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Residential exposure to outdoor air pollution and post-bronchodilator lung function deficits in mid-adult life

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To the editor

The World Health Organization estimates that outdoor air pollution is linked to 4.2 million premature deaths globally and is a major contributor to the burden of chronic obstructive pulmonary disease (COPD) (1). There is good evidence implicating outdoor air pollution in reducing lung function growth (2), but evidence supporting its contribution to fixed airflow obstruction in adults is less clear (2-4). Pollution-related reductions in both FEV_1 and FVC with a non-obstructive pattern i.e. preserved FEV_1/FVC have mainly been reported previously, with contributions from individual pollutants being inconclusive (5). Our research group has reported similar spirometric findings with residential markers of nitrogen dioxide (NO_2) and distance from a major road (DMR) in the relatively unpolluted setting of Australia (6, 7).

We now extend our investigation to include pollution-related influences on diffusing capacity ($D_L$co) and static lung volumes in middle-age. This is especially relevant given recent literature which raised the possibility of pollution-related, radiological features of interstitial lung disease (8). Thus, we aimed to examine physiological evidence of a potential restrictive pollution-lung function process and its potential modification by smoking.

We analyzed data from the Tasmanian Longitudinal Health Study (TAHS) cohort, details of which have been published (7). Briefly, children born in 1961 and in school in Tasmania in 1968 (n=8,583, 99%) were retraced and resurveyed during 2002–2005 (n=5,729 respondents). A subpopulation that attended multiple previous surveys was then enriched for asthma and current respiratory symptoms and invited to participate in a laboratory study during 2006–2008 (n=2,373). Post-bronchodilator (BD) spirometry (n=1,389), $D_L$co and static lung volumes were measured in accordance with the corresponding ATS/ERS 2005 standard. Predicted values were derived using established reference values (Global Lung Initiative 2012) and equations (Thompson and colleagues 2008, and Quanjer and colleagues 1993). Written informed consent

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was obtained from all participants (Ethics: University of Melbourne 040375). Some results of the current study have been previously reported in conference abstracts (9-11).

Residential addresses of participants were geocoded and distance to the nearest freeway, highway and/or arterial road calculated (6, 7). For the year of lung function testing, mean annual outdoor nitrogen dioxide (NO_2) concentrations were estimated using a validated satellite-based land-use regression model [validation R^2= 66%, RMSE= 2ppb [25%], mean bias= –0.2ppb] (12, 13), as a proxy for long-term exposure to the complex mixture of mainly traffic-related air pollution (TrAP) pollutants (14). Multivariable linear regression included an interaction term with a 3-category variable that captured both ever/never smoking and pack-years. Results were scaled to an interquartile range increase in annual mean NO_2 exposure, which in this sample was 2.2 ppb. Results did not change when adjusting for sampling weights to account for sampling based on respiratory characteristics (data not shown).

Baseline participant characteristics have been summarized in Table 1. Across the entire population, the median NO_2 concentration was 3.66 parts per billion [ppb, interquartile range 2.95, 5.15], and 28% (n=346) of participants lived within 200m of a major road.

Across all participants, exposure to NO_2 was associated with reduced lung diffusing capacity ($D_L$co) in an exposure-response manner, independent of smoking history (Table 2, $p<0.001$). Main associations were also seen between NO_2 concentration and decreased TLC and FRC levels, although modest in magnitude (Table 2, $p=0.032$ and $p=0.022$ respectively).

Interactions between the effects of residential markers of air pollution and smoking on lung function were mainly seen for DMR (Table 2). Compared with living ≥200m from a major

road, DMR<200m was associated with lower post-BD FEV_1/FVC levels, but only for ever-smokers with a <10 pack-year history (z-score –0.38, p=0.008, p-interaction=0.002, Table 2). This estimate which refers to the difference per unit change in exposure was equivalent to a reduction of 3.46 (95%CI: 1.18–5.74, p=0.003)% predicted. It was statistically greater than for never smokers or heavier ever-smokers with ≥10 pack-year history (p-interaction=0.001 and 0.004 respectively). Conversely, DMR-related reductions in TLC and FRC were seen only for never smokers, where the reduction in TLC of –0.22 SD (95%CI: –0.37, –0.06) was equivalent to 226 (44–409) mL or 3.6 (1.0–6.1)% predicted.

This is the most comprehensive cross-sectional investigation of outdoor air pollution and lung function abnormality beyond spirometry in a middle-aged population to date, and in a relatively low pollution setting. Specifically, we have uncovered an exposure-response relationship between higher residential NO_2 exposure and lower $D_L$co levels that was independent of smoking. We also provided supporting evidence of an obstructive influence for those smoking <10 pack-years and living within 200m of a major road, which paradoxically was not apparent for smokers with a greater pack-year history. While the NO_2-related increase in RV suggested an obstructive effect with air trapping in heavier smokers, the static lung volumes for non-smokers residing within 200m of a major road support the co-presence of a restrictive lung process that might potentially influence the FEV_1/FVC ratio.

We acknowledge that our exposure measure was based on residential addresses, so combining with work addresses may have improved exposure accuracy. Similarly, we performed a cross-sectional analysis without either back-extrapolating a cumulative exposure of NO_2 beyond a year or factoring in any residential mobility and/or duration. While no single pollutant is an ideal proxy for TrAP, NO_2 is preferred as a marker of this complex mixture (14). Our

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nationwide satellite-based LUR model allowed us to assign exposures consistently, although estimations might be less accurate near pollutant "hot-spots" such as road intersections or localised industry (12). A similar exposure model for particulate matter of aerodynamic diameter <2.5μm ($PM_{2.5}$) was not available at the time but $PM_{2.5}$ contributes only around 20% to TrAP in Australia.

We have captured differing but complementary information from two different residential markers of TrAP. Notably, we observed adverse exposure-response influence of NO_2 on lung diffusing capacity at ambient levels well below the National Environment Protection Measure of 30ppb, adding to the debate on optimal threshold levels. This finding, combined with other features of a mixed obstructive/restrictive lung function pattern, supports the possibility of lung parenchymal damage from interstitial inflammatory, fibrotic (8) and/or emphysematous processes. Further evaluation using multiple, serial lung function measurements, high-resolution computed tomography chest scans and possibly multi-breath nitrogen washout techniques would be useful.

TABLE 1. Baseline participant characteristics by smoking history

Characteristic	Smoking history (N=1228) †		
	Never smoker (n=536)	Ever, up to 10 pack-years (n=276)	Ever, 10+ pack-years (n=416)
Age (mean years, SD)	44.9 (0.9)	44.8 (0.9)	44.9 (0.8)
Sex (% male)	278 (52)	122 (44)	234 (56)
Current smokers [N(%)]	0 (0)	78 (28)	260 (63)
Pack-years [median (IQR)]	0 (0)	2.45 (0.8, 6)	23 (15, 30)
NO_2 exposure [ppb, median (IQR)]	3.8 (3.0, 5.5)	3.7 (3.1, 5.3)	3.5 (2.8, 4.8)
DMR <200m [N(%)]	152 (28)	67 (24)	119 (29)
Post-BD FEV_1/FVC ‡	–0.08 (0.9)	–0.14 (1.0)	–0.59 (1.1)
Lung diffusing capacity ($D_L$co) ‡	+0.36 (0.8)	+0.25 (0.9)	–0.16 (0.8)
Static lung volumes ‡			
Total lung capacity	+0.35 (0.8)	+0.46 (0.8)	+0.46 (0.8)
Functional residual capacity	–0.05 (0.8)	+0.04 (0.8)	+0.08 (0.8)
Residual volume	–0.02 (0.8)	+0.001 (0.9)	+0.26 (0.9)
RV/TLC	–0.40 (0.6)	–0.44 (0.6)	–0.18 (0.6)

Abbreviations: DMR, distance from a major road; FEV_1/FVC, ratio between forced expiratory volume in 1 second and forced vital capacity; IQR, interquartile range; NO_2, nitrogen dioxide; ppb, parts per billion; py, pack-years; RV/TLC, ratio between residual volume and total lung capacity; SD, standard deviation

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† Those with complete data for analyses with post-bronchodilator spirometry; complete cases for $D_L$co (corrected for hemoglobin and carboxyhemoglobin) and static lung volumes were n=993 and n=1077 respectively

‡ Lung function results expressed in mean (SD) z-score, where z-scores represent the standard deviation from the normal predicted mean

TABLE 2. Multivariable main associations between residential markers of outdoor air pollution and lung function, and interactions by smoking history †‡

		Residential marker of outdoor air pollution [z-scores (SD), 95%CI]		
Continuous lung function outcomes §		**N**	**Distance from a major road (<200m) ‖**	**NO_2 exposure (per IQR) ††**
Main associations				
Post-BD FEV_1/FVC		1228	–0.03 (–0.19, +0.11)	–0.003 (–0.07, +0.06)
Diffusing capacity ($D_L$co)		1037	–0.05 (–0.17, +0.06)	–0.11 (–0.17, –0.06) ***
Static lung volumes				
	TLC	1120	–0.10 (–0.20, +0.01)	–0.06 (–0.11, –0.005) *
	FRC	1111	–0.14 (–0.24, –0.04) **	–0.06 (–0.11, –0.01) *
	RV	1110	–0.10 (–0.21, +0.02)	–0.02 (–0.08, +0.03)
	RV/TLC	1110	–0.03 (–0.12, +0.05)	+0.01 (–0.03, +0.05)

Interactions between the effects of residential pollution and smoking	**Overall p[int]**	**Smoking subgroups [z-scores (SD), 95%CI] ‡**		
		Never smoker (n=486)	**Ever-smoker, up to 10 py (n=268)**	**Ever-smoker ≥10py (n=362)**
DMR				

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Post-BD FEV_1/FVC	0.002‡‡	+0.10 (–0.07, +0.28)	–0.38 (–0.66, –0.10) **	+0.10 (–0.15, +0.34)
TLC	0.199	–0.22 (–0.37, –0.06) **	+0.03 (–0.22, +0.27)	–0.03 (–0.35, +0.29)
FRC	0.046	–0.29 (–0.43, –0.14) ***	+0.05 (–0.19, +0.29)	–0.08 (–0.28, +0.11)
NO_2 exposure §				
RV	0.161	–0.07 (–0.13, +0.01)	–0.08 (–0.19, +0.04)	+0.13 (+0.01, +0.23) *

Definition of abbreviations: ATS/ERS, American Thoracic Society/ European Respiratory Society; BD, bronchodilator; DMR, distance from a major road; FEV_1/FVC, ratio between forced expiratory volume in 1 second and forced vital capacity; FRC, function residual capacity; N, regression number, IQR, interquartile range; NO_2, nitrogen dioxide; p[int], p-interaction value; RV, residual volume; TLC, total lung capacity

**p<0.05 **p<0.01 ***p<0.001*

† Multivariable linear models were adjusted for participant occupation and education at an individual and zip-code level, household cooking and heating, and season; body mass index categories were additional adjustments for static lung volume models

‡ Stratified results by smoking subgroup were only reported if p-interaction < 0.2, otherwise see result for the main association

§ Continuous lung function outcomes were standardized by age, sex, height (and ethnicity) using Global Lung Initiative reference values (spirometry), Thompson et al 2008 ($D_L$co), Quanjer et al 1993 (static lung volumes) and adjusted for body temperature and ambient pressure saturation with water vapor (BTPS) in accordance with ATS/ERS 2005 standards

ǁ Reference group = those residing ≥200m from a major road; z-scores refer to the difference per unit change in exposure

†† Analyzed as a continuous variable; z-scores have been scaled per IQR increase in mean annual NO_2 exposure (i.e. 2.2 parts per billion)

‡‡ p-interaction value across 3 smoking groups; p[int] values between 2 groups were p=0.001 (ever-smokers <10py versus never smokers) and p=0.004 (ever-smokers <10py versus ≥10py)

REFERENCES

1. WHO air pollution. Ambient air pollution: health impacts https://www.who.int/airpollution/ambient/health-impacts/en/ Accessed 28.10.18.
2. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, Romieu I, Silverman EK, Balmes JR. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; 182: 693-718.
3. Schikowski T, Mills IC, Anderson HR, Cohen A, Hansell A, Kauffmann F, Kramer U, Marcon A, Perez L, Sunyer J, Probst-Hensch N, Kunzli N. Ambient air pollution: a cause of COPD? *Eur Respir J* 2014; 43: 250-263.
4. Schikowski T, Adam M, Marcon A, Cai Y, Vierkotter A, Carsin AE, Jacquemin B, Al Kanani Z, Beelen R, Birk M, Bridevaux PO, Brunekeef B, Burney P, Cirach M, Cyrys J, de Hoogh K, de Marco R, de Nazelle A, Declercq C, Forsberg B, Hardy R, Heinrich J, Hoek G, Jarvis D, Keidel D, Kuh D, Kuhlbusch T, Migliore E, Mosler G, Nieuwenhuijsen MJ, Phuleria H, Rochat T, Schindler C, Villani S, Tsai MY, Zemp E, Hansell A, Kauffmann F, Sunyer J, Probst-Hensch N, Kramer U, Kunzli N. Association of ambient air pollution with the prevalence and incidence of COPD. *Eur Respir J* 2014; 44: 614-626.
5. Adam M, Schikowski T, Carsin AE, Cai Y, Jacquemin B, Sanchez M, Vierkotter A, Marcon A, Keidel D, Sugiri D, Al Kanani Z, Nadif R, Siroux V, Hardy R, Kuh D, Rochat T, Bridevaux PO, Eeftens M, Tsai MY, Villani S, Phuleria HC, Birk M, Cyrys J, Cirach M, de Nazelle A, Nieuwenhuijsen MJ, Forsberg B, de Hoogh K, Declerq C, Bono R, Piccioni P, Quass U, Heinrich J, Jarvis D, Pin I, Beelen R, Hoek G, Brunekreef B, Schindler C, Sunyer J, Kramer U, Kauffmann F, Hansell AL, Kunzli N, Probst-Hensch N. Adult lung function and long-term air pollution exposure. ESCAPE: a multicentre cohort study and meta-analysis. *Eur Respir J* 2015; 45: 38-50.
6. Bowatte G, Lodge CJ, Knibbs LD, Lowe AJ, Erbas B, Dennekamp M, Marks GB, Giles G, Morrison S, Thompson B, Thomas PS, Hui J, Perret JL, Abramson MJ, Walters H, Matheson MC, Dharmage SC. Traffic-related air pollution exposure is associated with allergic sensitization, asthma, and poor lung function in middle age. *J Allergy Clin Immunol* 2017; 139: 122-129 e121.
7. Bowatte G, Erbas B, Lodge CJ, Knibbs LD, Gurrin LC, Marks GB, Thomas PS, Johns DP, Giles GG, Hui J, Dennekamp M, Perret JL, Abramson MJ, Walters EH, Matheson MC, Dharmage SC. Traffic-related air pollution exposure over a 5-year period is associated with increased risk of asthma and poor lung function in middle age. *Eur Respir J* 2017; 50.
8. Sack C, Vedal S, Sheppard L, Raghu G, Barr RG, Podolanczuk A, Doney B, Hoffman EA, Gassett A, Hinckley-Stukovsky K, Williams K, Kawut S, Lederer DJ, Kaufman JD. Air pollution and subclinical interstitial lung disease: the Multi-Ethnic Study of Atherosclerosis (MESA) air-lung study. *Eur Respir J* 2017; 50.
9. Perret J, Bowatte G, Knibbs LD, Lodge C, Johns D, Lowe A, Thomas P, Giles G, Morrison S, Walters EH, Abramson M, Dharmage S. Nitrogen dioxide is adversely associated with transfer factor of carbon monoxide in a dose-response manner [abstract]. *Respirology* 2018; 23: TO 036.
10. Perret J, Bowatte G, Knibbs LD, Johns D, Lodge C, Lowe A, Bui DS, Matheson M, Thompson B, Morrison S, Giles G, Walters EH, Abramson M, Dharmage S. Relationships between nitrogen dioxide exposure, post-bronchodilator airflow obstruction and gas transfer in middle-age [abstract]. *Eur Respir J* 2018; 52: PA5067.

AJRCCM Articles in Press. Published on 20-March-2019 as 10.1164/rccm.201811-2139LE

11. Perret JL, Bowatte G, Lodge CJ, Knibbs LD, Lowe AJ, Burgess JA, Thompson BR, Thomas P, Morrison S, Markos J, Abramson MJ, Walters EH, Matheson MC, Dharmage SC. Nitrogen dioxide exposure and its interaction with smoking on measures of chronic obstructive pulmonary disease [abstract]. *International Society of Environmental Epidemiology abstract book* 2017; THC03: 022.
12. Knibbs LD, Hewson MG, Bechle MJ, Marshall JD, Barnett AG. A national satellite-based land-use regression model for air pollution exposure assessment in Australia. *Environ Res* 2014; 135: 204-211.
13. Knibbs LD, Coorey CP, Bechle MJ, Cowie CT, Dirgawati M, Heyworth JS, Marks GB, Marshall JD, Morawska L, Pereira G, Hewson MG. Independent Validation of National Satellite-Based Land-Use Regression Models for Nitrogen Dioxide Using Passive Samplers. *Environ Sci Technol* 2016; 50: 12331-12338.
14. Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects. Special Report 17. Boston, Massachusetts: Health Effects Institute; 2010.