

Ambient Air Pollution and Dysanapsis: Associations with Lung Function and Chronic Obstructive Pulmonary Disease in the Canadian Cohort Obstructive Lung Disease Study

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Abstract

Rationale: Outdoor air pollution is a potential risk factor for lower lung function and chronic obstructive pulmonary disease (COPD). Little is known about how airway abnormalities and lung growth might modify this relationship.

Objectives: To evaluate the associations of ambient air pollution exposure with lung function and COPD and examine possible interactions with dysanapsis.

Methods: We made use of cross-sectional postbronchodilator spirometry data from 1,452 individuals enrolled in the CanCOLD (Canadian Cohort Obstructive Lung Disease) study with linked ambient fine particulate matter (PM_{2.5}) and nitrogen dioxide (NO₂) air pollution estimates. Dysanapsis, or the ratio of the airway-to-lung volume calculated from thoracic computed tomography images, was used to examine possible interactions.

Measurements and Main Results: In adjusted models, 101.7 ml (95% confidence interval [CI], −166.2 to −37.2) and

115.0 ml (95% CI, −196.5 to −33.4) lower FEV₁ were demonstrated per increase of 2.4 µg/m³ PM_{2.5} and 9.2 ppb NO₂, respectively. Interaction between air pollution and dysanapsis was not statistically significant when modeling the airway-to-lung ratio as a continuous variable. However, a 109.8 ml (95% CI, −209.0 to −10.5) lower FEV₁ and an 87% (95% CI, 12% to 213%) higher odds of COPD were observed among individuals in the lowest, relative to highest, airway-to-lung ratio, per 2.4 µg/m³ increment of PM_{2.5}.

Conclusions: Ambient air pollution exposure was associated with lower lung function, even at relatively low concentrations. Individuals with dysanaptic lung growth might be particularly susceptible to inhaled ambient air pollutants, especially those at the extremes of dysanapsis.

Keywords: chronic airflow obstruction; chronic obstructive pulmonary disease; air quality; pulmonary function test; computed tomography

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A complete list of CanCOLD Collaborative Research Group members may be found before the beginning of the REFERENCES.

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At a Glance Commentary

Scientific Knowledge on the

Subject: Air pollution is now recognized by the World Health Organization as the single biggest environmental health risk. Long-term air pollution exposure has been linked to reduced lung growth in children, as well as lung function decline and increased chronic obstructive pulmonary disease (COPD) prevalence and incidence in adults. Recent studies show that a mismatch between airway tree caliber and lung size (i.e., dysanaptic lungs) is associated with a higher risk of COPD. Few studies on COPD have been conducted in locations with relatively low pollution concentrations, and little is known about how air pollution exposure interacts with host factors such as abnormalities of airway and lung growth.

What This Study Adds to the

Field: This is the first study in Canada to examine associations of long-term ambient air pollution exposure with lung function and spirometrically confirmed COPD. This study shows statistically and clinically significant effects of ambient air pollution exposure on lung function, even at low concentrations compared to many countries around the world. For the first time, this study also shows that individuals with dysanaptic lungs may be more susceptible to the long-term effects of air pollution exposure on lung function and COPD.

Chronic obstructive pulmonary disease (COPD) is the most common cause of hospital admissions among chronic illnesses

in Canada (1). In 2015, 3.2 million people lost their lives to COPD globally, making it one of the world's leading causes of death (2). Although tobacco smoke is recognized as the single most important risk factor for the development and progression of COPD, 25–45% of individuals with COPD have never smoked (3). Considering the global burden of COPD, identifying risk factors beyond tobacco smoking and determining interactions among them are of utmost importance to inform preventive strategies, clinical diagnosis, and management.

COPD is a complex heterogeneous disease resulting from interactions between environment, lifestyle, and genotype (4). Numerous nontobacco COPD risk factors have been proposed (5), and it has been demonstrated that heterogeneity in COPD prevalence is partly explained by variations in associated risk factors (6). Ambient air pollution has been identified as a potential risk factor for COPD (7). Outdoor air pollution is estimated to have caused 4.2 million deaths in 2015, more than 800,000 of which were attributable to COPD (8). The biological plausibility of air pollution as a risk factor for COPD has been demonstrated (9), and exposure to ambient air pollution such as fine particulate matter (PM_{2.5}) and nitrogen dioxide (NO₂) has been linked to slower lung function growth in children and adolescents (10, 11) and to lower lung function as well as higher chronic bronchitis, emphysema, and COPD prevalence and incidence in adults (7, 12–16). Although the effects of air pollution on lung health appear modest relative to tobacco use, its ubiquitous nature leads to a substantial population burden (8).

A better understanding of how air pollution exposure interacts with other individual-level characteristics can shape strategies to mitigate its impact. A recent observational study involving 6,529 Canadian and U.S. adults showed that dysanapsis, or a mismatch of airway tree caliber to lung size, appears to be a significant risk factor for COPD (17). Small airway size has also been shown to increase

the susceptibility of respiratory symptoms amongst teenagers without asthma after exposure to wildfire smoke (18). Particle deposition modeling suggests that airway tree anatomy plays a vital role in deposition patterns in the lung (19) and could therefore influence health risks associated with inhaled particle pollution.

The primary objective of the current study was to evaluate the relationship of PM_{2.5} and NO₂ ambient air pollution exposure with lung function and COPD in the Canadian population, making use of data from the CanCOLD (Canadian Cohort Obstructive Lung Disease) study. The secondary objective of the study was to assess if individuals characterized by smaller airways relative to lung size (i.e., dysanaptic lungs) are more susceptible to the impacts of ambient air pollution on lung function and COPD. We hypothesized that exposure to PM_{2.5} and NO₂ air pollution is associated with lower lung function and higher prevalence of COPD, even at relatively low concentrations typically seen in Canada, and that abnormalities in airway and lung growth increase disease susceptibility.

Methods

Study Population

We used spirometry, chest computed tomography scan, and covariates from the first (i.e., baseline) assessment of the CanCOLD study (20), a population-based cohort of noninstitutionalized adults aged 40 years and older. CanCOLD participants were recruited from the COLD (Canadian Obstructive Lung Disease) prevalence study in two groups: 1) individuals with airflow obstruction on the basis of the Global Initiative for Chronic Obstructive Lung Disease criteria (4) (i.e., postbronchodilator [post-BD] FEV₁/FVC ratio of <0.70; and 2) sex- and age-matched (± 2 years) peers without COPD (i.e., post-BD FEV₁/FVC ≥ 0.70) split between ever- and never-smokers. Between 2009 and 2015, 1,561 individuals

Data Sharing: The CanCOLD (Canadian Cohort Obstructive Lung Disease) study makes deidentified data available for research on respiratory health. Information on how to submit a data access application can be found on the CanCOLD website at www.cancold.ca.

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completed their baseline assessment in data collection sites in nine Canadian cities: Vancouver (n = 435), Montreal (n = 355), Kingston (n = 136), Halifax (n = 127), Calgary (n = 129), Ottawa (n = 116), Saskatoon (n = 104), Québec City (n = 85), and Toronto (n = 74). Most CanCOLD participants lived within the boundaries of each city rather than in the urban periphery. Details on the study sampling methodology can be found elsewhere (20). Informed consent was obtained from all participants, and the CanCOLD study protocol was approved by the institutional review boards of each site. CanCOLD is registered at ClinicalTrials.gov under ID: NCT00920348.

Outcome Assessment

Baseline lung function was assessed for each participant using spirometry (before and 15 min after inhalation of 200 µg salbutamol) by trained technicians according to American Thoracic Society and European Respiratory Society guidelines (21). The main outcomes for our study were post-BD FEV₁, FVC, FEV₁/FVC ratio, and COPD prevalence (defined as a post-BD FEV₁/FVC ratio of <0.70) at baseline assessment. In separate analyses, COPD prevalence was defined using NHANES III (National Health and Nutrition Examination Survey) reference values for the lower limit of normal (LLN) (22). Individuals with an FEV₁/FVC ratio

below the LLN were classified as having COPD.

Ambient Air Pollution Exposure

PM_{2.5} and NO₂ data distributed by CANUE (Canadian Urban Environmental Health Research Consortium) (23) were linked to CanCOLD participants' six-digit residential postal codes at baseline assessment as indicators of long-term, chronic exposure. PM_{2.5} is inhalable particles with a diameter of 2.5 micrometers or less. Key emission sources for PM_{2.5} are industry, wildfire smoke, residential wood heating, cooking, agriculture, and vehicle traffic. On average, about half of PM_{2.5} is a result of atmospheric chemistry forming from gaseous emissions of sulfur dioxide, nitrogen oxides, ammonia, and volatile organic compounds. Three-year running averages of PM_{2.5} concentrations before baseline assessment were estimated across a 1 × 1-kilometer grid covering North America using NASA Moderate resolution Imaging Spectroradiometer, Multi-angle Imaging SpectroRadiometer, and Sea-viewing Wide Field-of-view Sensor satellite instruments, with aerosol vertical profiles and scattering properties simulated by the Goddard Earth Observing System chemical transport model (GEOS-Chem) (24). To adjust for any residual bias in the satellite-derived PM_{2.5} estimates, a geographically weighted regression incorporating ground-based observations was then applied (24). Good agreement was found with cross-validated

surface observations across North America ($R^2 = 0.70$). Annual average NO₂ concentrations in parts per billion were estimated for each postal code location using a national land-use regression model for the year 2006 (25) and adjusted for the year of baseline assessment up to 2012 using air quality monitoring station data. NO₂ is considered an indicator of traffic-related air pollution, which is a complex mixture of gases and particles, including ultrafine particles (diameter of 0.1 µm or less). The land-use regression NO₂ model included road length, 2005–2011 satellite NO₂ estimates, area of industrial land use within 2 km, and summer rainfall as predictors of regional NO₂ variation (25). Deterministic gradients were used to model local scale variation related to roads (i.e., traffic) (25). The final NO₂ model showed good performance, explaining 73% of the variation in measurements from national air pollution surveillance monitoring data with a root mean square error of 2.9 ppb. For both pollutants, we used two variables in our main analyses: 1) interquartile range (IQR) increases; and 2) categorical air pollution concentrations (low, medium, and high) on the basis of the range of exposure in the population.

Computed Tomography Scan for Dysanapsis Measurement

CanCOLD participants underwent inspiratory chest computed tomography scans at baseline assessment. Dysanapsis was

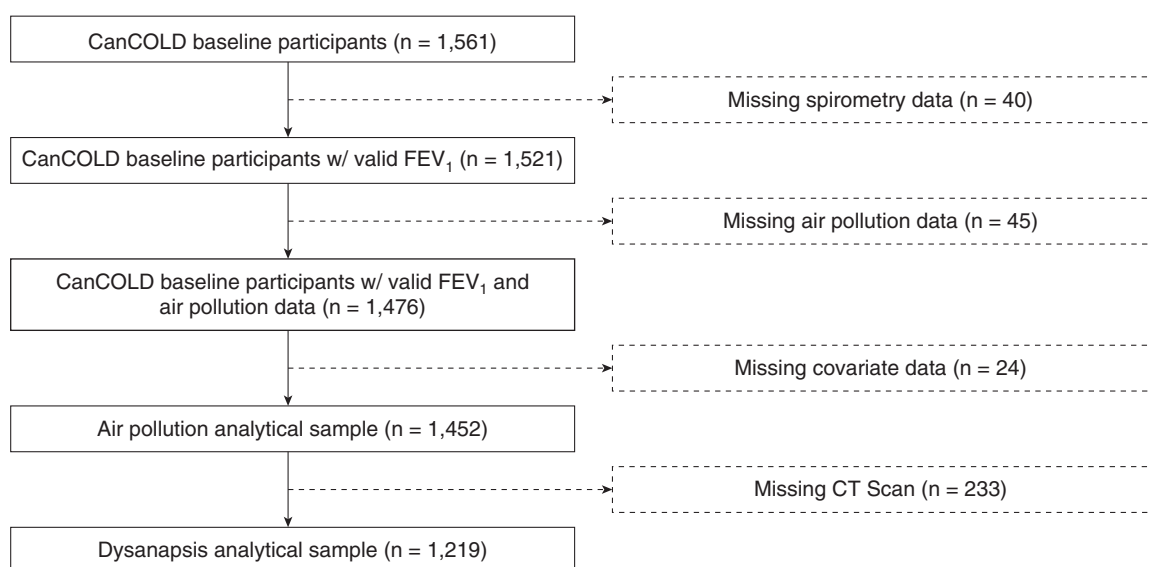


Figure 1. Study population, missing data, and exclusions flow diagram. CanCOLD = Canadian Cohort Obstructive Lung Disease; CT = computed tomography.

determined by measuring the airway-to-lung ratio from thoracic computed tomography images or the geometric mean of airway lumen diameters (cm) measured at 19 standard anatomic locations divided by the cube-root of total lung volume in cubic centimeters (17). A lower airway-to-lung ratio indicates smaller airways relative to lung size, and higher values indicate larger airways relative to lung size. We used a

continuous airway-to-lung ratio variable as well as a quartiles-based variable for analyses.

Covariates, Potential Confounders, and Subgroups

Predefined covariates included age (yr), sex, body mass index (BMI), educational attainment (high school or lower vs. postsecondary education), tobacco status

(never, former, current smokers), pack-years smoking, environmental tobacco smoke at home, biomass fuel exposure, and respiratory medication intake in the past year. Detailed definitions of these variables are found in the online supplement. In sensitivity analyses, we also adjusted for neighborhood-level socioeconomic status by including a material deprivation index (26) linked to residential postal codes of participants and modeled as

Table 1. Baseline Characteristics of Canadian Cohort Obstructive Lung Disease Study Participants*

Characteristic	Total (N = 1452)	COPD (n = 691; 47.6%)	Non-COPD (n = 761; 52.4%)
Sociodemographic factor			
Sex, n (%)			
Male	815 (56.1)	412 (59.6)	403 (53.0)
Female	637 (43.9)	279 (40.4)	358 (47.0)
Age, mean (SD), yr	66.6 (9.8)	67.3 (10.1)	66.0 (9.5)
BMI, mean (SD), kg/m ²	27.7 (5.3)	27.5 (5.31)	27.8 (5.24)
Education, n (%)			
No postsecondary	328 (22.6)	179 (25.9)	149 (19.6)
Some postsecondary	1124 (77.4)	512 (74.1)	612 (80.4)
Tobacco and biomass smoke exposure			
Tobacco status, n (%)			
Never smoker	514 (35.4)	192 (27.8)	322 (42.3)
Ex-smoker	718 (49.4)	370 (53.5)	348 (45.7)
Current smoker	220 (15.2)	129 (18.7)	91 (12.0)
Pack-years smoking, mean (SD)	26.1 (23.8)	31.6 (24.3)	19.8 (21.6)
Environmental tobacco smoke, n (%)			
Never	836 (57.6)	370 (53.5)	466 (61.2)
Ever	616 (42.4)	321 (46.5)	295 (38.8)
Lifetime biomass exposure, n (%), yr			
<10	1249 (86.0)	596 (86.3)	653 (85.8)
≥10	203 (14.0)	95 (13.7)	108 (14.2)
Respiratory health			
FEV ₁ , L	2.55 (0.81)	2.33 (0.78)	2.76 (0.77)
FEV ₁ (% predicted)	91.7 (20.2)	82.3 (19.3)	100 (17.1)
FVC, L	3.68 (1.07)	3.78 (1.11)	3.59 (1.02)
FVC (% predicted)	99.0 (17.2)	100 (17.9)	97.8 (16.4)
FEV ₁ /FVC (%)	69.5 (10.3)	61.1 (8.14)	77.1 (4.63)
Airflow limitation severity, n (%)			
Mild (GOLD 1)	—	388 (56.2)	N/A
Moderate (GOLD 2)	—	264 (38.2)	N/A
Severe (GOLD 3)	—	38 (5.5)	N/A
Very severe (GOLD 4)	—	1 (0.1)	N/A
Respiratory medication, n (%)			
None	1124 (77.4)	446 (64.5)	678 (89.1)
≥1	328 (22.6)	245 (35.5)	83 (10.9)
Asthma, n (%)			
Nonasthmatic	1107 (76.2)	470 (68.0)	637 (83.7)
Asthmatic	345 (23.8)	221 (32.0)	124 (16.3)
Childhood hospitalization for respiratory illness, n (%)			
No	1352 (93.2)	630 (91.3)	722 (94.9)
Yes	99 (6.8)	60 (8.7)	39 (5.1)
Missing	1	1	0
Dysanapsis			
Airway-to-lung ratio			
Fourth quartile (highest)	296 (24.3)	87 (14.6)	209 (33.5)
Third quartile	305 (25.0)	117 (19.6)	188 (30.2)
Second quartile	305 (25.0)	165 (27.7)	140 (22.5)
First quartile (lowest)	313 (25.7)	227 (38.1)	86 (13.8)
Missing	233	95	138

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; N/A = not applicable.

*For 1,452 participants with complete data for baseline age, BMI, education, tobacco status, pack-years smoking, environmental tobacco smoke at home, biomass fuel exposure, respiratory medication intake, spirometry, and ambient nitrogen dioxide exposure.

quintiles on the basis of its distribution across Canada. Finally, to identify population subgroups that might be susceptible to the long-term effects of air pollution exposure on lung function and COPD, sex, smoking status, self-reported physician diagnosis of asthma, and history of childhood hospitalization for a breathing problem before the age of 10 years were used.

Statistical Analyses

We generated summary statistics for outcomes, covariates, confounders, and subgroup variables, as well as for ambient air pollution concentrations. Cross-sectional linear regression models were used to assess the associations between ambient PM_{2.5} and NO₂ air pollution exposure and post-BD FEV₁, FVC, and FEV₁/FVC ratio after adjusting for age, sex, BMI, educational attainment, tobacco status, pack-years of smoking, environmental tobacco smoke, biomass exposure, and current respiratory medication intake. To control for the potential effects of unmeasured confounders which vary by assessment site and to assess the impact of intraurban (as opposed to interurban) air pollution exposure, the CanCOLD data collection site was used as an additional adjustment factor. In sensitivity analyses, associations of air pollution concentrations with pre-BD lung function were also assessed. Adjusted logistic regression models were used to assess the relationship between air pollution exposure and odds of COPD prevalence, defined using the fixed ratio (FEV₁/FVC < 0.7; main analyses) and LLN (sensitivity analyses) thresholds. In sensitivity analyses, we also adjusted for neighborhood material deprivation to adjust for other community-level confounders. Subgroup analyses and tests for interactions were conducted by stratifying analyses by 1) sex (men vs. women); 2) smoking status (current vs. former or never); 3) physician diagnosis of asthma; and 4) hospitalization as a child for a breathing problem. We assessed interactions between air pollution and dysanapsis on FEV₁ and COPD by modeling the airway-to-lung ratio as a continuous variable as well as quartiles. Mean baseline difference in FEV₁ and the relative difference in odds of COPD per IQR increase in air pollutant concentrations were estimated, adjusting for the same covariates as listed above. Interactions were assessed using product terms between air pollutant concentrations and airway-to-lung ratio. The explanatory

power of the interactions between each air pollutant and dysanapsis (as quartiles) on FEV₁ was also assessed using F tests. Finally, all analyses were conducted without CanCOLD data collection site adjustment to assess its impact on results. The R statistical software version 3.6.0 (27) was used throughout.

Results

Figure 1 shows the study population flow diagram and final analytical samples. Study participants had a mean age of 66.6 years and BMI of 27.7 kg/m², 56% were men, and fewer than one in four participants did not have postsecondary education (Table 1). Approximately one-third of participants had never smoked, two out of five participants reported environmental tobacco smoke exposure, and 14% reported biomass fuel exposure at home. Baseline post-BD FEV₁, FVC, and FEV₁/FVC ratio were 2.55 L (SD = 0.81), 3.68 L (SD = 1.07), and 0.69 (SD = 0.10), respectively. Just fewer than half of the individuals had COPD, the majority of whom were classified as having mild COPD (GOLD1). Approximately 1 in 4 participants reported respiratory medication intake in the past 12 months or a physician diagnosis of asthma, and fewer than 1 in 10 had been hospitalized before the age of 10 years for a breathing problem. In all CanCOLD cities combined, mean ambient PM_{2.5} and NO₂ concentrations were 6.9 µg/m³ (IQR, 2.4 µg/m³) and 12.8 ppb (IQR, 9.2 ppb), respectively (Figure 2). Within-city pollutant concentration IQRs ranged from 0.5 to 4.1 PM_{2.5} µg/m³ and from 1.5 to 5.2 NO₂ ppb (Figure 2).

Air Pollution Relationship with Lung Function and COPD

Associations of air pollution with lung function and COPD are presented in Table 2. Higher concentrations of both PM_{2.5} and NO₂ air pollution exposure were associated with statistically significant lower FEV₁. Positive though not statistically significant associations were found between exposure to pollutants and COPD prevalence. Additionally, adjusting models for neighborhood material deprivation attenuated PM_{2.5} associations with FEV₁, but all other associations remained similar (see Table E1 in the online supplement). When defining COPD using the LLN

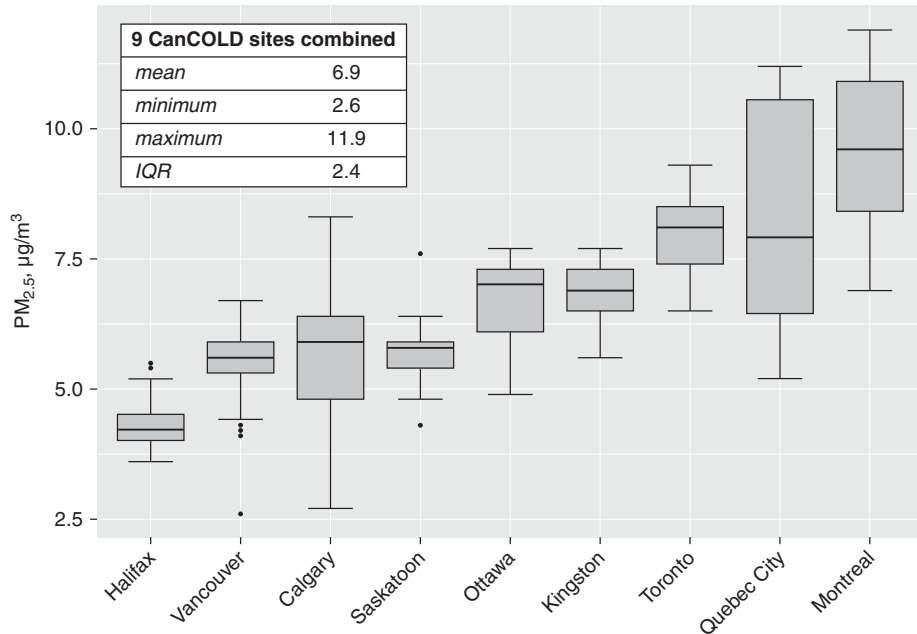
threshold, statistically significant positive associations were found for COPD prevalence and ambient NO₂ exposure (Table E2). We also found statistically significant lower FVC amongst individuals living in areas with high compared to low PM_{2.5} and NO₂ (Table E3). Associations of ambient air pollutant concentrations with pre-BD and post-BD lung function were very similar (Table E4).

Analyses by sex, smoking status, asthmatic status, and childhood hospitalization for a breathing problem did not reveal any notable differences across subgroups or statistically significant interactions (Tables E5–E8). In models without CanCOLD site adjustment, associations between air pollution exposure and lung function were attenuated (see Tables E9 and E10).

Interaction of Air Pollution Exposure and Dysanapsis on Lung Function and COPD

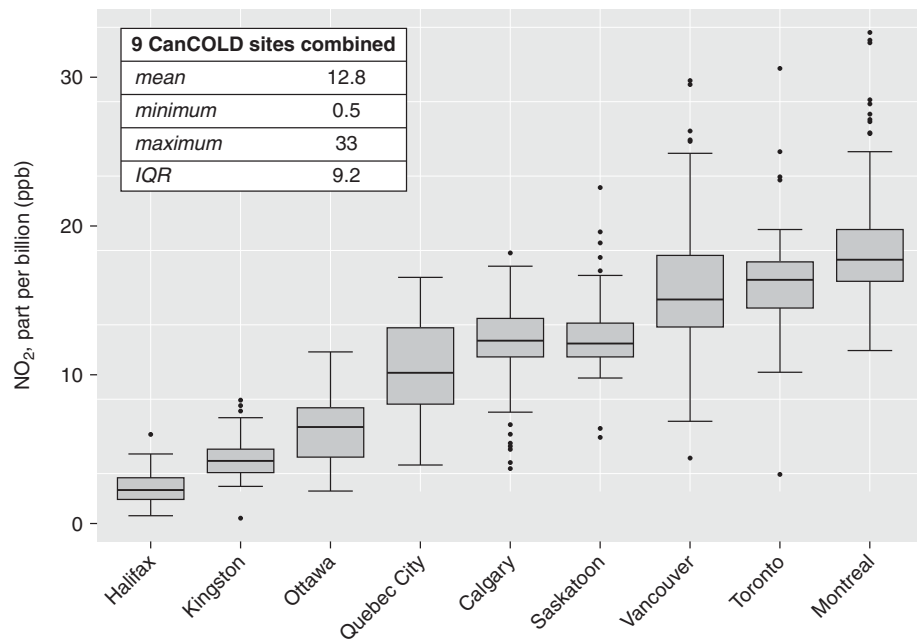
Tables 3 and 4 show interactions between air pollution exposure and dysanapsis on FEV₁ and COPD prevalence. No statistically significant interactions were found when modeling the airway-to-lung ratio as a continuous linear term (Table 3). However, there was evidence of interaction between PM_{2.5} air pollution exposure and dysanapsis for both FEV₁ (*P*-value interaction = 0.030) and COPD (*P*-value interaction = 0.015) when comparing lowest to highest airway-to-lung ratio quartiles (Table 4). After accounting for confounding factors, FEV₁ was 109.8 ml (95% confidence interval [CI], –209.0 to –10.5 ml) lower amongst individuals in the lowest compared to highest airway-to-lung ratio quartile, per IQR increase in PM_{2.5}. An IQR increment in PM_{2.5} concentrations was also associated with 87% (95% CI, 12% to 213%) higher odds of COPD amongst individuals in the lowest relative to highest airway-to-lung ratio quartile. Interactions between PM_{2.5} concentrations and the second and third quartiles of airway-to-lung ratio (relative to the highest quartile) were nonsignificant (Table E11). A significant interaction between PM_{2.5} and dysanapsis on FEV₁ was found when using the F test (*P*-value = 0.042) (Table E12). Finally, no significant interactions were found between NO₂ exposure and dysanapsis.

A PM_{2.5} concentrations



mean	4.3	5.6	5.6	5.7	6.7	6.9	8.0	8.4	9.6
minimum	3.6	2.6	2.7	4.3	4.9	5.6	6.5	5.2	6.9
maximum	5.5	6.7	8.3	7.6	7.7	7.7	9.3	11.2	11.9
IQR	1.6	0.6	1.6	0.5	1.2	0.8	1.1	4.1	2.5

B NO₂ concentrations



mean	2.4	4.4	6.2	10.4	12.2	12.7	15.8	16.2	18.2
minimum	0.5	2.5	2.2	3.9	3.7	5.8	4.4	3.3	11.6
maximum	6.0	8.3	11.5	16.6	18.2	22.6	29.8	30.6	33.0
IQR	1.5	1.6	3.4	5.2	2.6	2.3	4.8	3.1	3.5

Figure 2. Fine particulate matter (PM_{2.5}) and nitrogen dioxide (NO₂) ambient air pollution concentrations at the residences of the CanCOLD study participants. CanCOLD = Canadian Cohort Obstructive Lung Disease; IQR = interquartile range.

Table 2. Relationship of Air Pollution Exposure with Lung Function and Chronic Obstructive Pulmonary Disease

Exposure	n	Lung Function		COPD	
		FEV ₁ (ml) β (95% CI)	FEV ₁ /FVC (%) β (95% CI)	Cases/Noncases	OR (95% CI)
PM _{2.5} (continuous) (per IQR increase = 2.4 µg/m ³)	1,451	-101.7 (-166.2 to -37.2)	-0.6 (-1.7 to 0.5)	691/760	1.17 (0.89 to 1.54)
PM _{2.5} (categorical), µg/m ³					
Low (2.6 to 5.6)	404	Reference	Reference	199/205	Reference
Medium (5.7 to 8.7)	768	-108.0 (-188.8 to -27.3)	-1.1 (-2.4 to 0.3)	361/407	1.13 (0.80 to 1.59)
High (8.8 to 11.9)	279	-261.9 (-391.7 to -132.1)	-2.3 (-4.5 to -0.1)	131/148	1.57 (0.90 to 2.73)
NO ₂ (per IQR increase = 9.2 ppb)	1,452	-115.0 (-196.5 to -33.4)	-1.1 (-2.5 to 0.3)	691/761	1.19 (0.84 to 1.68)
NO ₂ (categorical), ppb					
Low (0.5 to 11.3)	507	Reference	Reference	227/280	Reference
Medium (11.4 to 22.1)	881	-87.1 (-190.9 to 16.8)	-0.8 (-2.5 to 1.0)	431/450	1.30 (0.84 to 2.03)
High (22.2 to 33)	64	-268.84 (-434.21 to -103.47)	-2.6 (-5.4 to 0.2)	33/31	1.58 (0.78 to 3.18)

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; NO₂ = nitrogen dioxide; OR = odds ratio; PM_{2.5} = fine particulate matter.

All models are adjusted for age, sex, body mass index, educational level (high school or lower vs. postsecondary education), tobacco status (never smoker, former smoker, or current smoker), pack-years smoking, environmental tobacco smoke at home, biomass fuel exposure, respiratory medication intake, and Canadian Cohort Obstructive Lung Disease study site. Statistically significant results are shown in bold.

Discussion

In this cross-sectional analysis of the CanCOLD study, a pan-Canadian population-based cohort, we demonstrated associations between ambient air pollution exposure and lower lung function. Notably, ambient PM_{2.5} and NO₂ air pollution exposure were associated with lower FEV₁, even at low concentrations relative to many countries across the world. Positive associations were also seen between outdoor air pollution exposure and COPD prevalence, though results did not reach statistical significance. No statistically

significant interactions between air pollution and dysanapsis were found when modeling the airway-to-lung ratio as a continuous variable. However, individuals in the lowest quartile of the airway-to-lung ratio were more susceptible to the impacts of PM_{2.5} exposure on lung function and COPD than those in the highest airway-to-lung ratio quartile.

To our knowledge, this is the first study in Canada to examine associations of long-term ambient air pollution exposure with lung function and spirometrically confirmed COPD. Our findings are supported by other Canadian studies that used health

administrative data to indirectly ascertain COPD. A recent study by Shin and colleagues following 5.1 million adults in the province of Ontario for a period of 15 years found positive associations between PM_{2.5} and NO₂ and incident COPD identified from health administrative data (14). Positive associations between long-term ambient air pollution exposure and incident COPD derived from health administrative database records have also been reported amongst individuals living in Toronto (28) and Vancouver (29).

The current study showed a 101.7 ml (95% CI, -166.2 to -37.2) lower FEV₁ per

Table 3. Interactions between Air Pollution and Airway-to-Lung Ratio on FEV₁ and Chronic Obstructive Pulmonary Disease Prevalence

	Difference in FEV ₁ , β (95% CI), ml	
	Airway-to-Lung Ratio (per IQR Decrease)	P Value Interaction
PM _{2.5} (per IQR increase = 2.4 µg/m ³)	-38.3 (-82.2 to 5.6)	0.087
NO ₂ (per IQR increase = 9.2 ppb)	19.4 (-37.7 to 76.4)	0.505
	Difference in COPD OR (95% CI)	
	Airway-to-Lung Ratio (per IQR Decrease)	P Value Interaction*
PM _{2.5} (per IQR increase = 2.4 µg/m ³)	1.26 (0.98 to 1.62)	0.065
NO ₂ (per IQR increase = 9.2 ppb)	1.03 (0.77 to 1.40)	0.826

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; NO₂ = nitrogen dioxide; OR = odds ratio; PM_{2.5} = fine particulate matter.

Airway-to-lung ratio modeled using continuous linear terms. All models are adjusted for age, sex, body mass index, educational level (high school or lower vs. postsecondary education), tobacco status (never smoker, former smoker, or current smoker), pack-years smoking, environmental tobacco smoke at home, biomass fuel exposure, respiratory medication intake, dysanapsis (continuous), and Canadian Cohort Obstructive Lung Disease study site. Statistically significant results are shown in bold.

*To test for interactions, a product term was included between air pollution and continuous airway-to-lung ratio.

Table 4. Interactions between Air Pollution and Airway-to-Lung Ratio on FEV₁ and Chronic Obstructive Pulmonary Disease Prevalence

	Difference in FEV ₁ (ml), β (95% CI)				P Value Interaction*
	All Participants	Highest Quartile of Airway-to-Lung Ratio	Lowest Quartile of Airway-to-Lung Ratio	Difference between Highest and Lowest Quartile	
PM _{2.5} (per IQR increase = 2.4 $\mu\text{g}/\text{m}^3$)	-107.0 (-175.9 to -38.0)	-70.8 (-160.5 to 18.9)	-180.5 (-273.9 to -87.2)	-109.8 (-209.0 to -10.5)	0.030
NO ₂ (per IQR increase = 9.2 ppb)	-149.5 (-234.7 to -64.2)	-185.0 (-306.5 to -63.4)	-145.3 (-254.8 to -35.7)	39.7 (-89.9 to 169.4)	0.548

	Difference in COPD OR (95% CI)				P Value Interaction*
	All Participants	Highest Quartile of Airway-to-Lung Ratio	Lowest Quartile of Airway-to-Lung Ratio	Relative Difference between Highest and Lowest Quartile	
PM _{2.5} (per IQR increase = 2.4 $\mu\text{g}/\text{m}^3$)	1.22 (0.89 to 1.69)	0.96 (0.62 to 1.48)	1.79 (1.11 to 2.88)	1.87 (1.12 to 3.13)	0.015
NO ₂ (per IQR increase = 9.2 ppb)	1.18 (0.8 to 1.75)	1.04 (0.58 to 1.89)	1.55 (0.90 to 2.65)	1.48 (0.78 to 2.81)	0.220

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; NO₂ = nitrogen dioxide; OR = odds ratio; PM_{2.5} = fine particulate matter.

Highest versus lowest airway-to-lung ratio quartiles. All models are adjusted for age, sex, body mass index, educational level (high school or lower vs. postsecondary education), tobacco status (never smoker, former smoker, or current smoker), pack-years smoking, environmental tobacco smoke at home, biomass fuel exposure, respiratory medication intake, dysanapsis (quartiles), and Canadian Cohort Obstructive Lung Disease study site. Statistically significant results are shown in bold.

*To test for interactions, a product term was included between air pollution and airway-to-lung ratio quartiles.

2.4 $\mu\text{g}/\text{m}^3$ increase in ambient PM_{2.5} concentrations and positive though nonsignificant associations with COPD prevalence. Associations between PM_{2.5} and FEV₁ are consistent, though generally larger when compared to results from previous studies. A recent cross-sectional study of United Kingdom Biobank participants found an 83.13 ml lower FEV₁ per 5 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} concentrations (13). This study also showed higher odds of COPD with increases in PM_{2.5} (13). A meta-analysis of five European cohorts by Adam and colleagues found a 13.98 ml lower FEV₁ per 10 $\mu\text{g}/\text{m}^3$ increment in NO₂ but no significant associations with PM_{2.5} (30). Using four of these same cohorts, a meta-analysis by Schikowski and colleagues did not find any statistically significant associations between either NO₂ or PM_{2.5} air pollution exposure and the prevalence or incidence of COPD (31). Finally, using data from the U.S. Framingham Heart Study, Rice and colleagues found a 13.5 ml lower FEV₁ per 2 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} but no associations between PM_{2.5} concentrations and COPD (32). The higher associations found in our study might partially be explained by the older population in the CanCOLD cohort

relative to previous studies. Research has shown that older individuals are more susceptible to the long-term effects of air pollution exposure on lung function (33), respiratory symptoms (34), and respiratory mortality (35, 36). Adjustment for the CanCOLD site variable might also have contributed to stronger associations; when the CanCOLD site variable was removed from our models, results were attenuated and overlapped with CIs of previous studies. Weaker associations when leaving out site adjustment might indicate that within-city contrasts in air pollution are responsible for most of the impact of air pollution on lung health. This, in turn, highlights the need for more research on local traffic-related air pollution exposure, which is the dominant contributor to intraurban variations in pollutant concentrations in these cities.

To minimize the health impacts of air pollution, the World Health Organization (WHO) established a threshold of 10 $\mu\text{g}/\text{m}^3$ for annual mean concentrations of PM_{2.5} in 2005. Mean annual PM_{2.5} concentrations in the CanCOLD population were below 2005 WHO air quality guidelines and well below the mean annual concentrations seen in

many international cities (Figure 3). This indicates that even at relatively low concentrations, ambient air pollution exposure impacts lung health. Consistent with our results, a recent pooled analysis of COPD hospital discharge data from three cohorts in Denmark and Sweden found statistically significant positive associations between long-term exposure to PM_{2.5} and NO₂ and COPD development, even at concentrations below the current European Union, United States, and WHO guidelines (37). Similar conclusions of adverse effects of low-concentration PM_{2.5} air pollution on COPD risk have been reported in the Canadian study by Shin and colleagues (14). Such findings have informed revisions to WHO air quality guidelines. In September 2021, the WHO released new air quality guidelines, recommending annual average thresholds of 5 $\mu\text{g}/\text{m}^3$ for PM_{2.5} (down from 10 $\mu\text{g}/\text{m}^3$) and 10 $\mu\text{g}/\text{m}^3$ for NO₂ (down from 40 $\mu\text{g}/\text{m}^3$). This study supports the decision to strengthen WHO guidelines as our results suggest efforts to adhere to these stricter air quality guidelines will help reduce the impacts of ambient air pollution on accelerated lung function decline and COPD burden.

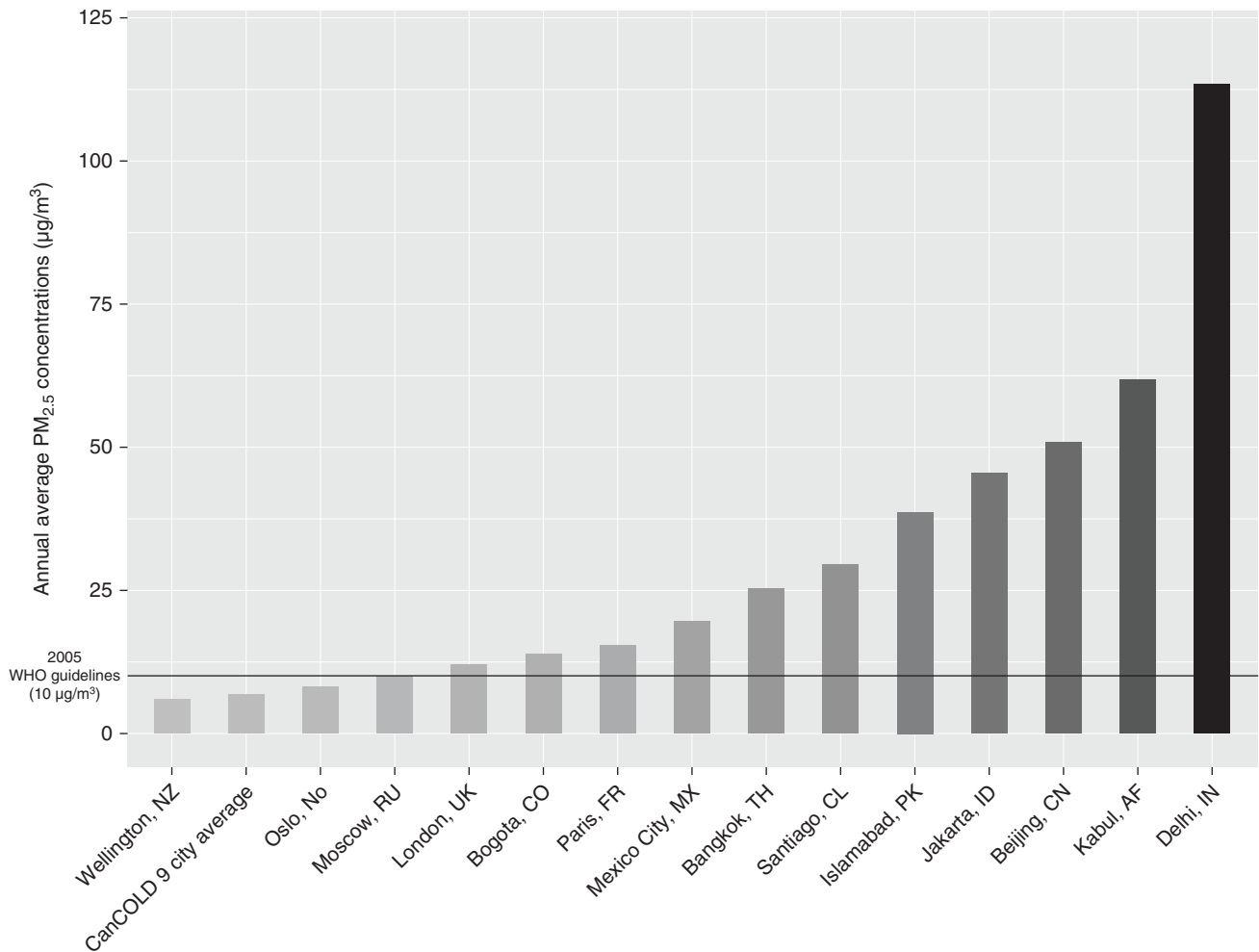


Figure 3. Annual average PM_{2.5} concentrations, CanCOLD study nine-city average and international capital cities. Adapted from IQAir (42). CanCOLD = Canadian Cohort Obstructive Lung Disease; PM_{2.5} = fine particulate matter; WHO = World Health Organization.

A recent analysis of the CanCOLD data with two other cohorts from the United States showed that a lower airway-to-lung ratio was associated with a significantly higher risk of COPD, even among never-smokers (17). For the first time, our results show that in addition to being a COPD risk factor, dysanapsis might also modify the impact of inhaled outdoor air pollutants on lung function and COPD. Lung morphology and fluid dynamics are major factors affecting particle deposition in the airways (19). Increased particulate velocities and greater airway impaction in individuals with smaller and narrower airways in proportion to lung volume might help explain the increased susceptibility to air pollution exposure amongst individuals with dysanaptic lungs seen in our study. Although air pollution exposure in the perinatal period

and during childhood and adolescence has been shown to adversely affect lung function and lung development (10, 38), our study suggests that early-life lung development could also play a role in protecting from or increasing susceptibility to air pollution-induced lower lung function and COPD in adulthood.

The current study has many strengths, starting with the fact that it is the first to use a population-based cohort sample to investigate the relationship of ambient air pollution exposure with lung function and spirometrically defined COPD in Canada. Past Canadian studies exploring associations between air pollution exposure and COPD have generally made use of administrative health data, which have the advantage of very large sample sizes but can lead to over or underdiagnosis of COPD. Furthermore, such

studies do not allow controlling for important individual-level confounders such as tobacco use. In addition, although most international studies with spirometry data have used prebronchodilator lung function, postbronchodilator spirometry testing in our study allowed us to better discriminate participants with reversible obstruction from those with limited airway reversibility, which mirrors the population of individuals most likely to have COPD. This is also the first study to date to examine interactions between air pollution and dysanapsis on lung function and COPD prevalence.

Among the limitations of this study, the cross-sectional analyses conducted herein do not allow the drawing of causal inferences concerning associations. Although CanCOLD has conducted two follow-up visits since the baseline assessment used in

our study, the median follow-up time remains relatively short, at approximately 3 years. Longitudinal analyses will be conducted once sufficient follow-up time is accrued via a fourth in-site assessment. Second, statistically significant interactions were observed only for the highest versus lowest quartiles of airway-to-lung ratio but not for intermediate quartiles or when modeling interactions as continuous linear terms. This may be because of a nonlinear or threshold of dysanapsis modifying the PM_{2.5} association with lung function or a chance observation, and therefore requires validation in an independent cohort. Also, our study only ascertained air pollution at the time of recruitment and residential location. No data on residential mobility in the years before enrollment were available. However, we do not believe this is a major limitation in the current study of older Canadians. According to Canadian census data, individuals aged 15 to 40 years old constitute the majority of internal migration in Canada, whereas those aged 40 years or more show relatively low residential mobility rates (39). Nonetheless, although we assumed exposure at the baseline residential address of CanCOLD participants is representative of recent past exposures, this is not necessarily the case, as some participants might have moved shortly before study enrollment.

Cumulative air pollution exposures over many years and assessment of time-activity patterns of study participants would help reduce the potential for exposure misclassification. Further, the 1 × 1-kilometer grids used to estimate PM_{2.5} concentrations are likely the coarsest resolution useful in characterizing within-city variations in ambient PM_{2.5} concentrations in larger Canadian cities. Although modeling PM_{2.5} at a finer spatial scale could sharpen the assessment of within-city contrasts, at this scale, it would be less clear what aspects of the urban air pollution mixture such an empirical model is actually representing (i.e., some specific component of PM_{2.5} and/or some covarying gaseous pollutants). Finally, we cannot rule out the possibility that the association between the presence of COPD and our index of dysanapsis was, in part, artifactual with our indices caused by the anatomic impact of COPD. We think this is unlikely, however, as the index of dysanapsis used in the study has 1) been shown to be associated with COPD independent of tobacco smoking and other standard COPD risk factors (17); and 2)

extends to the peripheral airway tree (40) (the primary site of noxious particulate-associated COPD pathobiology) (41). Although COPD is associated with larger lung volumes, most individuals with COPD in our study had mild disease (56%) (Table 1) and a low likelihood of hyperinflation.

Conclusions

Chronic exposure to ambient air pollution is associated with clinically relevant lower lung function, even at relatively low concentrations. We also observed stronger relationships between ambient PM_{2.5} exposure and both FEV₁ and COPD among those in the lowest than highest airways relative to lung size quartiles, indicating that there is a positive interaction between dysanapsis and air pollution. Our results, therefore, suggest that individuals with dysanaptic lung growth might be particularly susceptible to inhaled air pollutants. These new findings highlight the need to further reduce ambient air pollution concentrations and can help inform clinical management by identifying individuals with increased susceptibility to air pollutants. External validation of our results using other cohorts with computed tomography scans and spirometry data should be pursued. Longitudinal analyses are also needed to further examine these relationships. ■

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