumulative EU-years (without weighted by exposure intensity) and lung function decline (N=723)

Cumulative Exposures-Unit years	**ΔFEV$_1$** (mL/year)		**ΔFVC** (mL/year)		**ΔFEV$_1$/FVC** (%/year)	
	β (95%CI) †	**p-value**	**β (95%CI) †**	**p-value**	**β (95%CI) †**	**p-value**
Biological dust	0.1 (-0.08, 0.3)	0.25	-0.03 (-0.3, 0.3)	0.84	0.0 (-0.002, 0.004)	0.46
Mineral dust	-0.04 (-0.2, 0.1)	0.63	-0.01 (-0.3, 0.3)	0.93	-0.0 (-0.004, 0.001)	0.31
Gases/fumes	-0.1 (-0.3, 0.4)	0.12	-0.2 (-0.4, 0.1)	0.25	-0.0 (0.004, 0.002)	0.33
Fungicides	-0.02 (-0.2, 0.2)	0.79	0.02 (-0.2, 0.3)	0.91	-0.0 (-0.002, 0.004)	0.76
Herbicides	0.03 (-0.2, 0.3)	0.76	0.02 (-0.3, 0.4)	0.89	0.001 (-0.002, 0.01)	0.49
Insecticides	-0.04 (-0.2, 0.2)	0.70	-0.03 (-0.3, 0.3)	0.87	0.0 (-0.002, 0.004)	0.39
Aromatic solvents	-0.3 (-0.5, -0.03)	0.06	-0.3 (-0.7, 0.1)	0.16	0.001 (-0.006, 0.004)	0.65
Chlorinated solvents	-0.2 (-0.4,0.0)	0.06	-0.1 (-0.5, 0.2)	0.38	-0.002 (-0.006, 0.002)	0.25
Other solvents	0.0 (-0.2, 0.2)	0.99	-0.3 (-0.7, 0.1)	0.10	0.001 (-0.003, 0.005)	0.70
Metals	-0.1 (0.3, 0.1)	0.19	-0.2 (-0.5, 0.1)	0.19	-0.001 (-0.005, 0.002)	0.41

† Adjusted for sex, height, smoking, pack-years, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weights; the models with exposures to biological dust, mineral dust, gases/fumes and VGDF were additionally adjusted for all type of pesticides, the models with exposures to fungicides, herbicides and insecticides additionally adjusted for VGDF, and the models with exposures to solvents and metals were additionally adjusted for both all type of pesticides and VGDF

Table E7: Associations between ever exposures and lung function decline using complete case analysis and multiple imputation (n=767)

Exposures	ΔFEV$_1$ (mL/year)		ΔFVC (mL/year)		ΔFEV$_1$/FVC (%/year)	
	β (95%CI)		β (95%CI)		β (95%CI)	
	Complete case †	Imputed *	Complete case †	Imputed *	Complete case †	Imputed *
Biological dust	0.5 (-7.7, 8.7)	0.6 (-7.4, 8.6)	-9.3 (-22.2, 3.6)	-10.8 (-23.4, 1.7)	0.05 (-0.1, 0.2)	0.09 (-0.3, 0.3)
Mineral dust	-4.6 (-13.1, 4.0)	-3.6 (-11.9, 4.6)	3.7 (-9.7, 17.2)	2.2 (-10.8, 15.2)	**-0.2 (-0.3, -0.02)**	-0.4 (-0.5, 1.0)
Gases/fumes	**-11.4 (-20.0, -2.9)**	**-10.7 (-19.1, -2.4)**	-4.9 (-18.6, 8.6)	-6.5 (-19.7, 6.6)	**-0.2 (-0.4, -0.1)**	-0.5 (-0.8, 0.4)
Fungicides	-2.4 (-13.3,8.4)	-0.9 (-20.7, 18.9)	-3.0 (-20.1,14.1)	0.3 (-30.9, 31.5)	0.04 (-0.2, 0.2)	1.2 (-0.9, 3.2)
Herbicides	-4.9 (-16.0,6.3)	-12.3 (-37.1, 12.5)	-6.5 (24.1,11.1)	-12.5 (-51.5, 26.6)	0.1 (-0.1, 0.3)	1.5 (-0.9, 2.2)
Insecticides	-2.8 (-14.3,8.6)	-3.9 (-25.9, 18.1)	-6.5 (-24.6, 11.6)	-10.9 (-45.5, 23.7)	0.2 (-0.1, 0.4)	2.3 (-0.5, 3.3)
Aromatic solvents	**-15.5 (-24.8, -6.3)**	**-14.8 (-23.5, -6.2)**	**-14.1 (-28.8, -0.7)**	-13.6 (-27.2, 0.1)	-0.05 (-0.2, 0.1)	-0.8 (-0.6, 0.8)
Chlorinated solvents	**-11.6 (-21.5,-1.6)**	**-12.0 (-21.3, -2.6)**	-3.8 (-19.6, 12.1)	-5.4 (-20.2, 9.4)	-0.1 (-0.3, 0.04)	-0.6 (-1.0, 0.7)
Other solvents	-6.1 (-14.6, 2.4)	**-7.8 (-15.3, -0.3)**	**-13.2 (-26.6, -0.2)**	**-13.3 (-25.0, -1.5)**	0.02 (-0.1, 0.2)	0.4 (-0.5, 1.2)
Metals	**-11.3 (-21.9, -0.7)**	**-10.9 (-20.9, -1.1)**	**-17.5 (-34.3, -0.8)**	**-16.4 (-32.0, -0.9)**	-0.1 (-0.3, 0.1)	-0.6 (-0.8, 0.4)

† Adjusted for sex, height, smoking, pack-years, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weights; the models with exposures to biological dust, mineral dust, gases/fumes and VGDF were additionally adjusted for all type of pesticides, the models with exposures to fungicides, herbicides and insecticides additionally adjusted for VGDF, and the models with exposures to solvents and metals were additionally adjusted for both all type of pesticides and VGDF

* Auxiliary variables were childhood lung function (FEV$_1$) and baseline baseline (2002 to 2008 follow-up) raw lung function (FEV$_1$)

Table E8: Effect modification by smoking status and asthma status on the relationship between cumulative EU-years to aromatic solvents and lung function decline stratified by smoking and asthma status (N=694)

Cumulative exposure-unit years to aromatic solvents	Ever smoker † β (95% CI)	Never-smoker † β (95% CI)	p-trend for effect modification	Asthmatic § β (95% CI)	Non-asthmatic § β (95% CI)	p-trend for effect modification
ΔFEV$_1$ (mL/year)	**-0.7 (-1.2, -0.25)**	-0.4 (-1.1, 0.4)	0.42	**-0.9 (-1.7, -0.2)**	**-0.6 (-0.9, -0.1)**	0.35
ΔFVC (mL/year)	**-1.1 (-1.8, -0.44)**	-0.4 (-1.5, 0.7)	0.29	**-1.5 (-2.7, -0.4)**	**-0.8 (-1.5, -0.1)**	0.27
ΔFEV$_1$/FVC (%/year)	0.1 (-0.1, 0.1)	0.1 (0.01, 0.2)	0.96	0.0 (-0.01, 0.01)	0.0 (-0.0, 0.01)	0.91

†Adjusted for height, sex, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weights; the models with exposures to solvents were additionally adjusted for both all type of pesticides and VGDF

§ Adjusted for height, smoking, pack-years, childhood and adulthood socioeconomic status, and sampling weights; the models with exposures to solvents were additionally adjusted for both all type of pesticides and VGDF

Table E9: Spearman Rank Correlations between the exposures as ever and never exposures in the 2002 to 2008 and 2010 to 2012 follow-ups

	Dusts				Pesticides			Solvents			
Correlation	**Biological Dust**	**Mineral Dust**	**Gases and Fumes**	**VGDF**	**Fungicides**	**Herbicides**	**Insecticides**	**Aromatic solvents**	**Chlorinated solvents**	**Other solvents**	**Metals**
Biological Dust		0.47	0.54	0.63	0.38	0.35	0.34	0.26	0.04	0.37	0.05
Mineral Dust			0.60	0.58	0.39	0.37	0.36	0.47	0.32	0.31	0.47
Gases and Fumes				0.90	0.27	0.25	0.24	0.38	0.30	0.43	0.32
VGDF					0.25	0.22	0.22	0.35	0.27	0.45	0.29
Fungicides						0.90	0.86	0.24	-0.03	0.04	0.04
Herbicides							0.83	0.24	-0.02	0.03	0.05
Insecticides								0.22	-0.02	0.01	0.03
Aromatic solvents									0.55	0.59	0.54
Chlorinated solvents										0.52	0.63
Other solvents											0.41

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Figure legends

Figure E1: Overall statistical approaches

Figure E2: Summary of confounding variables adjustment in each steps of statistical analyses