

RESEARCH

Open Access



Concentration-dependent increase in symptoms due to diesel exhaust in a controlled human exposure study

Juma Orach, Christopher Francis Rider, Agnes Che Yan Yuen and Christopher Carlsten*

Abstract

Background: Traffic-related air pollution (TRAP) exposure causes adverse effects on wellbeing and quality of life, which can be studied non-invasively using self-reported symptoms. However, little is known about the effects of different TRAP concentrations on symptoms following controlled exposures, where acute responses can be studied with limited confounding. We investigated the concentration–response relationship between diesel exhaust (DE) exposure, as a model TRAP, and self-reported symptoms.

Methods: We recruited 17 healthy non-smokers into a double-blind crossover study where they were exposed to filtered air (FA) and DE standardized to 20, 50, 150 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ for 4 h, with a ≥ 4 -week washout between exposures. Immediately before, and at 4 h and 24 h from the beginning of the exposure, we administered visual analog scale (VAS) questionnaires and grouped responses into chest, constitutional, eye, neurological, and nasal categories. Additionally, we assessed how the symptom response was related to exposure perception and airway function.

Results: An increase in DE concentration raised total ($\beta \pm$ standard error = 0.05 ± 0.03 , $P = 0.04$), constitutional (0.01 ± 0.01 , $P = 0.03$) and eye (0.02 ± 0.01 , $P = 0.05$) symptoms at 4 h, modified by perception of temperature, noise, and anxiety. These symptoms were also correlated with airway inflammation. Compared to FA, symptoms were significantly increased at 150 $\mu\text{g}/\text{m}^3$ for the total (8.45 ± 3.92 , $P = 0.04$) and eye (3.18 ± 1.55 , $P = 0.05$) categories, with trends towards higher values in the constitutional (1.49 ± 0.86 , $P = 0.09$) and nasal (1.71 ± 0.96 , $P = 0.08$) categories.

Conclusion: DE exposure induced a concentration-dependent increase in symptoms, primarily in the eyes and body, that was modified by environmental perception. These observations emphasize the inflammatory and sensory effects of TRAP, with a potential threshold below 150 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$. We demonstrate VAS questionnaires as a useful tool for health monitoring and provide insight into the TRAP concentration–response at exposure levels relevant to public health policy.

Keywords: Controlled human exposures, Symptoms, Diesel exhaust, Particulate matter, Airways

Introduction

Traffic-related air pollution (TRAP) exposure causes adverse health effects and is a risk factor for morbidity worldwide [1–3]. The effects of pollution on subjective wellbeing and quality of life [4], in particular, can be assessed non-invasively using self-reported symptoms questionnaires [5–7]. Symptoms are also robust indicators of the pollution-associated exacerbation of cardiopulmonary diseases [6, 8–10] and are correlated with

*Correspondence: carlsten@mail.ubc.ca

Air Pollution Exposure Laboratory, Division of Respiratory Medicine, Department of Medicine, Vancouver Coastal Health Research Institute, The University of British Columbia, Vancouver, BC, Canada



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

other clinical health measures, such as fractional exhaled nitric oxide (FeNO) [11] and forced expiratory volume in 1 s (FEV₁) [12, 13].

Diesel exhaust (DE) consists of gases and particulate matter (PM), including a particularly harmful fraction with a diameter < 2.5 µm (PM_{2.5}), that interacts with cells at mucosal surfaces to instigate inflammation, oxidative stress, epithelial damage and sensory nerve activation [1, 14]. In addition to the systemic response mobilized by these interactions, PM with diameter < 0.1 µm (PM_{0.1}) may directly translocate into the blood to propagate systemic inflammation [15, 16]. Additional roles have been proposed for psychological factors, such as exposure perception [17], in affecting pollution-associated symptoms.

Concentration–response (C–R) relationships help elucidate the link between exposures and effects and have been used to investigate symptom responses over a broad range of TRAP concentrations in epidemiological studies [9, 10, 18, 19]. In controlled human exposure (CHE) studies, where residual confounding is limited, the acute effects of TRAP exposure on symptoms have also been studied, commonly using diesel exhaust (DE) as a model of TRAP [20–24]. However, the C–R relationship between TRAP exposure and symptoms is relatively unexplored in CHE studies [25]. An improved understanding of the link between air pollution and symptoms, and the role of perception in this relationship, is crucial in evaluating the impacts of air pollution on wellbeing.

In this study, we investigated the C–R relationship for self-reported symptoms after controlled human exposures. We hypothesized that higher DE concentrations would increase symptoms. Additionally, we studied the role of environmental perception in this C–R relationship. Lastly, we investigated the relationship between symptoms and clinical measures of airway function and inflammation. We report concentration-dependent effects of TRAP on symptoms that could inform future strategies to assess the impacts of air exposure non-invasively.

These results have previously been reported in the form of a conference abstract [26].

Methods

Controlled diesel exhaust exposures

The Diesel Induces Concentration-dependent Effects (DICE) study (NCT03234790) was a double-blind crossover study approved by the University of British Columbia Research Ethics Board (H16-03053). Healthy non-smokers aged 19–49 were recruited using referrals and online advertisements. Following informed consent, participants were screened for respiratory and cardiac abnormalities by the study physician. Participants were included if they were healthy, aged 19–49, non-smokers,

and able to communicate and complete study procedures. Exclusion criteria included pregnancy/breast-feeding, conflicting time commitments and inhaled corticosteroid use. Before each study visit participants completed a standard common cold questionnaire to confirm that they did not have upper respiratory tract infection symptoms and were asked to withhold caffeine and bronchodilator use. Visits were postponed by at least 4 weeks if a possible respiratory infection was reported. Participants were exposed to filtered air (FA) and DE standardized to 20, 50, 150 µg/m³ PM_{2.5} over four separate visits at the Air Pollution Exposure Laboratory [27]. These PM_{2.5} concentrations are common in DE exposure studies [28], and approximate real world urban [29] and occupational [30] levels. Exposures were completed in randomized orders with each separated by a ≥ 4-week washout period. In the event of substantial spikes in ambient air pollution, exposures were postponed by at least 4 weeks. DE was generated by an EPA Tier 3-compliant, 6.0 kW Coliseum GY6000 generator, with a 406 cc Yanmar L 100 EE 4-stroke diesel engine with a constant 2.5 kW load, which upon failure in February 2021, was replaced by a 4.5 kW 1B30E Hatz EPA/Euro-Stage Tier 5-compliant engine (for all exposures for participants 14–17) to reflect contemporary technology. Exposure details for the diesel engines are presented in Additional file 1: Table S1. During the exposures, participants exercised intermittently on a stationary bike for 15 min/h at a power-to-weight ratio estimated to achieve a ventilation rate of 15 L/min/m².

Questionnaires

Symptoms typically associated with air pollution exposure in the literature [17, 24, 31] were evaluated by the participants using a visual analog scale (VAS) [32, 33] questionnaire (Additional File 1: Figure S1) pre-exposure, 4 h and 24 h post-exposure. To assess exposure perception, participants responded to a VAS questionnaire about the environment in the exposure booth and were asked if they thought their exposure was to FA or DE.

Spirometry

Lung function was measured by spirometry before, and at 4 h and 24 h from the start of the exposure according to American Thoracic Society/European Respiratory Society guidelines [34]. Airway responsiveness was measured by the methacholine response before and at 24 h from the start of the exposure using the 2-min tidal breathing technique [35]. Novo-Salbutamol HFA (TEVA; ON, CA) was administered following the baseline methacholine challenge to restore lung function. Methacholine provocation concentration to cause a 20% drop in FEV₁ (PC₂₀) was estimated using the appropriate equations [36, 37].

FeNO

FeNO was measured using a NIOX VERO[®] machine (NIOX, ON, CA) machine before and at 4 h and 24 h from the start of exposures according to American Thoracic Society/European Respiratory Society guidelines [38].

Statistical analyses

Measurements of VAS questionnaires were completed by at least 2 technicians independently, entered into REDCAP 10.4.0 (© 2021 Vanderbilt University) and checked for consistency and accuracy using in-built REDCAP tools. Baseline values for all outcomes were subtracted from values at subsequent timepoints to obtain delta values. To limit the penalty for multiple comparisons, symptoms were analyzed at the category level (summarized in Table 1) similar to Carlsten et al. [17].

Linear mixed effects models, with a participant-specific intercept to adjust for repeated measures, were used to assess the effects of DE exposure on symptoms (package nlme_3.1-157). To estimate the C–R, a model (1) of symptom category delta values and PM_{2.5} was fitted, while in model (2) symptom category delta values and controlled exposure condition groups were fitted

to identify potential effects thresholds. To evaluate the effect of perception on symptoms from DE exposure, a model (3) was fit with participant's perception of environment/exposure as a modifier of the relationship between symptoms and PM_{2.5}.

$$Y_{i,j} = \beta_1(PM_{2.5}) + \beta_0 + \mu_i + \varepsilon_{i,j}$$

$$Y_{i,j} = \beta_1(\text{exposure condition group}) + \beta_0 + \mu_i + \varepsilon_{i,j}$$

$$Y_{i,j} = \beta_1(PM_{2.5}) * \text{perception} + \beta_0 + \mu_i + \varepsilon_{i,j}$$

where $i = i$ th individual, $j = j$ th repeated measurement, $\beta_1 =$ slope, $\beta_0 =$ overall intercept, $\mu =$ participant intercept, $\varepsilon =$ error term.

Model assumptions were checked and where appropriate, data were log-transformed. Correlations between outcomes were calculated using repeated measures correlations (rmcorr package V.0.4.5). All statistical analysis was performed using R version 4.2.0. $P \leq 0.05$ were considered statistically significant, while P values 0.051–0.1 were considered to be “trending towards significance”.

Results

Study population

Of the 20 participants enrolled in the study, 15 completed all exposures and were included in the analysis. Additionally, 2 participants who did not complete one of four exposures (one in each of the DE50 and DE150 categories) were included in the analysis to give a total of 17 participants (Table 2).

Table 1 Symptom questions and categories

Symptom category	Question
Chest	Please rate your level of throat irritation
	Do you feel a need to cough?
	Do you suffer from shortness of breath right now?
	Are you currently experiencing a whistling or hissing sound while breathing?
	Are you experiencing chest pain?
Constitutional	Is your skin itchy or dry?
	Are you sweating right now?
	Do you have a fever right now?
	How would you rate your general wellbeing?
Eye	Do your eyes itch or sting?
	Please rate how dry your eyes are right now
	Are your eyes running or watering?
Neurological	Do you feel sleepy or drowsy?
	Do you have a headache right now?
	Do you find it difficult to concentrate?
	Are you currently feeling nauseous?
Nose	Does your nose feel irritated, itchy, stinging or dry?
	Do you currently have a runny nose?
	Is your nose blocked right now?

Symptom scores (standardized to a 10 cm scale) were summed within each category and also as a total including all categories for analysis

Table 2 A summary of participant demographics

Characteristics	Mean (95% CI)
Sex (male/female)	9/8
Age	28.18 (23.89, 32.46)
BMI	24.74 (22.52, 26.95)
FEV ₁	3.64 (3.25, 4.04)
FEV ₁ %predicted	98.88 (94.61, 103.16)
FVC	4.49 (3.99, 4.99)
FEV ₁ :FVC	0.82 (0.78, 0.85)
FeNO (ppb)	23.29 (15.66, 30.93)
PC ₂₀	> 128 mg/mL

Age, BMI and lung function measures were recorded at the screening visit. Methacholine FeNO and PC₂₀, which were not recorded at the screening visit, are based on average pre-exposure values for all the exposures. PC₂₀ > 16 are considered normally responsive according to the European Respiratory Society Technical Standard

BMI, body-mass index; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PC₂₀, methacholine provocation concentration causing a 20% drop in FEV₁

The remaining 3 participants withdrew from the study due to scheduling constraints. Details are summarized in flow diagram in Additional file 1: Figure S2.

Exposure characteristics

Exposure data are presented by nominal PM_{2.5} exposure group and diesel engine in Additional file 1: Table S1. While there were differences between the engines across some measures (most notably more ultrafine particles and hence total particles with the newer Tier 5 engine, at similar levels of PM_{2.5}, as expected given the older engine was subject to combustion inefficiency over years of operation), engine type did not significantly modify symptom responses (Additional file 1: Table S2).

DE induced a concentration-dependent increase in total, eye, and constitutional symptoms

At 4 h post-exposure, DE induced a concentration-dependent increase in total symptoms ($\beta \pm$ standard error = 0.05 ± 0.03 , $P=0.04$), driven by the constitutional (0.01 ± 0.01 , $P=0.03$) and eye (0.02 ± 0.01 , $P=0.05$) symptom categories (Fig. 1). Of the underlying questions, participants primarily reported itching and stinging in the eyes ($P=0.03$) and itchiness or dryness of the skin ($P=0.06$).

Redoing this analysis with only the 15 participants that completed all four exposures did little to change the output, but eye category symptoms were no longer significantly changed ($P>0.1$) and hence total symptoms moved to borderline significance ($P=0.05-0.1$). However, this analysis is adversely affected by outliers in the smaller dataset.

Compared to FA, DE at $150 \mu\text{g}/\text{m}^3$ induced an increase in total (8.45 ± 3.92 , $P=0.04$) and eye (3.18 ± 1.55 , $P=0.05$) symptoms, and a trend towards significance in the constitutional (1.49 ± 0.86 , $P=0.09$) and nasal (1.71 ± 0.96 , $P=0.08$) symptoms (Fig. 2). These effects were all absent at 24 h.

The symptom concentration–response was modified by environmental perception

Increasing perception of noise (-0.07 ± 0.03 , $P=0.01$) and temperature (-0.06 ± 0.03 , $P=0.02$) attenuated the concentration-dependent increase in total symptoms, driven by effects in both the eye (noise effect = -0.02 ± 0.01 , $P=0.02$; temperature effect = -0.03 ± 0.01 , $P=0.01$) and constitutional categories (noise effect = -0.01 ± 0.01 , $P=0.03$) (Table 3). Anxiety enhanced the concentration-dependent increase in constitutional symptoms (0.01 ± 0.00 , $P=0.03$).

However, symptom responses were not modified by participants perception of whether they were exposed to

DE or FA (Fig. 3). Participant sex did not modify symptoms (data not shown).

The symptom concentration–response was correlated with airway inflammation

The concentration–response for total symptoms was moderately positively correlated with ΔFeNO at 4 h ($r=0.29 \pm 0.13$, $P=0.04$) and 24 h ($r=0.39 \pm 0.12$, $P<0.00$) driven by effects in the constitutional and eye categories (details summarized in Table 4). Symptoms were not correlated with methacholine PC₂₀ and FEV₁.

Discussion

Exposure to air pollution is associated with adverse health effects, whose impact on wellbeing and quality of life can be assessed using symptoms [5–7]. Current knowledge on the effects of TRAP on symptoms could be improved by better understanding of their C–R relationship. In this study, we investigated and identified concentration-dependent increases in symptoms that were modified by environmental perception.

We observed a significant concentration-dependent increase in total symptoms driven primarily by eye and constitutional symptoms. PM and gases routinely interact with exposed surfaces of the body such as the skin [39, 40] and eyes [41] where they may be inflammatory. In the eyes, these pollutants can cause dryness and irritation [41, 42] through oxidative stress [43], mucin disruption, and loss of microvilli, corneal and goblet cells [14, 44, 45]. In the airways, PM_{2.5} can enter the alveoli where it induces inflammation and oxidative stress that may result in systemic immune mobilization [15, 46]. This “spill over”, in addition to the penetration of PM_{0.1} into the blood stream, may cause adverse neurological, constitutional, and systemic effects. PM_{2.5}, the primary surrogate for DE concentration in our analyses, was correlated with other pollutants in the DE mixture. Thus, gases and TVOCs may have a role in the symptom response attributed to PM_{2.5} here, but readers should not infer cause due to any particular aerosol component as this model exposure is a paradigm of traffic-related air pollution with PM_{2.5} simply used as a metric for reasonably standardizing conditions upon a common parameter. The correlation between symptoms and airway inflammation in our study lends credence to inflammation as a potential physiological pathway through which air pollutants cause symptoms. However, the symptom response was unaccompanied by changes in lung function, similar to other acute exposure studies assessing similar endpoints [20, 47]. This absence of changes in lung function after acute air pollution exposure is likely due to resilience to acute

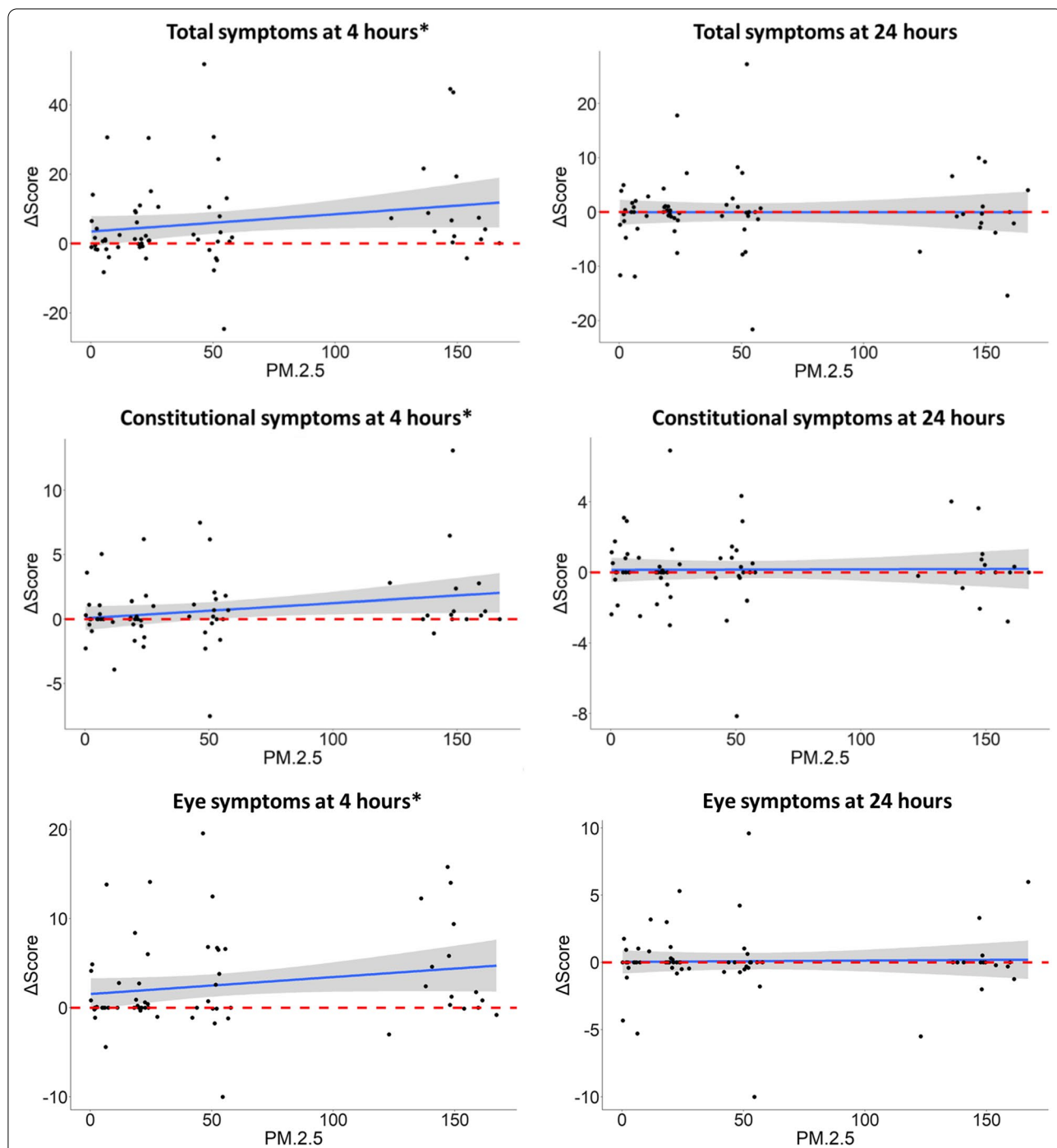


Fig. 1 Diesel exhaust (DE) concentration–response for symptom categories. Symptoms were recorded before, and at 4 and 24 h after the start of exposures to filtered air and diesel exhaust (DE) standardized to 20, 50 and 150 μg/m³ PM_{2.5}. X axes show change in symptom scores from baseline, while Y axes show PM_{2.5} concentrations (μg/m³). Shaded grey regions represent 95% confidence intervals, and the horizontal dashed lines represent 0 (no change from baseline). Linear mixed effects models were fitted with participant ID as a random effect: **P* ≤ 0.05

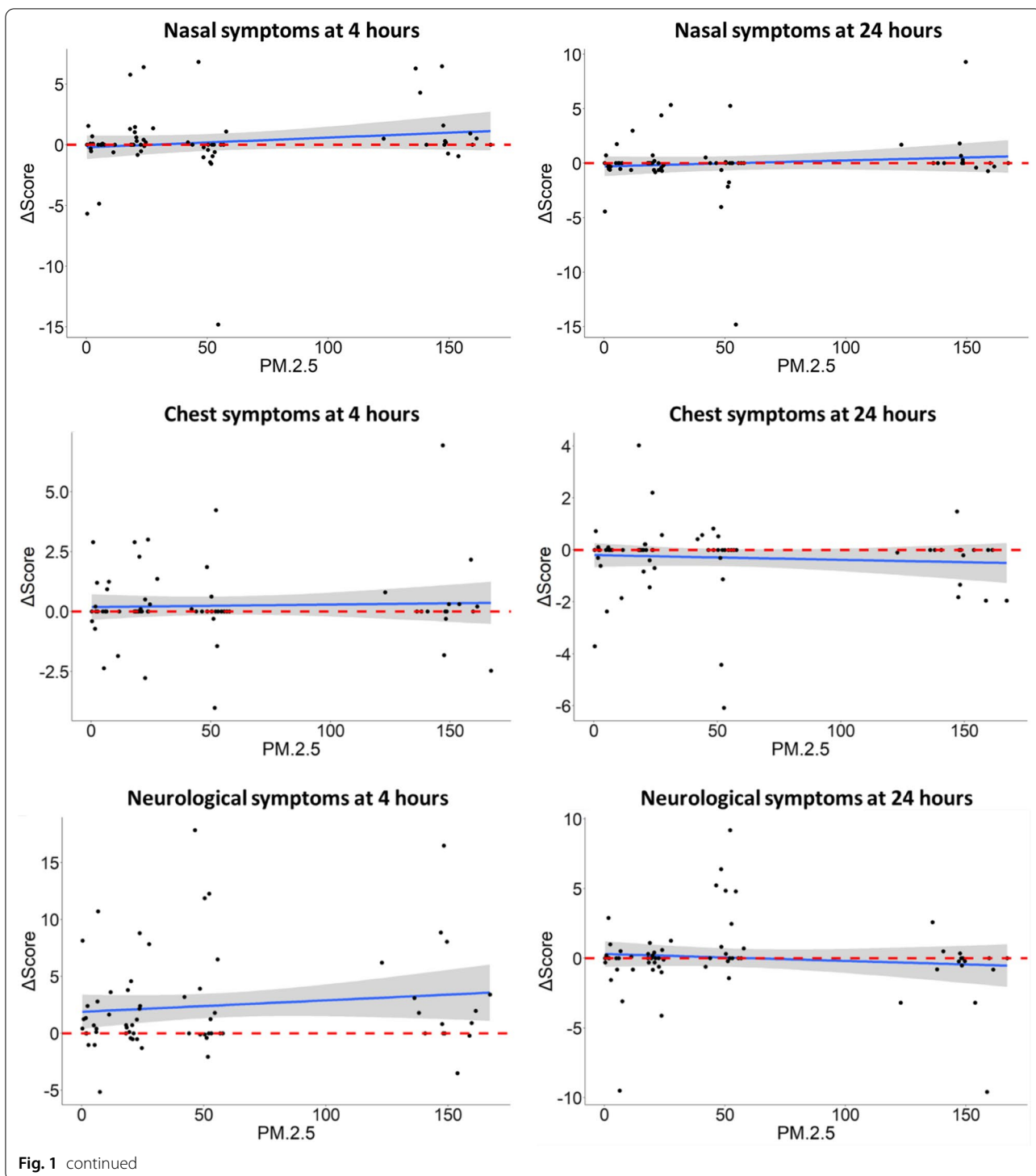
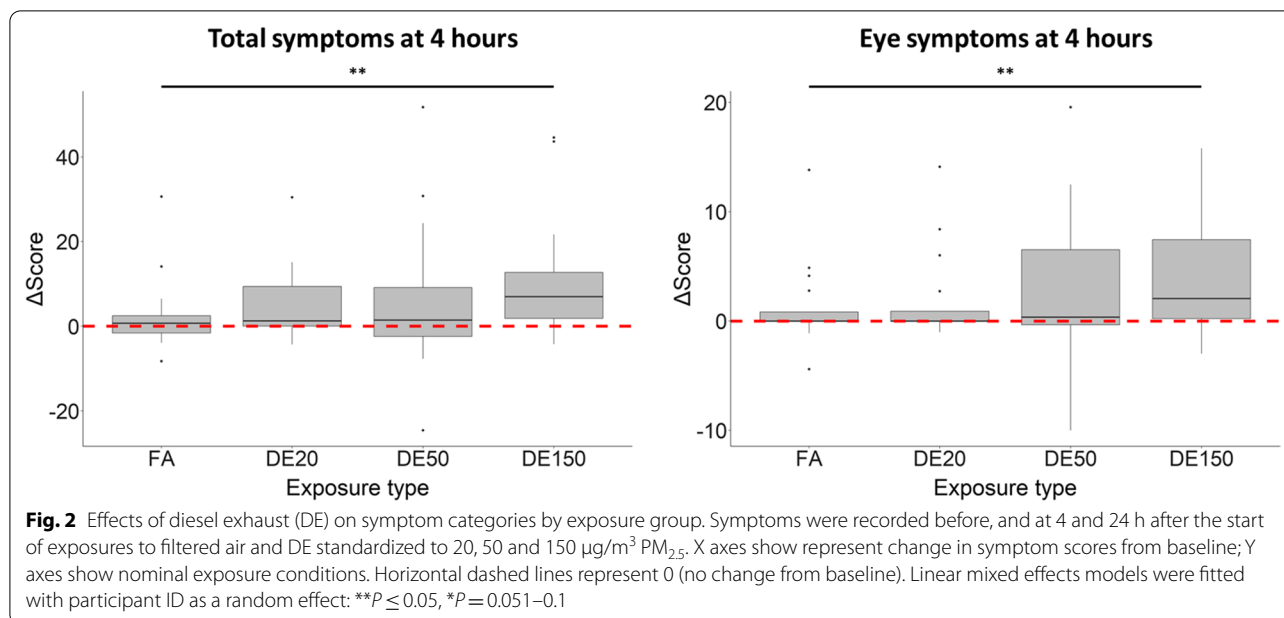


Fig. 1 continued



low-concentration DE exposures in healthy populations and has been corroborated by other controlled exposure studies [28, 48, 49].

Our findings are consistent with reports of DE-induced eye and constitutional symptoms in other controlled exposure studies [21–24, 50]. Notably, we did not observe any of the neurological or airway symptoms reported by these studies and others [47]. In contrast, other studies, which included rhinitis [51] and metabolic syndrome patients [17], did not report effects on symptoms. Interestingly, Carlsten et al. (2013) also reported a prominent role of perceived exposure condition (DE vs FA) in symptoms after DE exposure, albeit not as an effect modifier [17].

The symptom response that we observed was modified by perceived environmental temperature, noise, and anxiety. Higher temperatures and noise levels attenuated the increase in total, eye and constitutional symptoms, while anxiety enhanced constitutional symptoms. Known relationships between air pollution exposure and temperature [52–56], noise [57, 58] and anxiety [59–61] in epidemiological literature are mixed and vary by endpoints. For example, air pollution acts synergistically with and directly on temperature and anxiety respectively in some studies [52, 55, 60], but not others [59, 61]. Notably, these studies investigated ambient (not perceived) temperature and noise, and only explored anxiety as a direct effect of air pollution. In controlled human exposure studies, where ambient temperature and noise are relatively constant, the relationship between air pollution and environmental perception is relatively unexplored. Some

studies have investigated the direct effects of air pollution exposure and noise, reporting no significant effect on anxiety symptoms [22] and deleterious effects on other endpoints [62, 63]. Since ambient temperature and noise were consistent throughout our study, the interactions we observed could reflect a delineation between the perceived and true (measured) environment. This “mismatch” could be explained individual or localized psychological and physiological factors like sensitivity, discomfort and annoyance, which independently influence environmental perception and subjective symptoms [64–67]. While the underlying psychological triggers in our experimental setting are unclear, it is possible that a primary feeling, such as discomfort, influenced perception. For example, discomfort associated with anxiety may be responsible for anxiety-related enhancement of symptoms. Similarly, the discomfort due to perceived coldness, which is associated with eye irritation [68], may explain the attenuation of symptoms with increasing perceived temperature. The attenuation of symptoms by increased perceived noise is surprising, considering that others have reported symptom enhancement [64, 65, 69]. Interestingly, overall perceived exposure condition (DE or FA) did not modify symptoms, which indicates effective experimental blinding of symptom responses, but this analysis may be limited by unbalanced comparison groups. Different participant demographics, in addition to methodological differences, such as statistical approaches, endpoints, exposure levels and durations, limit direct comparisons between our work and others. The unknown psychological triggers and relatively small

Table 3 Concentration–response effect modification by environmental perception

Symptom category (at 4 h)	Perception measure	β (SE)	P value
Total	Lighting	−0.02 (0.03)	0.44
	Glare	−0.01 (0.01)	0.29
	Noise	−0.07 (0.03)	0.01
	Temperature	−0.06 (0.03)	0.02
	Humidity	−0.03 (0.05)	0.50
	Air circulation	0.03 (0.03)	0.30
	Air quality	−0.03 (0.04)	0.52
	Odor	0.03 (0.03)	0.23
	Ventilation	0.00 (0.01)	0.72
	Anxiety	0.02 (0.02)	0.38
	Constitutional	Lighting	−0.01 (0.01)
Glare		0.00 (0.00)	0.50
Noise		−0.01 (0.01)	0.06
Temperature		−0.01 (0.01)	0.03
Humidity		0.00 (0.01)	0.96
Air circulation		0.01 (0.01)	0.32
Air quality		0.01 (0.01)	0.34
Odor		0.01 (0.01)	0.09
Ventilation		0.00 (0.00)	0.55
Anxiety		0.01 (0.00)	0.03
Eyes		Lighting	0.01 (0.01)
	Glare	−0.01 (0.00)	0.23
	Noise	−0.02 (0.01)	0.02
	Temperature	−0.03 (0.01)	0.01
	Humidity	0.00 (0.02)	0.91
	Air circulation	0.01 (0.01)	0.19
	Air quality	−0.03 (0.02)	0.13
	Odor	0.01 (0.01)	0.27
	Ventilation	0.00 (0.00)	0.60
	Anxiety	0.00 (0.01)	0.94

Symptom scores were summed into categories

Significant effects ($P < 0.05$) are bolded

interaction effect sizes, highlight the need for corroboration and further exploration in future studies. Our study is the first DE exposure study to use multiple exposure concentrations to examine the linear C-R relationship between TRAP and symptoms and examine interactions with environmental perception.

The significant increase in symptoms at $150 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$, compared to FA, is consistent with an effect threshold below $150 \mu\text{g}/\text{m}^3$, similar to a threshold below $140 \mu\text{g}/\text{m}^3$ of total suspended particles suggested by Mølhave et al. [70]. Moreover, Vilcassim et al. reported an increase in symptoms when participants travelled from low ($< 35 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$) to high ($> 100 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$) pollution cities [18], estimating a $40 \mu\text{g}/\text{m}^3$ threshold. The resolution of symptoms at 24 h after acute exposure in our study is consistent with recovery after the cessation of air pollution exposure observed by Vilcassim et al. and Mølhave et al. [18, 70]. The transient nature of symptoms, relatively small effect sizes and absence of a strong relationship with lung function may indicate that these effects are often subclinical in this healthy population. Nevertheless, our findings are important to biological plausibility and may provide useful estimates and potential thresholds for assessing the health impacts of air pollution in a healthy population.

Although the exposure duration in this study is the longest for a controlled DE study to date, it does not fully replicate complex typically day-to-week long real-world exposures [28]. Secondly, our study recruited a relatively small sample of healthy non-smokers and may not be sufficiently generalizable to other populations [71]. Thus, future studies may delve further into susceptibility factors that modify the C-R relationship, as well as physiological mechanisms associated with reported symptoms. Lastly, we report relatively novel findings of perceived environmental modifiers of the air pollution exposure symptom response that warrant replication in future studies.

In this controlled DE exposure study, we detailed a concentration–response relationship between particulate matter and self-reported symptoms, and identified perceived temperature, noise, and anxiety as potential modifiers of this relationship. Our research not only highlights the utility of visual analog scale questionnaires as non-invasive tools for assessing the health effects of air pollution, but also provides effect estimates and modifiers over a range of epidemiologically relevant $\text{PM}_{2.5}$ levels. This may be crucial in adopting self-reported questionnaires as non-invasive tools for health monitoring and developing public health guidelines for air pollution.

(See figure on next page.)

Fig. 3 Effect of perception on the concentration–response between diesel exhaust (DE) and symptoms. Symptoms data was recorded before, and at 4 and 24 h after the start of exposures to filtered air and DE standardized to 20, 50 and $150 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$. Y axes show change in symptom scores from baseline; X axes show $\text{PM}_{2.5}$ concentrations ($\mu\text{g}/\text{m}^3$). Shaded grey regions represent 95% confidence intervals, and the horizontal dashed lines represent 0 (no change from baseline). Linear mixed effects models were fitted with perceived exposure condition as an interaction term and participant ID as a random effect

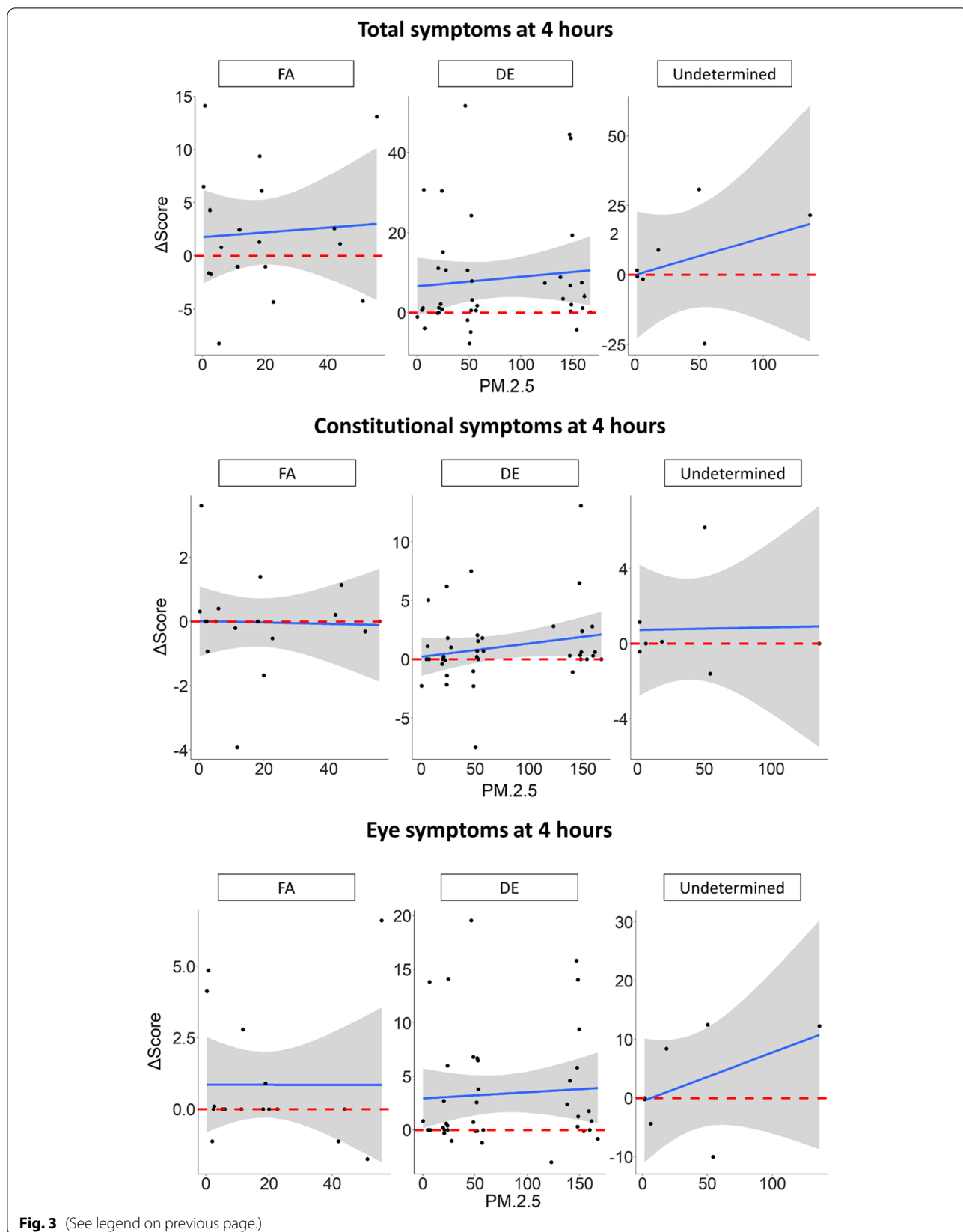


Fig. 3 (See legend on previous page.)

Table 4 Repeated measures correlations between change in symptoms and airway function measures

Symptom category (at 4 h)	Correlate	Timepoint (h)	r (std error)	P value
Total	Percentage Δ FeNO	4	0.29 (0.13)	0.04
		24	0.39 (0.12)	< 0.00
	Percentage Δ FEV ₁	4	0.04 (0.14)	0.78
Constitutional	Percentage Δ FeNO	24	0.07 (0.14)	0.64
		24	−0.06 (0.15)	0.71
	Percentage Δ FEV ₁	4	0.12 (0.14)	0.41
		24	0.34 (0.13)	0.02
	Δ log PC ₂₀	4	0.04 (0.14)	0.79
		24	0.17 (0.14)	0.24
Eyes	Percentage Δ FeNO	24	−0.02 (0.15)	0.91
		4	0.32 (0.13)	0.02
	Percentage Δ FEV ₁	24	0.40 (0.12)	< 0.00
		4	0.04 (0.14)	0.78
	Δ log PC ₂₀	24	0.09 (0.14)	0.55
	24	−0.07 (0.15)	0.65	

Symptom scores were summed into categories

Significant effects ($P < 0.05$) are bolded

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12989-022-00506-6>.

Additional file 1. Supplemental tables and figures.

Acknowledgements

We are grateful to the research volunteers that participated in this research study. We appreciate the support of all the staff at the Air Pollution Exposure Laboratory and the Lung Center at the Vancouver General Hospital. We thank Dr. Neeloffer Mookherjee, Ms. Carley Schwartz, Mr. Parteek Johal, Mr. Goldman Lam, Mr. Kevin Lau, Ms. Bora, Ms. Ayman Azhar and Ms. Shuyu Fan for their contributions to the DICE project. Finally, we thank the Vancouver Coastal Health Research Institute and University of British Columbia for institutional support.

Author contributions

JO: conceptualization, formal analysis, investigation, data curation, writing—original draft, writing—review and editing, visualization. CFR: conceptualization, methodology, formal analysis, writing—review and editing. ACYY: methodology, investigation, writing—review and editing, project administration. CC: conceptualization, methodology, writing—review and editing, supervision, funding acquisition. All authors read and approved the final manuscript.

Funding

This research study was funded by Occupational Health and Safety Alberta (095221549) and Manitoba Worker's Compensation Board (RWIP17-03). JO was supported by a WorkSafe BC Training Award (R3019-TG05). CFR was supported by Vancouver Coastal Health Research Institute—Centre for Respiratory, Cardiac and Critical Care Medicine, BC Lung Association/MITACS Accelerate, and

Michael Smith Foundation for Health Research Fellowships. CC was supported by the Canada Research Chairs Program.

Availability of data and materials

The datasets supporting the conclusions of this article are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the University of British Columbia Research Ethics Board (H16-03053). Informed consent was obtained before volunteer participation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they do not have any competing interests.

Received: 23 July 2022 Accepted: 14 November 2022

Published online: 23 November 2022

References

- Leikauf GD, Kim S-H, Jang A-S. Mechanisms of ultrafine particle-induced respiratory health effects. *Exp Mol Med*. 2020. <https://doi.org/10.1038/s12276-020-0394-0>.
- Muñoz X, Barreiro E, Bustamante V, Lopez-Campos JL, González-Barcala FJ, Cruz MJ. Diesel exhausts particles: their role in increasing the incidence of asthma. Reviewing the evidence of a causal link. *Sci Total Environ Elsevier*. 2019;652:1129–38.
- Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet*. 2017;389:1907–18.
- Orru K, Orru H, Maasikmets M, Hendrikson R, Ainsaar M. Well-being and environmental quality: Does pollution affect life satisfaction? *Qual Life Res*. 2016;25:699–705.
- Hegseth MN, Oftedal BM, Höper AC, Aminoff AL, Thomassen MR, Svendsen MV, et al. Self-reported traffic-related air pollution and respiratory symptoms among adults in an area with modest levels of traffic. *PLoS One*. 2019. <https://doi.org/10.1371/journal.pone.0226221>.
- Williams AM, Phaneuf DJ, Barrett MA, Su JG. Short-term impact of PM 25 on contemporaneous asthma medication use: behavior and the value of pollution reductions. *Proc Natl Acad Sci USA*. 2019;116:5246–53.
- Chambers L, Finch J, Edwards K, Jeanjean A, Leigh R, Gonem S. Effects of personal air pollution exposure on asthma symptoms, lung function and airway inflammation. *Clin Exp Allergy*. 2018;48:798–805. <https://doi.org/10.1111/cea.13130>.
- Pirozzi CS, Mendoza DL, Xu Y, Zhang Y, Scholand MB, Baughman RP. Short-term particulate air pollution exposure is associated with increased severity of respiratory and quality of life symptoms in patients with fibrotic sarcoidosis. *Int J Environ Res Public Health*. 2018;15:1077.
- Yu O, Sheppard L, Lumley T, Koenig JQ, Shapiro GG. Effects of ambient air pollution on symptoms of asthma in seattle-area children enrolled in the CAMP study. *Environ Health Perspect JSTOR*. 2000;108:1209.
- Wu S, Ni Y, Li H, Pan L, Yang D, Baccarelli AA, et al. Short-term exposure to high ambient air pollution increases airway inflammation and respiratory symptoms in chronic obstructive pulmonary disease patients in Beijing, China. *Environ Int*. 2016. <https://doi.org/10.1016/j.envint.2016.05.004>.
- Bjerner L, Alving K, Diamant Z, Magnussen H, Pavord I, Piacentini G, et al. Current evidence and future research needs for FeNO measurement in respiratory diseases. *Respir Med*. 2014;2014:830–41.
- Torén K, Schiöler L, Lindberg A, Andersson A, Behndig AF, Bergström G, et al. The ratio FEV 1 /FVC and its association to respiratory symptoms—a Swedish general population study. *Clin Physiol Funct Imaging*. 2021;41:181–91. <https://doi.org/10.1111/cpf.12684>.

13. Betchley C, Koenig JQ, Van Belle G, Checkoway H, Reinhardt T. Pulmonary function and respiratory symptoms in forest firefighters. *Am J Ind Med.* 1997;31:503–9.
14. Tan G, Li J, Yang Q, Wu A, Qu D-Y, Wang Y, et al. Air pollutant particulate matter 2.5 induces dry eye syndrome in mice. *Sci Rep.* 2018;8:17828.
15. Huff RD, Carlsten C, Hirota JA. An update on immunologic mechanisms in the respiratory mucosa in response to air pollutants. *J Allergy Clin Immunol.* 2019. <https://doi.org/10.1016/j.jaci.2019.04.012>.
16. Glencross DA, Ho T-R, Camiña N, Hawrylowicz CM, Pfeffer PE. Air pollution and its effects on the immune system. *Free Radic Biol Med.* 2020. <https://doi.org/10.1016/j.freeradbiomed.2020.01.179>.
17. Carlsten C, Oron AP, Curtiss H, Jarvis S, Daniell W, Kaufman JD. Symptoms in response to controlled diesel exhaust more closely reflect exposure perception than true exposure. *PLoS One.* 2013;2013:8.
18. Vilcassim MJR, Thurston GD, Chen LC, Lim CC, Saunders E, Yao Y, et al. Exposure to air pollution is associated with adverse cardiopulmonary health effects in international travellers. *J Travel Med.* 2019. <https://doi.org/10.1093/jtm/taz032/5486057>.
19. Barraza-Villarreal A, Sunyer J, Hernandez-Cadena L, Escamilla-Nunñez MC, Sienra-Monge JJ, Ramírez-Aguilar M, et al. Air pollution, airway inflammation, and lung function in a cohort study of Mexico City Schoolchildren. *Environ Health Perspect.* 2008;116:832–8.
20. Gren L, Dierschke K, Mattsson F, Assarsson E, Kraus AM, Kåredal M, et al. Lung function and self-rated symptoms in healthy volunteers after exposure to hydrotreated vegetable oil (HVO) exhaust with and without particles. *Part Fibre Toxicol BioMed.* 2022;19:9. <https://doi.org/10.1186/s12989-021-00446-7>.
21. Mudway IS, Stenfors N, Duggan ST, Roxborough H, Zielinski H, Marklund SL, et al. An in vitro and in vivo investigation of the effects of diesel exhaust on human airway lining fluid antioxidants. *Arch Biochem Biophys.* 2004;423:200–12.
22. Laumbach RJ, Kipen HM, Kelly-Mcneil K, Zhang J, Zhang L, Liou PJ, et al. Sickness response symptoms among healthy volunteers after controlled exposures to diesel exhaust and psychological stress. *Environ Health Perspect.* 2011;119:945–50.
23. Rudell B, Ledin MC, Hammarström U, Stjernberg N, Lundbäck B, Sandström T. Effects on symptoms and lung function in humans experimentally exposed to diesel exhaust. *Occup Environ Med.* 1996;53:658–62.
24. Muala A, Sehlstedt M, Bion A, Österlund C, Bosson JA, Behndig AF, et al. Assessment of the capacity of vehicle cabin air inlet filters to reduce diesel exhaust-induced symptoms in human volunteers. *Environ Heal A Glob Access Sci Sour.* 2014;13:1.
25. Orach J, Rider CF, Carlsten C. Concentration-dependent health effects of air pollution in controlled human exposures. *Environ Int.* 2021;150:106424. <https://doi.org/10.1016/j.envint.2021.106424>.
26. Orach J, Rider CF, Yuen A, Carlsten C. Traffic-related air pollution induces a concentration-dependent increase in symptoms in a controlled human exposure study: B105 more calls to action. *AIR Pollut Expo Heal.* 2022. https://doi.org/10.1164/ajrcm-conference.2022.205.1_MeetingAbstracts.A3576.
27. Birger N, Gould T, Stewart J, Miller MR, Larson T, Carlsten C. The Air Pollution Exposure Laboratory (APEL) for controlled human exposure to diesel exhaust and other inhalants: characterization and comparison to existing facilities. *Inhal Toxicol.* 2011;23:219–25.
28. Long E, Carlsten C. Controlled human exposure to diesel exhaust: results illuminate health effects of traffic-related air pollution and inform future directions. *Part Fibre Toxicol.* 2022;19:1–35. <https://doi.org/10.1186/s12989-022-00450-5>.
29. Buzzard NA, Clark NN, Guffey SE. Investigation into pedestrian exposure to near-vehicle exhaust emissions. *Environ Heal A Glob Access Sci Sour.* 2009;2009:8.
30. Pronk A, Coble J, Stewart PA. Occupational exposure to diesel engine exhaust: a literature review. *J Expo Sci Environ Epidemiol.* 2009;2009:443–57.
31. Gong H, Linn WS, Sioutas C, Terrell SL, Clark KW, Anderson KR, et al. Controlled exposures of healthy and asthmatic volunteers to concentrated ambient fine particles in Los Angeles. *Inhal Toxicol.* 2003;15:305–25.
32. Aitken RCB. A growing edge of measurement of feelings [abridged]: measurement of feelings using visual analogue scales. *Proc R Soc Med.* 1969;62:989–93. <https://doi.org/10.1177/003591576906201006>.
33. Bausewein C, Farquhar M, Booth S, Gysels M, Higginson IJ. Measurement of breathlessness in advanced disease: a systematic review. *Respir Med.* 2007;101:399–410.
34. Graham BL, Steenbruggen I, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, et al. Standardization of spirometry 2019 update: an official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med.* 2019;200:E70–88.
35. Coates AL, Wanger J, Cockcroft DW, Culver BH, Carlsen KH, Diamant Z, et al. ERS technical standard on bronchial challenge testing: General considerations and performance of methacholine challenge tests. *Eur Respir J.* 2017. <https://doi.org/10.1183/13993003.01526-2016%5D>.
36. Sterk PJ, Fabbri LM, Quanjer PH, Cockcroft DW, O'Byrne PM, Anderson SD, et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. *Eur Respir J.* 1993;1993:53–83.
37. Jokic R, Davis EE, Cockcroft DW. Methacholine PC20 extrapolation. *Chest.* 1998;114:1796–7.
38. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: Interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med.* 2011;2011:602–15. <https://doi.org/10.1164/rccm.9120-11ST>.
39. Dijkhoff IM, Drasler B, Karakocak BB, Petri-Fink A, Valacchi G, Eeman M, et al. Impact of airborne particulate matter on skin: a systematic review from epidemiology to in vitro studies. *Part Fibre Toxicol.* 2020;17:35. <https://doi.org/10.1186/s12989-020-00366-y>.
40. Drakaki E, Dessinioti C, Antoniou CV. Air pollution and the skin. *Front Environ Sci.* 2014;2:156–7. <https://doi.org/10.1007/s00105-018-4349-5>.
41. Torricelli AAM, Novaes P, Matsuda M, Braga A, Saldiva PHN, Alves MR, et al. Correlation between signs and symptoms of ocular surface dysfunction and tear osmolarity with ambient levels of air pollution in a large metropolitan area. *Cornea.* 2013;32:e11–5.
42. Mo Z, Fu Q, Lyu D, Zhang L, Qin Z, Tang Q, et al. Impacts of air pollution on dry eye disease among residents in Hangzhou, China: a case-crossover study. *Environ Pollut.* 2019;246:183–9.
43. Yoon S, Han S, Jeon K-J, Kwon S. Effects of collected road dusts on cell viability, inflammatory response, and oxidative stress in cultured human corneal epithelial cells. *Toxicol Lett.* 2018;284:152–60.
44. Song SJ, Hyun S-W, Lee TG, Park B, Jo K, Kim C-S. New application for assessment of dry eye syndrome induced by particulate matter exposure. *Ecotoxicol Environ Saf.* 2020. <https://doi.org/10.1016/j.ecoenv.2020.111125>.
45. Mu N, Wang H, Chen D, Wang F, Ji L, Zhang C, et al. A novel rat model of dry eye induced by aerosol exposure of particulate matter. *Investig Ophthalmol Vis Sci.* 2022;63:39.
46. Kwon H-S, Ryu MH, Carlsten C. Ultrafine particles: unique physicochemical properties relevant to health and disease. *Exp Mol Med.* 2020;2020:1–11.
47. Xu Y, Barregard L, Nielsen J, Gudmundsson A, Wierzbicka A, Axmon A, et al. Effects of diesel exposure on lung function and inflammation biomarkers from airway and peripheral blood of healthy volunteers in a chamber study. *Part Fibre Toxicol.* 2013;10:60.
48. Landwehr KR, Larcombe AN, Reid A, Mullins BJ. Critical review of diesel exhaust exposure health impact research relevant to occupational settings: are we controlling the wrong pollutants? *Expo Heal.* 2021;2021:141–71. <https://doi.org/10.1007/s12403-020-00379-0>.
49. Ghio A, Sobus J, Pleil J, Madden M. Controlled human exposures to diesel exhaust. *Swiss Med Wkly.* 2012;2012:142.
50. Rudell B, Wass U, Hörstedt P, Levin JO, Lindahl R, Rannug U, et al. Efficiency of automotive cabin air filters to reduce acute health effects of diesel exhaust in human subjects. *Occup Environ Med.* 1999;56:222–31.
51. Larsson N, Brown J, Stenfors N, Wilson S, Mudway IS, Pourazar J, et al. Airway inflammatory responses to diesel exhaust in allergic rhinitis. *Inhal Toxicol.* 2013;25:160–7.
52. Wu S, Deng F, Hao Y, Wang X, Zheng C, Lv H, et al. Fine particulate matter, temperature, and lung function in healthy adults: findings from the HVNR study. *Chemosphere.* 2014. <https://doi.org/10.1016/j.chemosphere.2014.01.032>.
53. Nassan FL, Kelly RS, Kosheleva A, Koutrakis P, Vokonas PS, Lasky-Su JA, et al. Metabolomic signatures of the long-term exposure to air pollution and temperature. *Environ Heal.* 2021;20:3. <https://doi.org/10.1186/s12940-020-00683-x>.

54. Zanobetti A, Luttmann-Gibson H, Horton ES, Cohen A, Coull BA, Hoffmann B, et al. Brachial artery responses to ambient pollution, temperature, and humidity in people with type 2 diabetes: a repeated-measures study. *Environ Health Perspect*. 2014. <https://doi.org/10.1289/ehp.1206136>.
55. Li H, Bai H, Yang C, Chen R, Wang C, Zhao Z, et al. Acute effects of ambient temperature and particulate air pollution on fractional exhaled nitric oxide: a panel study among diabetic patients in Shanghai, China. *J Epidemiol Jpn Epidemiol Assoc*. 2017;27:584–9.
56. Anenberg SC, Haines S, Wang E, Nassikas N, Kinney PL. Synergistic health effects of air pollution, temperature, and pollen exposure: a systematic review of epidemiological evidence. *Environ Heal*. 2020;19:130. <https://doi.org/10.1186/s12940-020-00681-z>.
57. Huang J, Deng F, Wu S, Lu H, Hao Y, Guo X. The impacts of short-term exposure to noise and traffic-related air pollution on heart rate variability in young healthy adults. *J Expo Sci Environ Epidemiol*. 2013;23:559–64.
58. Biel R, Danieli C, Shekarrizfard M, Minet L, Abrahamowicz M, Baumgartner J, et al. Acute cardiovascular health effects in a panel study of personal exposure to traffic-related air pollutants and noise in Toronto, Canada. *Sci Rep*. 2020. <https://doi.org/10.1038/s41598-020-73412-6>.
59. Petrowski K, Bührer S, Strauß B, Decker O, Brähler E. Examining air pollution (PM10), mental health and well-being in a representative German sample. *Sci Rep*. 2021;11:18436.
60. Power MC, Kioumourtzoglou M-A, Hart JE, Okereke OI, Laden F, Weiskopf MG. The relation between past exposure to fine particulate air pollution and prevalent anxiety: observational cohort study. *BMJ*. 2015;350:h1111.
61. Vert C, Sánchez-Benavides G, Martínez D, Gotsens X, Gramunt N, Cirach M, et al. Effect of long-term exposure to air pollution on anxiety and depression in adults: a cross-sectional study. *Int J Hyg Environ Health*. 2017. <https://doi.org/10.1016/j.ijheh.2017.06.009>.
62. Stockfelt L, Xu Y, Gudmundsson A, Rissler J, Isaxon C, Brunskog J, et al. A controlled chamber study of effects of exposure to diesel exhaust particles and noise on heart rate variability and endothelial function. 2022.
63. Hemmingsen JG, Møller P, Jantzen K, Jönsson BAG, Albin M, Wierzbicka A, et al. Controlled exposure to diesel exhaust and traffic noise: effects on oxidative stress and activation in mononuclear blood cells. *Mutat Res Fundam Mol Mech Mutagen*. 2015;775:66–71.
64. Chiarini B, D'Agostino A, Marzano E, Regoli A. The perception of air pollution and noise in urban environments: a subjective indicator across European countries. *J Environ Manage*. 2020;263:110272. <https://doi.org/10.1016/j.jenvman.2020.110272>.
65. Martens AL, Reedijk M, Smid T, Huss A, Timmermans D, Strak M, et al. Modeled and perceived RF-EMF, noise and air pollution and symptoms in a population cohort—is perception key in predicting symptoms? *Sci Total Environ*. 2018;639:75–83. <https://doi.org/10.1016/j.scitotenv.2018.05.007>.
66. Peng M, Zhang H, Evans RD, Zhong X, Yang K. Actual air pollution, environmental transparency, and the perception of air pollution in China. *J Environ Dev*. 2019;28:78–105. <https://doi.org/10.1177/1070496518821713>.
67. Pantavou K, Lykoudis S, Psiloglou B. Air quality perception of pedestrians in an urban outdoor Mediterranean environment: a field survey approach. *Sci Total Environ*. 2017;574:663–70. <https://doi.org/10.1016/j.scitotenv.2016.09.090>.
68. Azuma K, Ikeda K, Kagi N, Yanagi U, Osawa H. Prevalence and risk factors associated with nonspecific building-related symptoms in office employees in Japan: relationships between work environment, Indoor Air Quality, and occupational stress. *Indoor Air*. 2015;25:499–511.
69. Lercher P, Schmitzberger R, Kofler W. Perceived traffic air pollution, associated behavior and health in an alpine area. *Sci Total Environ*. 1995;169:71–4.
70. Møhlhave L, Kjærgaard SK, Attermann J. Sensory and other neurogenic effects of exposures to airborne office dust. *Atmos Environ*. 2000;34:4755–66.
71. Helena Andersen MG, Loft S, Bønløkke JH, Saber AT, Vogel U, Møller P. Ambient combustion ultrafine particles and health: controlled human exposure studies. 2021. <https://www.novapublishers.com/wp-content/uploads/2021/02/Controlled-Human-Exposure-Studies.pdf>

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

