Environment International 97 (2016) 45–55

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

# Acute respiratory response to traffic-related air pollution during physical activity performance

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ARTICLE INFO

*Article history:*
Received 22 July 2016
Received in revised form 10 October 2016
Accepted 10 October 2016
Available online 21 October 2016

*Keywords:*
Traffic-related air pollution
Physical activity
Particulate matter
Short term
Crossover study
Inhalation exposure

ABSTRACT

*Background:* Physical activity (PA) has beneficial, whereas exposure to traffic related air pollution (TRAP) has adverse, respiratory effects. Few studies, however, have examined if the acute effects of TRAP upon respiratory outcomes are modified depending on the level of PA.
*Objectives:* The aim of our study was to disentangle acute effects of TRAP and PA upon respiratory outcomes and assess the impact of participants TRAP pre-exposure.
*Methods:* We conducted a real-world crossover study with repeated measures of 30 healthy adults. Participants completed four 2-h exposure scenarios that included either rest or intermittent exercise in high- and low-traffic environments. Measures of respiratory function were collected at three time points. Pre-exposure to TRAP was ascertained from land-use-modeled address-attributed values. Mixed-effects models were used to estimate the impact of TRAP and PA on respiratory measures as well as potential effect modifications.
*Results:* We found that PA was associated with a statistically significant increases of $FEV_1$ (48.5 mL, $p = 0.02$), $FEV_1$/FVC (0.64%, $p = 0.005$) and $FEF_{25-75\%}$ (97.8 mL, $p = 0.02$). An increase in exposure to one unit (1 μg/m$^3$) of $PM_{coarse}$ was associated with a decrease in $FEV_1$ (−1.31 mL, $p = 0.02$) and FVC (−1.71 mL, $p = 0.01$), respectively. On the other hand, for an otherwise equivalent exposure an increase of PA by one unit (1%Heart rate max) was found to reduce the immediate negative effects of particulate matter (PM) upon PEF ($PM_{2.5}$, 0.02 L/min, $p = 0.047$; $PM_{10}$, 0.02 L/min $p = 0.02$; $PM_{coarse}$, 0.03 L/min, $p = 0.02$) and the several hours delayed negative effects of PM upon FVC ($PM_{coarse}$, 0.11 mL, $p = 0.02$). The negative impact of exposure to TRAP constituents on $FEV_1$/FVC and PEF was attenuated in those participants with higher TRAP pre-exposure levels.
*Conclusions:* Our results suggest that associations between various pollutant exposures and respiratory measures are modified by the level of PA during exposure and TRAP pre-exposure of participants.


## 1. Introduction

Worldwide, in urban environments, millions of people are exposed daily to air pollution levels well above national and international standards (Chen and Kan, 2008; WHO, 2006). One major source of the observed air pollution is the high traffic-density of cities (Chen and Kan, 2008). Long-term exposure to traffic-related air pollution (TRAP) is associated with adverse health impacts such as respiratory symptoms, as well as increased morbidity and mortality (Hoek et al., 2013; Peters et al., 2012; Raaschou-Nielsen et al., 2012; Strak et al., 2010; Willers et al., 2013). TRAP contributes to these health outcomes among others by mechanisms involving oxidative stress and inflammation (Anderson et al., 2012; Delfino et al., 2009).

Health co-benefits of physical activity (PA) are well known and are often promoted in public health measures (Haskell et al., 2009; Kohl et al., 2012; Warburton et al., 2006). Among the adaptations of the respiratory system in response to exercise are an increase in ventilation rate and bronchodilation lasting beyond the exercise period (Anderton et al., 1979; Cheng et al., 2003; Crimi et al., 2002; Freedman et al., 1988;

*Abbreviations:* PA, physical activity; TRAP, traffic-related air pollution; LT, low traffic; HT, high traffic; $T_0$–$T_2$, time points of lung function measurements; HR, heart rate.

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http://dx.doi.org/10.1016/j.envint.2016.10.011
0160-4120/

Scichilone et al., 2010). Due to these respiratory adaptations, the volume of inhaled air and the fraction of air-suspended particles deposited in the respiratory tract are considerably higher during exercise compared to rest (Daigle et al., 2003; Jakob and Massling, 2007). Indeed, studies have shown that individuals deciding to perform PA in an urban environment risk a higher exposure to TRAP compared to sedentary individuals or people exercising indoors or in rural environments (van Wijnen et al., 1995; Watt et al., 1995).

Besides the above, a change from private-automobile usage to active mobility like cycling or walking is often promoted as a means of reducing TRAP levels in urban areas. However, opting for active transportation has been found to increase exposure to TRAP (Knibbs et al., 2011; Zuurbier et al., 2010), which could lead to a decrease in lung function in susceptible and healthy adults (McCreanor et al., 2007; Mu et al., 2014), and to a substantial increase in the inhaled dose of TRAP (Int Panis et al., 2010; Zuurbier et al., 2010; Zuurbier et al., 2009). To date, despite some previous studies (de Hartog et al., 2010; Kubesch et al., 2015), there is still reasonable doubt as to whether the conjunction between performing PA and being exposed to high levels of TRAP is either beneficial or detrimental for lung function.

It is therefore of scientific and public health interest to understand whether the respiratory effects of PA are modified when it is performed in an urban, highly-polluted environment. Moreover, since studies suggest that air pollution pre-exposure modifies respiratory function (Giles et al., 2012), the influence of participants pre-exposure is of interest. Many epidemiological studies assessing the acute respiratory effects of air pollutants only examine susceptible subpopulations (Bentayeb et al., 2012; Delfino et al., 2008; Lee et al., 2007; Lewis et al., 2005; McCreanor et al., 2007; O'Connor et al., 2008; Peacock et al., 2011; Qian et al., 2009; Weinmayr et al., 2010) and whether findings of these studies can be transferred to healthy individuals remains questionable. Furthermore, studies examining the respiratory short-term effects of an exposure to elevated levels of air pollution are still rare and not designed to examine effect modifications on a single pollutant level (Cole-Hunter et al., 2015a; Cole-Hunter et al., 2013; Mu et al., 2014). A large Danish cohort study found beneficial health effects of regular PA not to be moderated by the long term exposure to urban levels of air pollution (Andersen et al., 2015). However, whether this can be transferred to the short term effects of PA remains questionable. As such, our study was intended to assess the impact of PA on the acute relationship between respiratory function and surrounding levels of air pollution and to contribute to the growing body of evidence from studies examining healthy subpopulations. Identifying potential interdependent effects of air pollution and PA can help to advise public health measures such as encouraging active mobility.

The type of interaction terms we use in our models to examine the interdependence of the effects of two factors, assume that each factor modifies the effect of the other. Hence, for example, we cannot say what the effect of PA will be (to increase, decrease, or have no effect on the respiratory measure) unless we know that person's value for the level of TRAP exposure (and conversely, we cannot know the effect of TRAP exposure without knowing that person's level of PA).

## 2. Methods

### 2.1. Study design

Our study was conducted in Barcelona, Spain, between November 2013 and February 2014. A well-controlled crossover study design, comprising of four exposure scenarios performed in a random order, was chosen to disentangle the short-term effects of TRAP and PA on participants' respiratory function. These scenarios were defined by a combination of the exposure status (low or high TRAP environment) and the PA-status (rest or intermittent exercise). Each participant took part on four study days (turns), completing one exposure scenario a day. Six subjects were studied simultaneously on each study day, with three of them performing intermittent (moderate) PA (as 15-min intermittent cycle ergometry) while the other three volunteers rested. To avoid a diurnal effect, all experiments and measurements were scheduled at the same time during the day. On study days, participants arrived to the clinic at 06:45 for baseline measurements ($T_0$); afterwards, from 08:00 to 10:00 (i.e. morning traffic "rush hour") they were exposed to either low TRAP in a quiet seaside park (low traffic (LT) site) or high TRAP at a pedestrian overpass of a highway (high traffic (HT) site). Study sites were selected due to them representing low and high traffic-density areas and also their close proximity to the clinic where baseline health measurements were taken, and thus in-transit exposure of participants (and consequent exposure-response effect prior to study period) is minimized when moving from the clinic to the study site. These low and high definitions were confirmed by describing the sampled data while the study progressed – full exposure descriptions of each site are presented later as results (Table 2). To minimise prior exposure to TRAP and performance of PA, participants were requested to arrive prior to rush hour and via underground rail. Volunteers were transported by van (cycle-ventilated, windows closed) to either exposure site, which were of equivalent distance (approximately a one kilometre or five minute drive) from the clinic. The study days were scheduled on Tuesdays, Wednesdays, and Thursdays to avoid atypical weekend-related (commuting) TRAP levels. A two-hour exposure period was chosen as this was found to be a typical local average time spent in-transit over the course of a day (De Nazelle et al., 2013). Immediately after the two-hour exposure participants returned to the clinic to have the post-exposure ($T_1$) health measurements taken. Participants were then free to live their day normally for a period of 7 h, before returning to the clinic for the 7-hour-post-exposure ($T_2$) health measurements. We chose the free-living period to see whether acute effects observed immediately after exposure sustain and/or change over a period of 7 h if people were free to live their day normally, rather than as a scripted study procession. During the free-living period participants were carrying a Cambridge Personal Environmental Monitor (PEM) recording exposure data for NO, $NO_2$ and CO. Furthermore, heart rate (HR) was monitored with an ambulatory electrocardiography monitor (ModelCardioLight, Gem-Med, ESP).

Eligible participants were required to be: (1) in the age range of 18–60 yrs.; (2) non-smokers or ex-smokers (minimum one year without smoking); (3) not taking any medication (except contraception pill), nor any vitamins, nor any kind of allergy medication/treatment (at least for the last three months); (4) not being pregnant and not suffering from any chronic illness (high blood pressure, diabetes, pulmonary or cardiovascular diseases, etc.). Participants were required to abstain from high-intensity exercise, from alcohol, and from caffeine for at least 48, 24 and 4 h, respectively, before baseline measurements. The Ethic Review Committee of the Institut Municipal d'Investigatió Mèdica (IMIM) approved the study and prior to participation all participants gave written informed consent.

### 2.2. Physical activity monitoring

During the experiment, moderate PA performance was checked continuously by a fingertip pulse oximeter (Konica Minolta, Japan), being defined as a heart rate (HR) between 50 and 70% of an individual's predicted maximum HR, according to participant age and sex [males: $HR_{max} = 220 - (age)$; females: $HR_{max} = 206 - 0.88 * (age)$] (Gulati et al., 2010). Further, HR during the experiment (in parallel to oximetry) and free time was monitored with an ambulatory electrocardiography monitor (ModelCardioLight, Gem-Med, Spain).

### 2.3. Environmental exposure monitoring

Exposures at either study site were continuously monitored for ultra-fine particle (UFP; 0.01–1.0 μm) counts using a condensation particle counter (CPC, Model 3007, TSI, Minnesota, USA) (applied

correction factors, see Supplementary material, Part 1). Particulate matter mass with aerodynamic diameters of <2.5 μm ($PM_{2.5}$) and <10 μm ($PM_{10}$), along with size fractions, were monitored using a DustTrack (DRX, Model 8534, TSI, Minnesota, USA). Using data from the DustTrack and Harvard Impactor (HI) (Air Diagnostics and Engineering) collected during a previous study (Kubesch et al., 2015), $PM_{2.5}$ and $PM_{10}$ data from the DustTrack was gravimetrically calibrated with the equations [ $PM_{2.5} = (-6.17 + 6.28\sqrt[5]{PM_{2.5}})^2$ , $R^2 = 81.3\%$] and [ $PM_{10} = (0.15 + 0.98\sqrt[3]{PM_{10}})^3$, $R^2 = 88.7\%$]. Black carbon (BC) was measured with a portable aetholometer (Model AE-51, McAgee Scientific, California, USA) and corrected for filter attenuation (Kirchstetter and Novakov, 2007; Wang et al., 2011). Nitrogen monoxide (NO) concentration and total concentration of nitrogen oxides ($NO_x$) were measured using a nitric oxide monitor (Model 410 Nitric Oxide Monitor, 2B Technologies, Colorado, USA) in combination with a nitrogen dioxide ($NO_2$) converter (Model 401 $NO_2$ Converter, 2B Technologies, Colorado, USA). Temperature (T) and relative humidity (RH) were measured using a Q-Track (Model 7565, TSI, Minnesota, USA) and a Weather Station (Model WMR80, Oregon Scientific, Buckinghamshire, UK). $PM_{2.5}$ measurements were adjusted for RH using the correction factor ($CF = 1 + 0.25\frac{RH^2}{(1-RH)}$) (Ramachandran et al., 2003). Estimates for the pre-exposure of participants to particulate matter and gaseous constituents of TRAP one day prior to study days were obtained using a spatio-temporal model of the Barcelona region that was applied to participant home addresses (see Supplementary material, Part 1).

### 2.4. Respiratory health measurements

Respiratory function was assessed by spirometry using a portable EasyOne spirometer (Ndd Medical, Switzerland) in accordance with American Thoracic Society (ATS) and European Respiratory Society (ERS) standards (Miller et al., 2005). Forced expiratory volume in 1 s ($FEV_1$), forced vital capacity (FVC), peak expiratory flow (PEF) and mean forced expiratory flow between 25% and 75% of FVC ($FEF_{25-75\%}$) were measured each study day at $T_0$, $T_1$ and $T_2$ within a clinical setting. At each time point, at least three and a maximum of eight maneuvers (as described in the ATS/ERS standard) were tested. Maneuvers not fulfilling the within-maneuver acceptability criteria and reproducibility criteria as defined in the ATS/ERS standard were discarded. Remaining measurements were used to determine the best values of FVC and $FEV_1$. The ratio $FEV_1$/FVC, PEF and $FEF_{25-75\%}$ were taken from the measurement with the largest sum of FVC and $FEV_1$.

### 2.5. Statistical methods

To disentangle the independent and combined short-term effect of TRAP and PA upon respiratory function and assess the impact of participants pre-exposure levels, multivariate linear mixed models were constructed (see Supplementary material, Part 2) utilizing the nlme package for R (Pinheiro et al., 2012; Pinheiro and Bates, 2000). Participant ID was used as a random term, to account for correlations between repeated measures from individual participants. Furthermore, baseline respiratory function (baseline measurements were taken at the beginning of each study day) was added as a nested random effect to control for variations in the starting point of an individual over the course of the study. On the other hand, sex, age, temperature, relative humidity, and $NO_2$-pre-exposure were included as fixed effects in all models. Models were applied for each post-exposure time category separately as well as for the pooled data. For pooled data a categorical variable for time category was added as a fixed effect. Furthermore, as described by Baayen and associates, a by-subject slope for time category was added to the random term, to allow for a by-subject adjustment to the effect of time category (Baayen et al., 2008). Statistical significance was defined as $p \leq 0.05$. All analyses were performed using the R statistical software package version 3.1.3 (R Development Core Team, 2014).

#### 2.5.1. Models with categorical covariates

Our basic model used categorical variables for PA-status and traffic site to separate respiratory effects of TRAP and PA (Model CA1). To compare respiratory function across the four PA-status/traffic site scenarios a model with an independent categorical variable for scenario was applied using the scenario "Rest + HT" as a reference scenario (Model CA2).

#### 2.5.2. Models with continuous covariates

In order to examine effects of TRAP on a single pollutant level, we used a model with continuous covariates for pollutant level and PA that we ran for each pollutant separately (Model CO1).

#### 2.5.3. Interaction analysis

Potential interactions between PA, TRAP exposure and pre-exposure were examined by including respective first order interaction terms to the models. Interactions between PA and TRAP (Model IA1), PA and TRAP pre-exposure (Model IA2) and TRAP exposure and pre-exposure (Model IA3) were assessed. Continuous variables of interaction terms were centered.

#### 2.5.4. Stability analysis

Stability analyses included: 1) exclusion of participants that in comparison with other participants of the same gender showed a high variability in baseline measurements (see Supplementary material, Part 6 & 8); 2) exclusion of multiple measurements that were identified as outliers (see Supplementary material, Part 7 & 9); 3) inclusion of a covariate for the PA-level during the free living period (see Supplementary material, Part 10); 4) usage of percentage change from baseline as a dependent variable without baseline in the random-effect term (see Supplementary material, Part 11).

## 3. Results

### 3.1. Subject characteristics

We recruited 30 healthy adults, both males and females equally. Each participant completed each of the four exposure scenarios. One participant, however, was excluded from final data analyses as they reported symptoms of a reversible airflow obstruction, confirmed according to ATS/ERS criteria upon clinical analysis of spirometric data (Johns and Pierce, 2008; Miller et al., 2005; Pellegrino, 2005) (see Supplementary material, part 6). General demographic information and baseline respiratory measures of study participants are shown in Table 1.

### 3.2. Pollution levels

Average TRAP levels were significantly higher at the HT site compared to the LT site, particularly BC, UFP, $NO_X$ and NO which were up to seven times higher (Table 2).

There were high correlations ($r > 0.9$) between some TRAP components. However, correlations between PM fractions and the other measured TRAP constituents were weak to moderate, especially at the HT site. In general, correlations among pollutants tended to be lower at the HT site than at the LT site (see Supplementary material, Part 4). The fact that some of the pollutants were strongly correlated with each other was used to predict missing values of NO, $NO_X$ and BC via a simple linear regression model. For NO and $NO_X$ the interaction with UFP and site information was used to predict missing values (NO $R^2$-adj = 0.977 & $NO_X$ $R^2$-adj = 0.909), whereas for BC the relationship with NO and site information was used ($R^2$-adj = 0.911).

#### 3.2.1. Respiratory function

*3.2.1.1. Descriptive analysis.* Fig. 1 shows the percent change from baseline values of the respiratory function according to exposure and

**Table 1**
Demographic information, PA monitoring and baseline respiratory measures.

| | All | | Male | | Female | |
|---|---|---|---|---|---|---|
| | Mean | (Min-max) | Mean | (Min-max) | Mean | (Min-max) |
| Demographic information | | | | | | |
| Age (years) | 36.0 | (19–57) | 34.8 | (20–57) | 37.3 | (19–54) |
| BMI (kg/m2) | 24.3 | (18.2–38.8) | 24.5 | (22.0–28.4) | 24.0 | (18.2–38.8) |
| PA monitoring | | | | | | |
| HR rest (%HRmax) | 37.8 | (27.3–48.3) | 36.7 | (27.3–48.3) | 38.9 | (28.1–48.3) |
| HR PA (%HRmax) | 56.1 | (49.8–61.9) | 55.9 | (49.8–61.9) | 56.3 | (50.1–61.3) |
| | Int. | (95% CI) | Int. | (95% CI) | Int. | (95% CI) |
| Spatial pre-exposure | | | | | | |
| NO2 (ppb) | 44.0 | (34.1, 53.9) | 39.0 | (24.7, 53.4) | 49.3 | (35.4, 63.2) |
| Respiratory measures | | | | | | |
| PEF (L/min) | 542 | (491, 594) | 653 | (610, 697) | 423 | (387, 459) |
| FEV1 (L) | 3.7 | (3.3, 4.0) | 4.4 | (4.0, 4.7) | 2.9 | (2.6, 3.2) |
| FEV1/FVC (%) | 79.8 | (77.6, 82.0) | 79.3 | (76.5, 82.1) | 80.3 | (76.7, 84.0) |
| FVC (L) | 4.6 | (4.2, 5.0) | 5.5 | (5.2, 5.9) | 3.6 | (3.3, 3.9) |
| FEF25-75 (L/s) | 3.5 | (3.1, 4.0) | 4.1 | (3.5, 4.7) | 2.9 | (2.4, 3.4) |

BMI, body mass index; FEF25-75, mean forced expiratory flow between 25% and 75% of FVC; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, heart rate; Int., intercept; PA, physical activity; PEF, peak expiratory flow; SE, standard error; 95% CI, approximated 95% confidence interval for mixed-effects models.

time point. PA has been shown to increase all respiratory outcomes at $T_1$ except for PEF. However, this increase during $T_1$ is attenuated in the HT exposure scenario. Moreover, for all respiratory outcomes except for PEF, high TRAP exposure decreases the variability/difference between the Rest and PA condition. There were no consistent differences regarding respiratory outcomes during the second time point ($T_2$). These findings are consistent with scenario-specific mixed effect analyses (see Tables 3 & 4).

*3.2.1.2. Mixed effect analysis*

*3.2.1.2.1. Categorical covariates for PA and TRAP.* At the immediate post-exposure time-point ($T_1$), compared to baseline ($T_0$), PA significantly increased $FEV_1$ (48.5 mL, $p = 0.02$), $FEV_1$/FVC (0.64%, $p = 0.01$) and $FEF_{25–75\%}$ (97.8 mL, $p = 0.02$) (Table 3). Moreover, the test of effect modification by PA and TRAP has shown a statistically significant positive interaction in the analysis of PEF ($p = 0.05$). Furthermore, even for outcomes where no multiplicative interaction was observed the combined effect was higher than just an additive effect. On the other hand, higher levels of $NO_2$ pre-exposure reduced the positive effect of PA on $FEV_1$/FVC ($p = 0.05$). At the second post-exposure time-point ($T_2$), no significant associations were observed between exposure and respiratory outcomes. In contrast, in the pooled analysis of $T_1$ and $T_2$ measurements, PA shows an independent and statistically significant positive effect upon $FEV_1$/FVC ($p = 0.02$) and $FEF_{25–75\%}$ ($p = 0.05$).

**Table 2**
Site characteristics (low vs high traffic site).

| Pollutant | Study site | Mean | (95% CI) | *p*-Value |
|---|---|---|---|---|
| $NO_X$ (ppb) | Low traffic | 102 | (61–143) | |
| | High traffic | 685 | (555–815) | |
| | Contrast | 583 | | <0.001 |
| NO (ppb) | Low traffic | 77 | (41–113) | |
| | High traffic | 593 | (472–714) | |
| | Contrast | 515 | | <0.001 |
| Black Carbon (μg/m$^3$) | Low traffic | 6.9 | (3–11) | |
| | High traffic | 28.9 | (24–33) | |
| | Contrast | 22.0 | | <0.001 |
| UFP (particles/cm$^3$) | Low traffic | 45,992 | (32,608–59,376) | |
| | High traffic | 164,708 | (147,317–182,099) | |
| | Contrast | 118,717 | | <0.001 |
| $PM_{2.5}$ (μg/m$^3$) | Low traffic | 39 | (30–48) | |
| | High traffic | 82 | (72–92) | |
| | Contrast | 43 | | <0.001 |
| $PM_{10}$ (μg/m$^3$) | Low traffic | 65 | (37–92) | |
| | High traffic | 123 | (99–146) | |
| | Contrast | 58 | | 0.005 |
| $PM_{coarse}$ (μg/m$^3$) | Low traffic | 27 | (9–45) | |
| | High traffic | 41 | (27–55) | |
| | Contrast | 14 | | 0.25 |
| Temperature (°C) | Low traffic | 12 | (10–14) | |
| | High traffic | 11 | (10–13) | |
| | Contrast | −0.6 | | 0.65 |
| Relative humidity (%) | Low traffic | 56 | (48–65) | |
| | High traffic | 57 | (50–63) | |

Means are based on the 2 h measurements during the morning rush hour (8:00–10:00). Particulate matter particles are categorized based on their aerodynamic diameter as $PM_{10}$ (<10 μm), $PM_{coarse}$ (2.5 μm–10 μm), $PM_{2.5}$ (<2.5 μm) and UFP (<0.1 μm). PM, particulate matter; TRAP, traffic-related air pollution; UFP, ultrafine particles; NO, nitrogen monoxide; NOX, nitrogen oxides.

*3.2.1.2.2. Continuous covariates for PA and TRAP.* When using single pollutant models, it is shown that an increase in the continuous measurement of the concentration of $PM_{coarse}$ during the exposure time was statistically significantly associated with a reduction in $FEV_1$ ($-1.31$ mL $*$ m$^3$/μg, $p = 0.02$) and FVC ($-1.71$ mL $*$ m$^3$/μg, $p = 0.02$) in the immediate post-exposure assessment. These associations remained significant in our pooled analysis (Table 4, A). Results of our interaction model IA1 indicate that PA alleviates the negative effects that PM has upon lung function (Table 4, B). More specifically, with PEF as a dependent variable, we found a positive interaction between PA and particulate constituents of TRAP when restricting our analysis to measurements of $T_1$. An increase in PA statistically significantly reduces the negative impact $PM_{2.5}$ ($p = 0.05$), $PM_{10}$ ($p = 0.02$) and $PM_{coarse}$ ($p = 0.02$) have on PEF. Moreover, in our seven hour post-exposure assessment ($T_2$) the interaction analysis indicates that PA modifies the effect of $PM_{coarse}$ on FVC. Interestingly, in our stability analysis this interaction turned statistically significant. For example, after excluding seven measurements from our analysis that were an outlier for at least two respiratory outcomes, we found that an increase in PA by one unit (1%HRmax) alleviates the delayed negative effects of $PM_{coarse}$ on FVC by 0.11 mL ($p = 0.02$) (see Supplementary material, Part 9, Table S14).

Furthermore, assessing interactions between single pollutant concentrations and participants TRAP pre-exposure, we found that an increase in TRAP pre-exposure statistically significantly reduces the negative impact certain TRAP constituents have upon $FEV_1$/FVC and PEF, respectively (Table 4, C). Moreover, pre-exposure seems to modify the respiratory effects of PA during the exposure period. Despite not being statistically significant, results of our IA2 model indicate that an increase in participants pre-exposure reduces the beneficial effects of PA during the exposure period (Table 4, D). In addition, an increase in $NO_X$ leads to a dilation of upper airways (bronchodilation) 7 h after exposure (Table 4, E).

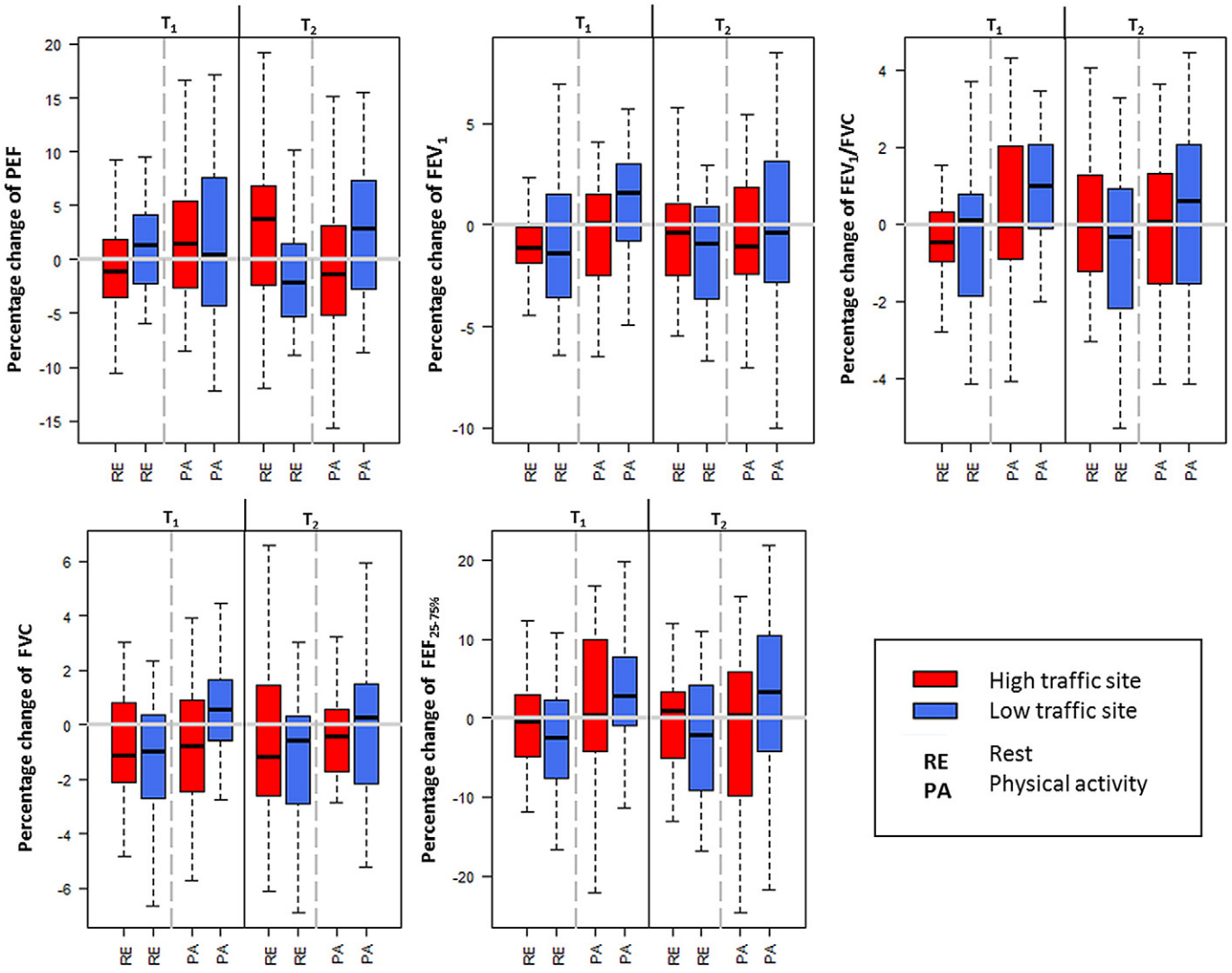


**Fig. 1.** Percentage changes from baseline values of respiratory function, grouped according to exposure scenarios and post-exposure time points ($T_1$ and $T_2$). Horizontal lines in each box show median values and boxes span the 25th (Q1) and 75th (Q3) percentiles. The upper whisker extends further until the smaller of the both values max(x) and Q3 + 1.5 × IQR. The lower whisker accordingly extends further until the greater of the both values min(x), Q1 − 1.5 × IQR. Values lying outside of this range are not shown in the plots. IQR, Interquantile range.

## 4. Discussion

We have shown that healthy individuals experience a short-term significant increase in the function of the upper respiratory airway for several hours after performing PA even in highly-polluted environments. However, high TRAP (compared to low TRAP) exposure attenuated immediate respiratory benefits of PA. More specifically, individuals experienced a short-term fall in the function of the high and low respiratory airways, independent of the PA level, after acute exposure to high $PM_{coarse}$ concentrations. However, we found an interaction between PA and particulate constituents of TRAP, suggesting that PA alleviates negative effects that $PM_{2.5}$, $PM_{10}$ and $PM_{coarse}$ have on respiratory airways. Moreover, participants' pre-exposure to TRAP appears to modify studied respiratory responses to PA and TRAP significantly. We found evidence that pre-exposure weakens the inverse association between TRAP exposure and $FEV_1$/FVC and the positive association between PA and $FEV_1$/FVC and PEF, respectively.

### 4.1. Site characteristics

Pollutant levels in general were approximately the same as in a previous study of the same city, however this previous study saw a higher contrast in pollutant concentrations between study sites due to a different LT site used (being a market square bordered by roads and buildings instead of an open seaside park) (Kubesch et al., 2015). UFP concentrations were within the typical range observed in urban environments and showed the expected spatial variation between exposure sites (Cole-Hunter et al., 2015b; Knibbs et al., 2011; Kumar et al., 2014). However, the average UFP counts observed at the HT site were considerably higher than those found in previous real-world exposure studies of other cities, in the UK (McCreanor et al., 2007), the Netherlands (Strak et al., 2010) and Belgium (Bos et al., 2013). Furthermore, air pollution levels at our HT site were rather comparable with those categorized in other experimental studies as “high air pollution” or “traffic site” (Jarjour et al., 2013; Weichenthal et al., 2011) while mean particle concentrations at our HT site were comparable with exposures measured in chamber studies (Gong et al., 2008; Samet et al., 2009).

### 4.2. Respiratory health

Baseline health characteristics of our study participants are comparable to measures reported in other studies of healthy adults, including that previously done in the same city (Kubesch et al., 2015; Strak et al., 2010; Weichenthal et al., 2011).

**Table 3**
Associations between respiratory outcomes, PA-status, exposure site and pre-exposure.

| RM | Model | Estimate | Time point 1 ($T_1$) | | | Time Point 2 ($T_2$) | | | Pooled $T_1$ and $T_2$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Coeff. | 95% CI | p | Coeff. | 95% CI | p | Coeff. | 95% CI | p |
| PEF (L/min) | | PA | 8.1 | (−4.0, 20.2) | 0.19 | 1.8 | (−7.3, 10.9) | 0.70 | 3.7 | (−4.4, 11.9) | 0.36 |
| | CA1 | High TRAP site | −2.5 | (−14.6, 9.6) | 0.68 | 6.6 | (−2.5, 15.7) | 0.15 | 3.8 | (−4.4, 12.0) | 0.36 |
| | | Rest & LT | 14.4 | (−2.4, 31.3) | **0.09** | −13.7 | (−26.5, −0.9) | **0.04** | −5.18 | (−16.8, 6.5) | 0.38 |
| | | PA & HT | 19.9 | (3.1, 36.7) | **0.02** | −5.2 | (−17.9, 7.5) | 0.42 | 2.4 | (−9.2, 14.0) | 0.68 |
| | CA2 | PA & LT | 10.8 | (−5.9, 27.5) | 0.20 | −4.9 | (−17.6, 7.7) | 0.44 | −0.2 | (−11.7, 11.3) | 0.97 |
| | IA1 | PA*Exp. | 23.5 | (−0.2, 47.2) | **0.05** | −13.9 | (−31.9, 4.0) | 0.13 | −2.6 | (−19.0, 13.7) | 0.75 |
| | IA2 | PA*Pre–exp. | 0.04 | (−0.37, 0.44) | 0.85 | 0.2 | (−0.12, 0.48) | 0.24 | 0.1 | (−0.13, 0.41) | 0.31 |
| | IA3 | Exp.*Pre–exp. | 0.09 | (−0.30, 0.47) | 0.66 | −0.1 | (−0.36, 0.21) | 0.61 | −0.03 | (−0.29, 0.23) | 0.84 |
| $FEV_1$ (mL) | | PA | 48.5 | (8.7, 88.3) | **0.02** | 6.3 | (−36.6, 49.2) | 0.77 | 30.4 | (−5.0, 65.8) | **0.09** |
| | CA1 | High TRAP site | −17.8 | (−57.6, 22.0) | 0.38 | 25.8 | (−17.1, 68.7) | 0.24 | 0.9 | (−34.5, 36.3) | 0.96 |
| | | Rest & LT | 20.3 | (−36.6, 77.1) | 0.48 | −25.3 | (−86.6, 36.0) | 0.41 | 0.70 | (−49.9, 51.3) | 0.98 |
| | | PA & HT | 51.0 | (−5.7, 107.6) | **0.08** | 6.7 | (−54.4, 67.8) | 0.83 | 32.0 | (−18.4, 82.4) | 0.21 |
| | CA2 | PA & LT | 66.4 | (10.2, 122.6) | **0.02** | −19.5 | (−80.1, 41.1) | 0.52 | 29.5 | (−20.5, 79.5) | 0.24 |
| | IA1 | PA*Exp. | 4.84 | (−75.0, 84.6) | 0.90 | 0.8 | (−85.2, 86.9) | 0.98 | 3.2 | (−67.8, 74.2) | 0.93 |
| | IA2 | PA*Pre–exp. | −0.66 | (−1.98, 0.67) | 0.33 | 0.5 | (−0.90, 1.97) | 0.46 | −0.2 | (−1.34, 1.03) | 0.79 |
| | IA3 | Exp.*Pre–exp. | 0.08 | (−1.19, 1.35) | 0.90 | −0.2 | (−1.57, 1.16) | 0.76 | −0.04 | (−1.17, 1.09) | 0.94 |
| FEV1/FVC (%) | | PA | 0.64 | (0.20, 1.08) | 0.01 | 0.15 | (−0.35, 0.65) | 0.15 | 0.44 | (0.07, 0.81) | **0.02** |
| | CA1 | High TRAP site | −0.24 | (−0.68, 0.20) | 0.28 | −0.05 | (−0.55, 0.45) | 0.15 | −0.16 | (−0.53, 0.21) | 0.39 |
| | | Rest & LT | 0.29 | (−0.33, 0.92) | 0.36 | 0.04 | (−0.67, 0.76) | 0.91 | 0.19 | (−0.34, 0.71) | 0.49 |
| | | PA & HT | 0.69 | (0.07, 1.31) | **0.03** | 0.14 | (−0.57, 0.86) | 0.69 | 0.46 | (−0.06, 0.99) | **0.08** |
| | CA2 | PA & LT | 0.88 | (0.26, 1.50) | **0.01** | 0.20 | (−0.51, 0.91) | 0.58 | 0.60 | (0.07, 1.12) | **0.03** |
| | IA1 | PA*Exp. | 0.10 | (−0.78, 0.98) | 0.82 | −0.01 | (−1.02, 0.99) | 0.98 | 0.05 | (−0.7, 0.8) | 0.89 |
| | IA2 | PA*Pre–exp. | −0.01 | (−0.03, 0.00) | **0.05** | −0.005 | (−0.02, 0.01) | 0.56 | −0.01 | (−0.02, 0.00) | **0.10** |
| | IA3 | Exp.*Pre–exp. | 0.01 | (0.00, 0.02) | 0.11 | 0.01 | (−0.01, 0.02) | 0.43 | 0.01 | (0.00, 0.02) | 0.12 |
| FVC (mL) | | PA | 30.2 | (−14.9, 75.2) | 0.19 | 2.0 | (−40.4, 44.4) | 0.92 | 14.5 | (−22.6, 51.7) | 0.44 |
| | CA1 | High TRAP site | −2.8 | (−47.9, 42.3) | 0.90 | 30.8 | (−11.6, 73.2) | 0.15 | 15.9 | (−21.3, 53.0) | 0.40 |
| | | Rest & LT | −1.8 | (−66.2, 62.6) | 0.96 | −37.8 | (−98.4, 22.8) | 0.22 | −21.8 | (−74.8, 31.3) | 0.42 |
| | | PA & HT | 25.6 | (−38.6, 89.7) | 0.43 | −4.9 | (−65.3, 55.4) | 0.87 | 8.6 | (−44.2, 61.5) | 0.75 |
| | CA2 | PA & LT | 32.9 | (−30.8, 96.6) | 0.31 | −28.9 | (−88.8, 31.0) | 0.34 | −1.5 | (−53.9, 51.0) | 0.96 |
| | IA1 | PA*Exp. | −9.1 | (−99.5, 81.3) | 0.84 | −13.9 | (−98.9, 71.2) | 0.75 | −11.6 | (−86.1, 62.8) | 0.76 |
| | IA2 | PA*Pre–exp. | −0.2 | (−1.67, 1.35) | 0.84 | 1.0 | (−0.45, 2.36) | 0.18 | 0.5 | (−0.77, 1.71) | 0.45 |
| | IA3 | Exp.*Pre–exp. | −0.5 | (−1.96, 0.91) | 0.47 | −0.7 | (−2.00, 0.69) | 0.33 | −0.60 | (−1.78, 0.58) | 0.32 |
| $FEF_{25–75\%}$ (mL/s) | | PA | 97.8 | (14.0, 181.7) | **0.02** | 31.67 | (−77.9, 141.2) | 0.57 | 77.9 | (0.3, 155.5) | **0.05** |
| | CA1 | High TRAP site | −15.7 | (−99.6, 68.2) | 0.71 | 4.01 | (−105.6, 113.6) | 0.94 | −9.78 | (−87.4, 67.8) | 0.80 |
| | | Rest & LT | 24.9 | (−94.9, 144.7) | 0.68 | 7.1 | (−149.4, 163.6) | 0.93 | 19.22 | (−91.6, 130.1) | 0.73 |
| | | PA & HT | 107.0 | (−12.4, 226.3) | **0.08** | 42.7 | (−113.2, 198.6) | 0.59 | 87.3 | (−23.1, 197.7) | 0.12 |
| | CA2 | PA & LT | 113.6 | (−4.9, 232.1) | **0.06** | 27.8 | (−126.9, 182.6) | 0.72 | 87.9 | (−21.8, 197.5) | 0.11 |
| | IA1 | PA*Exp. | 18.2 | (−149.9, 186.4) | 0.83 | 21.9 | (−197.7, 241.6) | 0.84 | 18.7 | (−136.9, 174.2) | 0.81 |
| | IA2 | PA*Pre–exp. | −1.05 | (−3.85, 1.75) | 0.46 | 0.47 | (−3.19, 4.14) | 0.80 | −0.59 | (−3.18, 2.01) | 0.65 |
| | IA3 | Exp.*Pre–exp. | 1.98 | (−0.65, 4.62) | 0.14 | 1.26 | (−2.22, 4.74) | 0.47 | 1.76 | (−0.68, 4.21) | 0.15 |

**Description of models:** CA1: Adjusting for PA– and Exposure–status. CA2: Using categorical variable for scenario with "Rest & HT" as a reference. IA1–IA3: Interaction models assessing interactions between PA–status, Exposure–status and $NO_2$ pre–exposure. **Abbreviations:** Exp., Exposure status; $FEF_{25–75\%}$, Mean forced expiratory flow between 25% and 75% of FVC; FEV1, Forced expiratory volume in 1 s; FVC, Forced vital capacity; HT, High traffic site; LT, Low traffic site; p, p–value; PA, Physical activity (status); PEF, Peak expiratory flow; Pre–exp., Participants address–modeled $NO_2$ pre–exposure one day prior to study days; RM, Respiratory measure; 95% CI, Approximated 95% confidence interval for mixed–effects models. **Comments:** Rows of statistically significant estimates are highlighted in grey. P–Values ≤ 0.1 are in bold.

Previously, Kubesch and associates found that PA, compared to rest, increased $FEV_1$ by 34 mL, FVC by 29 mL and $FEF_{25–75\%}$ by 91 mL irrespective of the TRAP exposure status (Kubesch et al., 2015), whereas we found in a corresponding analysis statistically significant increases of $FEV_1$ (34 mL), $FEF_{25–75\%}$ (82 mL) and the ratio $FEV_1$/FVC (0.64%). In contrast to the study conducted by Kubesch and associates, we found substantial evidence for an interaction between the respiratory effects of PM and PA. We found that PA attenuates the negative effects PM has on upper and lower respiratory airways. Exposure to PM is affected by increased pulmonary ventilation during PA, in turn affecting PM impaction deposition (Finlay, 2001; Heyder, 2004; Matt, 2012; Tena and Clará, 2012). Therefore, we suggest that the increased airway flow during PA leads to an increased proportion of particles from the $PM_{2.5}$, $PM_{10}$ and $PM_{coarse}$ fraction already being deposited by means of impaction in

**Table 4**
Associations and interactions between respiratory outcomes, physical activity, pollutants and pre-exposure assessed using mixed effects models with continuous covariates.

| | | Time point 1 ($T_1$) | | | | | | | | | | Time Point 2 ($T_2$) | | | | | | | | | | Pooled $T_1$ and $T_2$ | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | CO1 | | | IA1 | | IA2 | | IA3 | | | CO1 | | | IA1 | | IA2 | | IA3 | | | CO1 | | | IA1 | | IA2 | | IA3 | | |
| | Estimate SP | Coeff. | 95% CI | p | Coeff. | p | Coeff. | p | Coeff. | p | | Coeff. | 95% CI | p | Coeff. | p | Coeff | p | Coeff. | p | | Coeff. | 95% CI | p | Coeff. | p | Coeff. | p | Coeff. | p | |
| PEF (l/min) | NOx (ppm) | −4.95 | (−23.1, 13.2) | 0.59 | 1.27 | 0.16 | 0.002 | 0.90 | 0.43 | 0.30 | | 13.59 | (0.1, 27.1) | **0.05** | E | −0.98 | 0.15 | 0.004 | 0.67 | −0.17 | 0.57 | 7.93 | (−4.3, 20.1) | 0.20 | −0.33 | 0.60 | 0.003 | 0.67 | 0.002 | 0.99 | |
| | NO (ppm) | −5.32 | (−25.7, 15.1) | 0.61 | 1.46 | 0.17 | 0.001 | 0.92 | 0.47 | 0.34 | | 14.31 | (−0.9, 29.6) | **0.07** | | −1.39 | **0.08** | 0.004 | 0.61 | −0.28 | 0.46 | 8.28 | (−5.5, 22.0) | 0.23 | −0.56 | 0.43 | 0.004 | 0.63 | −0.06 | 0.87 | |
| | BC ($10^4$µg/m$^3$) | −0.57 | (−5.4, 4.2) | 0.82 | 0.41 | 0.11 | 0.001 | 0.93 | 0.15 | 0.18 | | 3.26 | (−0.3, 6.8) | **0.07** | | −0.28 | 0.15 | 0.005 | 0.61 | −0.13 | 0.13 | 2.1 | (−1.1, 5.3) | 0.20 | −0.08 | 0.66 | 0.004 | 0.63 | −0.04 | 0.57 | |
| | UFP ($10^5$*cm$^{-3}$) | −0.19 | (−1.12, 0.75) | 0.69 | 0.07 | 0.17 | 0.001 | 0.92 | 0.02 | 0.37 | | 0.59 | (−0.11, 1.29) | **0.10** | | −0.06 | 0.11 | 0.005 | 0.60 | −0.01 | 0.38 | 0.35 | (−0.28, 0.98) | 0.27 | −0.02 | 0.50 | 0.004 | 0.62 | −0.004 | 0.78 | |
| | $PM_{2.5}$ (µg/m$^3$) | −0.06 | (−0.32, 0.21) | 0.68 | 0.02 | **0.05** | 0.001 | 0.91 | 0.008 | **0.08** | B | 0.15 | (−0.05, 0.35) | 0.13 | | −0.01 | 0.45 | 0.004 | 0.64 | −0.01 | 0.16 | 0.09 | (−0.08, 0.27) | 0.30 | 0.003 | 0.74 | 0.004 | 0.65 | −0.001 | 0.80 | |
| | $PM_{10}$ (µg/m$^3$) | −0.05 | (−0.21, 0.11) | 0.57 | 0.02 | **0.02** | 0.002 | 0.88 | 0.008 | **0.01** | C | 0.05 | (−0.08, 0.17) | 0.46 | | −0.001 | 0.82 | 0.005 | 0.61 | −0.003 | 0.11 | 0.02 | (−0.09, 0.13) | 0.69 | 0.004 | 0.35 | 0.004 | 0.62 | 0.000 | 0.90 | |
| | $PM_{coarse}$ (µg/m$^3$) | −0.089 | (−0.43, 0.25) | 0.61 | 0.03 | **0.02** | 0.002 | 0.87 | 0.014 | **0.004** | | −0.05 | (−0.32, 0.21) | 0.69 | | 0.01 | 0.57 | 0.01 | 0.50 | −0.004 | 0.25 | −0.05 | (−0.29, 0.18) | 0.66 | 0.01 | 0.14 | 0.005 | 0.54 | 0.002 | 0.56 | |
| $FEV_1$ (mL) | NOx (ppm) | −34.47 | (−93.3, 24.3) | 0.25 | −0.95 | 0.75 | −0.04 | 0.29 | 0.31 | 0.82 | | 34.6 | (−30.0, 99.1) | 0.29 | | 0.41 | 0.90 | 0.01 | 0.76 | 0.07 | 0.96 | −6.2 | (−58.9, 46.6) | 0.82 | −0.40 | 0.88 | −0.02 | 0.57 | 0.22 | 0.85 | |
| | NO (ppm) | −31.64 | (−98.0, 34.7) | 0.35 | −0.44 | 0.90 | −0.04 | 0.26 | 0.46 | 0.78 | | 37.8 | (−34.9, 110.4) | 0.30 | | 0.17 | 0.96 | 0.01 | 0.72 | −0.30 | 0.87 | −2.9 | (−62.2, 56.4) | 0.92 | −0.18 | 0.95 | −0.02 | 0.57 | 0.16 | 0.91 | |
| | BC ($10^4$µg/m$^3$) | −5.96 | (−21.6, 9.6) | 0.45 | −0.47 | 0.58 | −0.04 | 0.26 | 0.28 | 0.44 | | 9.82 | (−7.2, 26.8) | 0.25 | | −0.08 | 0.93 | 0.01 | 0.73 | −0.26 | 0.52 | 0.6 | (−13.3, 14.6) | 0.93 | −0.32 | 0.67 | −0.02 | 0.56 | 0.06 | 0.86 | |
| | UFP ($10^5$*cm$^{-3}$) | −1.28 | (−4.32, 1.75) | 0.40 | −0.02 | 0.91 | −0.04 | 0.26 | 0.01 | 0.94 | | 1.91 | (−1.40, 5.23) | 0.25 | | −0.05 | 0.75 | 0.01 | 0.73 | −0.05 | 0.51 | 0.04 | (−2.67, 2.75) | 0.97 | −0.03 | 0.81 | −0.02 | 0.56 | −0.02 | 0.78 | |
| | $PM_{2.5}$ (µg/m$^3$) | −0.55 | (−1.41, 0.31) | 0.21 | −0.03 | 0.41 | −0.04 | 0.29 | −0.001 | 0.95 | | 0.43 | (−0.52, 1.38) | 0.37 | | −0.005 | 0.91 | 0.01 | 0.75 | −0.01 | 0.55 | −0.15 | (−0.92, 0.62) | 0.70 | −0.02 | 0.54 | −0.02 | 0.58 | −0.01 | 0.72 | |
| | $PM_{10}$ (µg/m$^3$) | −0.50 | (−1.02, 0.01) | **0.06** | −0.01 | 0.63 | −0.04 | 0.35 | 0.004 | 0.69 | | 0.005 | (−0.57, 0.58) | 0.99 | | 0.01 | 0.80 | 0.02 | 0.68 | −0.01 | 0.37 | −0.30 | (−0.77, 0.16) | 0.20 | −0.005 | 0.82 | −0.02 | 0.66 | −0.002 | 0.84 | |
| | $PM_{coarse}$ (µg/m$^3$) | −1.31 | (−2.40, −0.21) | **0.02** | A | 0.002 | 0.96 | −0.03 | 0.40 | 0.02 | 0.29 | −0.71 | (−1.93, 0.52) | 0.26 | | 0.04 | 0.42 | 0.03 | 0.55 | −0.01 | 0.52 | −1.06 | (−2.04, −0.08) | **0.03** | A | 0.02 | 0.69 | −0.01 | 0.77 | 0.01 | 0.72 | |
| $FEV_1$/FVC (%) | NOx (ppm) | −0.36 | (−1.02, 0.30) | 0.28 | 0.01 | 0.76 | −0.001 | **0.09** | D | 0.03 | **0.06** | | 0.003 | (−0.75, 0.76) | 0.99 | | −0.02 | 0.55 | 0.000 | 0.42 | 0.01 | 0.49 | −0.212 | (−0.77, 0.35) | 0.45 | −0.003 | 0.92 | −0.001 | **0.10** | D | 0.02 | **0.09** |
| | NO (ppm) | −0.53 | (−1.27, 0.21) | 0.16 | 0.02 | 0.54 | −0.001 | **0.08** | 0.03 | **0.07** | | 0.002 | (−0.84, 0.85) | 1.00 | | −0.03 | 0.52 | 0.000 | 0.42 | 0.01 | 0.55 | −0.313 | (−0.94, 0.31) | 0.32 | 0.003 | 0.93 | −0.001 | **0.10** | | 0.02 | 0.11 | |
| | BC ($10^4$µg/m$^3$) | −0.08 | (−0.25, 0.10) | 0.38 | 0.005 | 0.60 | −0.001 | **0.08** | 0.012 | **0.004** | C | 0.020 | (−0.18, 0.22) | 0.84 | | −0.01 | 0.41 | 0.000 | 0.42 | 0.001 | 0.75 | −0.036 | (−0.18, 0.11) | 0.63 | −0.001 | 0.93 | −0.001 | **0.10** | | 0.01 | **0.03** | C |
| | UFP ($10^5$*cm$^{-3}$) | −0.02 | (−0.06, 0.01) | 0.19 | 0.001 | 0.61 | −0.001 | **0.08** | 0.002 | **0.04** | | −0.001 | (−0.04, 0.04) | 0.96 | | −0.002 | 0.31 | 0.000 | 0.42 | 0.000 | 0.63 | −0.014 | (−0.04, 0.01) | 0.34 | 0.000 | 0.84 | −0.001 | **0.10** | | 0.001 | **0.09** | |
| | $PM_{2.5}$ (µg/m$^3$) | −0.003 | (−0.01, 0.01) | 0.59 | 0.000 | 0.90 | −0.001 | **0.08** | 0.0004 | **0.03** | | 0.001 | (−0.01, 0.01) | 0.89 | | −0.001 | 0.31 | 0.000 | 0.41 | 0.000 | 0.48 | −0.001 | (−0.01, 0.01) | 0.82 | 0.000 | 0.65 | −0.001 | **0.10** | | 0.0003 | **0.05** | |
| | $PM_{10}$ (µg/m$^3$) | 0.000 | (−0.01, 0.01) | 0.92 | 0.000 | 0.97 | −0.001 | **0.07** | 0.0002 | **0.02** | | 0.000 | (−0.01, 0.01) | 0.99 | | 0.000 | 0.26 | 0.000 | 0.42 | 0.000 | 0.66 | 0.000 | (0.00, 0.01) | 0.98 | 0.000 | 0.52 | −0.001 | **0.09** | | 0.0002 | **0.06** | |
| | $PM_{coarse}$ (µg/m$^3$) | 0.004 | (−0.01, 0.02) | 0.53 | 0.000 | 0.71 | −0.001 | **0.05** | 0.00 | 0.11 | | −0.001 | (−0.02, 0.01) | 0.85 | | −0.001 | 0.30 | 0.000 | 0.43 | 0.000 | 0.88 | 0.002 | (−0.01, 0.01) | 0.66 | 0.000 | 0.41 | −0.001 | **0.07** | | 0.0002 | 0.25 | |
| FVC (mL) | NOx (ppm) | −16.07 | (−83.3, 51.1) | 0.64 | −1.73 | 0.61 | −0.01 | 0.76 | −0.96 | 0.53 | | 33.9 | (−30.2, 98.1) | 0.30 | | 0.163 | 0.96 | 0.04 | 0.30 | −0.74 | 0.61 | 11.0 | (−44.8, 66.8) | 0.70 | −0.73 | 0.79 | 0.02 | 0.64 | −0.82 | 0.52 | |
| | NO (ppm) | −4.84 | (−80.5, 70.9) | 0.90 | −1.92 | 0.63 | −0.01 | 0.73 | −1.08 | 0.56 | | 38.5 | (−33.7, 110.6) | 0.29 | | −0.24 | 0.95 | 0.04 | 0.28 | −1.35 | 0.45 | 18.7 | (−44.0, 81.3) | 0.56 | −1.02 | 0.75 | 0.02 | 0.63 | −1.21 | 0.43 | |
| | BC ($10^4$µg/m$^3$) | −2.05 | (−19.8, 15.7) | 0.82 | −0.83 | 0.39 | −0.01 | 0.73 | −0.22 | 0.61 | | 8.39 | (−8.6, 25.3) | 0.33 | | −0.05 | 0.96 | 0.04 | 0.28 | −0.46 | 0.25 | 3.6 | (−11.1, 18.3) | 0.63 | −0.43 | 0.59 | 0.02 | 0.63 | −0.35 | 0.31 | |
| | UFP ($10^5$*cm$^{-3}$) | −0.08 | (−3.54, 3.37) | 0.96 | −0.09 | 0.63 | −0.02 | 0.73 | −0.07 | 0.39 | | 2.02 | (−1.27, 5.31) | 0.22 | | −0.05 | 0.78 | 0.04 | 0.29 | −0.10 | 0.19 | 1.06 | (−1.80, 3.92) | 0.46 | −0.07 | 0.65 | 0.02 | 0.63 | −0.08 | 0.20 | |
| | $PM_{2.5}$ (µg/m$^3$) | −0.42 | (−1.40, 0.56) | 0.39 | −0.04 | 0.41 | −0.01 | 0.79 | −0.02 | 0.24 | | 0.38 | (−0.56, 1.32) | 0.43 | | 0.004 | 0.93 | 0.04 | 0.29 | −0.02 | 0.20 | 0.01 | (−0.81, 0.82) | 0.99 | −0.02 | 0.67 | 0.02 | 0.62 | −0.02 | 0.14 | |
| | $PM_{10}$ (µg/m$^3$) | −0.54 | (−1.13, 0.05) | **0.07** | 0.00 | 0.92 | −0.005 | 0.91 | −0.01 | 0.50 | | −0.04 | (−0.62, 0.53) | 0.89 | | 0.019 | 0.43 | 0.05 | 0.25 | −0.02 | 0.13 | −0.28 | (−0.78, 0.21) | 0.26 | 0.01 | 0.70 | 0.02 | 0.53 | −0.01 | 0.18 | |
| | $PM_{coarse}$ (µg/m$^3$) | −1.71 | (−2.94, −0.49) | **0.01** | A | 0.04 | 0.37 | 0.003 | 0.95 | 0.007 | 0.69 | | −0.83 | (−2.05, 0.39) | 0.18 | | 0.079 | **0.10** | B | 0.06 | 0.17 | −0.02 | 0.33 | −1.27 | (−2.29, −0.24) | **0.02** | A | 0.06 | 0.14 | 0.03 | 0.39 | −0.01 | 0.68 | |

**Description of models:** model CO1 with continuous variables for PA and exposure. Interaction models IA1–IA3 were designed to examine interactions between PA and single pollutants (IA1), PA and $NO_2$ pre–exposure (IA2) and single pollutants and $NO_2$–pre–exposure (IA3), respectively.
**Abbreviations:** BC, black coarse; $FEF_{25-75\%}$, Mean forced expiratory flow between 25% and 75% of FVC; $FEV_1$, Forced expiratory volume in 1 s; FVC, Forced vital capacity; IA, Interaction; PEF, peak expiratory flow; PM, particulate matter; UFP ultrafine particles; 95% CI, approximated 95% confidence interval for mixed–effects models. **Comments:** major findings are pointed out with A–E. Rows of statistically significant estimates are highlighted in grey. P–Values ≤ 0.1 are in bold. More detailed model outcomes and results of stability testings can be found in the Supplementary material part 8–12.

the nasopharyngeal region and therefore not being able to interfere with the effects PA has in the upper and lower airways. In contrast, the breathing pattern during rest may allow more particles of such fractions to reach upper and lower regions, thereby having the potential to counteract positive respiratory effects in these regions.

As suggested by a study conducted by Giles and associates which found that pre-exposure of study participants with diesel exhaust statistically significantly attenuates the respiratory effects of PA on lung function (Giles et al., 2012), we included a covariate for residential pre-exposure in our models to account for potential confounding. We choose participants' ambient exposure to $NO_2$ at the home address on the day before the experiment took place because it showed a high correlation with other residential pre-exposure estimates and was weakly correlated with TRAP constituents on study days (see Supplementary material, Part 4). Furthermore, we assumed that the pre-exposure during the night before study days is more relevant than the one during the day (Brasche and Bischof, 2005; Klepeis et al., 2001). Assuming that people were indoors at home during the night, we also expected gaseous constituents of air pollution to be more relevant than its particulate constituents (Koutrakis et al., 1991). We found various residential pre-exposure estimates to be significant in some of our single pollutant models. For example, we found that every single unit (ppm) increase of $NO_2$ pre-exposure was statistically significantly associated with a 1.51 mL increase of FVC (see Supplementary material, Part 9).

Considering the statistically significant association of TRAP pre-exposure estimates with respiratory outcomes together with the finding that TRAP pre-exposure modifies participants' responses to TRAP and PA suggests that the use of spatial pre-exposure estimates to prevent confounding by individual differences in pre-exposure may have been helpful to improve the precision of results. Considered in conjunction, these findings suggest that respiratory responses get saturated at higher cumulative doses of TRAP. We suggest that the limited variability of lung function parameters may lead to a non-linear exposure-response relationship between changes in pollutant concentration and changes in respiratory outcomes. This is supported by the fact that the variability of respiratory responses tended to be lower in the high TRAP environment compared to the low TRAP environment (see Fig. 1) and by another study conducted in Barcelona which found evidence that dose-response relationships between TRAP and physiological parameters are not always linear over the broad range of exposures (Cole-Hunter et al., 2015b).

Similar to a Canadian study (Weichenthal et al., 2011), our study stresses the fact that the timing of post-exposure measurements is important for capturing the adverse respiratory effects of air pollution. Some studies suggest that air pollution may not affect pulmonary function immediately following exposure cessation (Giles et al., 2012; Gong et al., 2008; Strak et al., 2010; Zuurbier et al., 2011). In contrast to these studies, but in-line with other studies our findings draw a consistent picture that an increase in air pollution is negatively associated with respiratory function immediately after exposure (Gong et al., 2008; McCreanor et al., 2007; Rundell et al., 2008). Compared to other studies we had a relatively long exposure period. Due to this the respiratory effects of air pollution may have already been manifested right after the exposure period. Despite named differences, a consistent finding of previous studies and the current study is that air pollution exposure during the performance of PA attenuates the beneficial effects PA has on lung function.

A study examining the effects of air pollution on 12 healthy cyclists showed small increases in lung function immediately after cycling, and after only 6 h the association between air pollution and lung function became negative (Strak et al., 2010). This is in line with our finding that the effects of PA and air pollution seem to manifest rapidly. We found lung function improvements immediately detectable after exposure, with only residuals of beneficial effects lasting until the second post-exposure time point. Furthermore, our findings are consistent with a study conducted in Berkeley, California, with 15 healthy adults. In this study, pulmonary function was compared after cycling on low-traffic and high-traffic routes. Non-significant increases in $FEV_1$ were found post-exercise on both routes and 4 h after cycling on the low-traffic routes, whereas a slight reduction was found 4 h after cycling on the high-traffic routes (Jarjour et al., 2013). Similarly, peak flow rate has been observed to improve (non-significantly) in healthy adults when measured immediately and 3 h after bicycle commuting (Cole-Hunter et al., 2013).

### 4.3. Study design and data analysis

The strength of our study is its unique design and the fact that participants were exposed under real-world conditions with a myriad of TRAP components. It allowed an exposure to a mix of airborne pollutants actually present in urban environments, which has been shown to lead to different health effects than those observed in chamber studies (Huang et al., 2012). However, compared to chamber studies drawbacks of our study design are that exposure conditions are less controllable. Furthermore, in our study only a representative fraction of TRAP components was measured, meaning unmeasured components could be involved in the observed associations.

There are epidemiological studies that have examined the acute health effects of TRAP exposure during PA (Peters et al., 2004; Weichenthal et al., 2011). However, a drawback of these studies is that they are not designed to disentangle the effects of air pollution from those of PA, nor their potential interdependency. The crossover-design we used, in which every individual serves as its own control, minimizes potential effects of confounding and overcomes the limitations stated above. Furthermore, adding respective interaction terms to our single pollutant models allows the examination of synergies among pollutants, that from both, public health and regulatory perspectives is a particular concern (Mauderly and Samet, 2009; Yu et al., 2013).

In general study conditions are less controllable in a real-world setting and confounding from time-varying factors is a distinct possibility. Therefore we adjusted for temperature and humidity in our mixed effects models. Furthermore, we used absolute measures and included the baseline measurement as a nested random effect, thereby explicitly accounting for the fact that participants baseline values varied over the course of the study. In contrast, using percentage change compared to baseline as dependent variable without the baseline in the random term, this information would not be considered explicitly in the analysis. Comparing both approaches (see Supplementary material, Part 10), it seems that models using absolute measures increase the specificity of the analysis and allow to separate the effects of single pollutants despite a high correlation among pollutants, whereas models using relative measures seem to have a higher sensitivity, readily allowing to detect overall modification effects. For example, using relative measures we found a statistically significant negative interaction between TRAP environment and PA-status for respiratory outcomes in at least one of our assessments ($T_1$, $T_2$, pooled data) (see Supplementary material, Part 11, Table S21).

We increased the complexity of our models in a stepwise approach in order not to have a bias in our results due to a misspecification of models. A lot of interactions we tested turned out not to be significant and therefore a basic model specification including interaction terms would not have been justified. However, after adding interaction terms the findings we made using our basic models (Model CA1 & CO1) stayed substantially equivalent.

A limitation of our study is potential confounding by non-residential pre-exposure and performance of PA during the commute to the study sites. However, we tried to minimise the impact of these confounding factors by the design of our study and models. Our models accounted for different levels of PA and non-residential pre-exposure indirectly by having the baseline respiratory measurement (baseline measurements were taken at the beginning of each study day) added as a nested random effect (see Supplementary material, Part 2). This was done to

control for variations in the starting point of an individual over the course of the study. Assuming that PA and non-residential pre-exposures during the commute had an effect on respiratory parameters of participants, our models partially account for different levels of pre-exposure. Despite that, we tried to minimise prior exposure to TRAP and performance of PA by requesting participants to arrive prior to rush hour and via underground rail. Furthermore, volunteers were transported by van (cycle-ventilated, windows closed) to either exposure site, which were of equivalent distance (approximately a one kilometre or five minute drive) from the clinic.

Model outcomes of our pooled models and for the second post-exposure time point may additionally be biased since we did not control for the PA-level and air pollution exposure during the free-living period. However, the air pollution exposure during the free-living period was relatively low compared to the exposure period, making a major impact on model outcomes unlikely. In contrast, the average HR during the free-living period was between the average HR measured during the Rest and PA-Scenario (compare Supplementary material, Part 1 & Tables 1& 2). Therefore we examined the influence of the physical activity level during the free-living period on observed associations, by adding the post-exposure estimate for HR to our models. However, substantial changes in model outcomes were not observed (see Supplementary material, Part 10).

Moreover, we were not able to blind participants completely to the exposure conditions and we cannot exclude that sex differences and different hormonal status within female participants influenced respiratory effects of PA and TRAP (Bellemare et al., 2003; Harms and Rosenkranz, 2008; Sheel et al., 2004). Indeed, a descriptive analysis of our data showed, that respiratory parameters respond considerably different in sexes (see Supplementary material, Part 5). Nevertheless, due to our limited sample size we did not continue with stratification by sex in our mixed effects analysis. In addition, by not restricting our study to one sex, we assure that the implications of our findings are applicable for the average population. However, as a method to reduce unexplained variance in the data, a stratified analysis by sex may be reasonable in future research.

The findings from our basic model using continuous variables, stayed stable after adding interaction terms to the model. In addition, we checked the stability of our results by excluding single participants or cases considered to be potentially influential and observed no substantial changes in estimated coefficients and *p*-values (see Supplementary material, Part 8 & 9). In general, during stability analysis, we rather found further significant covariates and interactions that confirm our findings. However, in order to improve the statistical reliability of results further, a more systematic analysis to detect influential data in mixed effects models based on the approach described by Nieuwenhuis and associates could be performed (Nieuwenhuis et al., 2012). Furthermore, future research gathering more data about synergistic effects among pollutants and the non-linear relationship between pollutant concentration and respiratory responses should help to improve model structures further and refine data analysis. Moreover, novel sensing technologies integrated with mobile phones like the PEM could be used to improve personal exposure and activity pattern estimates in different microenvironments (residential, non-residential, commute) thus reducing potential bias due to confounding of pre-study exposures further (Nieuwenhuijsen et al., 2015).

## 5. Conclusion

Healthy individuals after performing physical activity, even in highly-polluted environments, experience an acute increase in the upper respiratory airway function that remains significant over several hours. Nevertheless, individuals, independently of performing physical activity, suffer an acute fall in the function of the upper and lower respiratory airways after an increase of $PM_{coarse}$ concentrations. However, we found that PA could decrease the immediate and delayed negative impact of high PM concentrations upon respiratory airways, but further research is required. Furthermore, the respiratory effects of PA and TRAP exposure were found contingent on the level of TRAP pre-exposure of study participants.

## Funding

The work reported in this paper was part of the EXPOsOMICS project, which was supported by the 7th Framework Programme for Research and Technological Development of the EU (grant number FP7 GA 308610).

## Acknowledgement

Sincere thanks go to all study participants, the ESCAPE project (European Study of Cohorts for Air Pollution Effects) and Gerard Hoek (IRAS), Rob Beelen (IRAS), and Marta Cirach (CREAL) for their help in providing land-use-regression estimations, Tania Martinez (CREAL) for helpful technical support, Albert Ambros Rodoreda (CREAL) and Jose Barrera (CREAL) for helpful R support, David Rojas (CREAL) and Scott Weichenthal (McGill University, Canada) for reviewing the manuscript, Grisa Mocniek (Aerosol, Slovenia) for the provision of a microaethalometer (Magee Scientific, USA), and the Institute for Risk Assessment Sciences (IRAS) for the provision of a Harvard Impactor (HI).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2016.10.011.

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