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Modeled regional airway deposition of inhaled particles in athletes at exertion

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ABSTRACT

There is a paucity of data regarding mechanisms and effects of inhaled environmental particulate matter on athletic performance. To formulate a framework on which future studies may be developed relating regional airway deposition to subsequent performance in athletes, modeling is indicated.

Multiple-Path Particle Dosimetry (MPPD) computer modeling was utilized to predict the deposition of inhaled particles in 26 male athletes at increasing levels of exertion. Deposition doses of inhaled spherical, monodisperse particles of unit density (1 g/cm^3) measuring 0.05, 0.1, 1.0, 2.5, and 10.0 μm in diameter were calculated. Repeated measures ANOVA testing was used to test for differences in total and regional (naso-oro-pharyngo-laryngeal, tracheobronchial, and pulmonary) airway deposition at exertion.

Increasing exertion revealed statistically significant effects ($p < 0.01$) on deposition of all particle sizes in all airway regions. Overall total airway modeled deposition dose of all particle diameters increased as expected with increasing minute ventilation. Pulmonary deposition dose at exertion tapered off and decreased in the case of larger particles (2.5 and 10.0 μm), indicating that deposited doses in the pulmonary region (deep lung) may be reduced by greater deposition in larger airways at higher levels of exertion, depending on particle aerodynamic diameter.

To assess the impact of inhaled particulate matter on athletic performance, understanding regional deposition and subsequent physiologic impacts are critical steps. Future studies should focus on modeling realistic exposures and performing studies to elucidate mechanisms of injury in both bronchial and pulmonary airways that might impact performance.

1. Introduction

Potential adverse effects of inhaled particulate matter (PM) on cardiopulmonary function and overall performance in athletes are of particular interest in sports medicine. It is generally recognized that athletes competing in or practicing in environments where PM concentrations are high will likely have greater internal exposures due to increased minute ventilation in comparison to people who are not undergoing exertion. A few studies have examined the effects of particulate air pollution on athletic performance (Cakmak, Dales, Leech, & Liu, 2011; Cutrufello, Rundell, Smoglia, & Stylianides, 2011; Cutrufello, Smoliga, & Rundell, 2012; Rundell, 2012; Rundell, Slee, Caviston, & Hollenbach, 2008).

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Recent data suggests athletic performance is compromised by increased volumes of inhalation of dry air, emission-related aerosol particles, and pollutant gases during exercise (Rundell, Hoffman, Caviston, Bulbulian, & Hollenbach, 2007). Inhaled PM is thought to produce oxidative stress leading to airway and vascular injury, in both acute and chronic phases (EPA, 2010). However, additional data is needed with regard to performance, especially in athletes where effects may be inconspicuous.

The literature is predominantly focused on individuals with risk factors for cardiopulmonary disease, as PM is known to induce pulmonary inflammation, decreased lung function (Barraza-Villarreal et al., 2008; Cakmak et al., 2011; Cho et al., 2007; Donaldson & Tran, 2002; Larsson et al., 2007; Pietropaoli et al., 2004; Rundell, 2004; Rundell et al., 2008), pulmonary and systemic vascular dysfunction (Brook et al., 2002; Cutrufello et al., 2011; Frampton, 2007; Nurkiewicz et al., 2006, 2008; Rundell et al., 2007), increased resting blood pressure (Cutrufello et al., 2012; EPA, 2010), increased risk for cancer (Silverman et al., 2012), reduction in heart rate variability (Chang, Tang, Pan, & Chan, 2007; Magari et al., 2001), and ST segment depression (Lanki et al., 2006).

In the case of athletic performance, it is yet to be determined whether pulmonary (deep lung) effects of particulate deposition, and subsequent inflammation and oxidative stress in the acute phase, are of more or less concern than acute irritant and bronchoconstrictive effects of PM associated with inflammation in the more proximal tracheobronchial region. Individual variability in physiologic response to respiratory insult among athletes likely plays an important role with respect to performance. In order to advance a framework on which future studies may be developed, modeling inhaled particle deposition in athletes at exertion was performed. For this purpose, computerized modeling software considered reliable in the field of inhalation toxicology, and an appropriate study population were selected. The main purpose of this initial study was to elucidate how particle size and exertion level affect global and regional airway deposition in a single lung model representative of a male athlete. A second goal was to identify areas of needed future research based on modeled deposition efficiencies and doses in various portions of the respiratory tract.

1.1. Concern for PM exposure in athletes

There are two main concerns related to athletes during training and competing in locations impacted by air pollution: effects on performance, and acute and delayed effects on health. Unfortunately, there is a paucity of data for examining these impacts, especially with regard to performance. While occurrences of acute exposure at rest or exertion may or may not lead to long term sequelae in healthy athletes, high elevated ambient PM concentrations may affect the outcomes of competition (Cutrufello et al., 2012). Performance decrements of 3–5% have been estimated following PM exposure (Cutrufello et al., 2012). While this decrease in performance may initially appear inconsequential, a 3–5% performance loss during elite competition can have a substantial impact on success. Similar arguments may be made with regard to other populations that engage in extreme exertion, such as military personnel, fire fighters, and law enforcement officers.

The United States Environmental Protection Agency (EPA) recognizes the strong influence of particle size on pathologic potential and therefore focuses concern on particles 10 μm or less in aerodynamic diameter because they are small enough to pass through the oral and nasal passages, transiting into the lungs and potentially causing adverse health effects (Environmental Protection Agency, 2013). Unfortunately, the EPA does not routinely include airborne biological materials (plant matter, spores, pollen, etc.) in defining PM, possibly leading to a critical misconception that biological particles are less harmful than regulated non-biological components when it comes to impacting athletic performance.

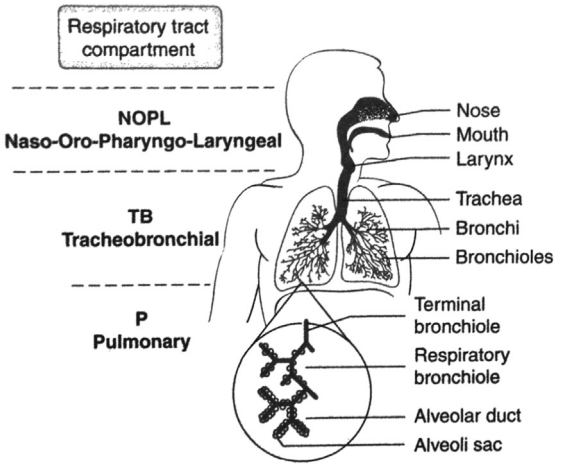

Fig. 1. Compartmental model of the NCRP (1997).
Source: The University of California Air Pollution Health Effects Laboratory, with kind permission.

1.2. Respiratory effects of exertion

Several physiological changes occur during exertion that may alter outcomes during or after exposure to PM. Compared to rest, walking may increase the rate of inhaled air volume by 2–3 times. During maximal exertion, minute volume can increase more than tenfold in humans (Phalen, 2009). Typically nasal breathing at rest shifts to oronasal breathing at exertion, mechanically decreasing upper airway resistance and resulting in a greater number of inhaled particles bypassing the protective action of nasal scrubbing, potentially increasing biologic impacts after subsequent deposition in the tracheobronchial or pulmonary lung regions. There may be several additional physiologic modifications during exercise that impact individual responses to air pollutant exposure, including changes in breathing pattern, widening of the larynx, altered mucous properties, and changes in tissue metabolism that may result in altered local sensitivity.

The notion of increased exertion leading to increased particle deposition is recognized based on increased ventilation during exercise. This, along with the simplified risk-related idea that all large particles are trapped in the nose while all small particles progress to the distal airways can lead to significant risk-related misinterpretations. In order to better understand particle deposition at exertion, regional particle deposition at rest must first be understood.

1.3. Airway regions and deposition mechanisms

The National Council on Radiation Protection and Measurements (NCRP, 1997) considers three airway regions (i.e. compartments for dose calculations) that comprise the total respiratory tract: naso-oro-pharyngo-laryngeal (NOPL), tracheobronchial (TB), and pulmonary (P) (Fig. 1).

In the NOPL region (beginning at the anterior nares and including airways through the larynx), both large and very small particles are efficiently deposited. Large particles possess inertia and are deposited by impaction at obstructions (e.g., hair, nasal turbinates, and airway bends), while smaller particles may deposit on proximal airway walls by the mechanism of Brownian diffusion (NCRP, 1997).

Beginning at the base of the larynx and encompassing the trachea and bronchial airways, the TB region faces particle deposition by mechanisms of inertial impaction, sedimentation, and diffusion. Particle deposition is more intense at airway bifurcations (Hofmann, 2011).

The alveolarized pulmonary region, including respiratory bronchioles, alveolar ducts, and alveolar sacs, is exposed to particles passing through both the NOPL and TB regions, and therefore available for deposition in the deep lung by settling, diffusion, or interception.

Table 1
Individual athlete tidal volumes (V_t) and breathing frequencies (f_b) at each level of treadmill exertion (obtained from Naranjo (2013) personal communication and used with permission).

Subject	V_t (L) Rest	V_t (L) Warm-up	V_t (L) 10.8 km/h	V_t (L) 12.6 km/h	V_t (L) 14.4 km/h	V_t (L) 16.2 km/h	f_b (min^{-1}) Rest	f_b (min^{-1}) Warm-up	f_b (min^{-1}) 10.8 km/h	f_b (min^{-1}) 12.6 km/h	f_b (min^{-1}) 14.4 km/h	f_b (min^{-1}) 16.2 km/h
1	0.57	1.22	1.92	2.1	2.25	2.5	22	37	41	46	53	57
2	0.39	1.57	1.65	1.72	2	2.16	20	27	38	42	43	54
3	0.74	2.09	1.97	2.1	2.09	2.51	17	36	39	40	40	43
4	1.26	1.36	2.25	2.23	2.28	2.37	12	22	30	34	38	42
5	0.87	1.09	2.03	1.88	2.02	2.32	17	38	42	57	58	57
6	0.99	1.97	1.88	2.21	2.42	2.45	18	26	25	27	30	45
7	0.94	1.5	1.72	1.72	1.96	2.52	14	31	33	38	46	48
8	0.84	1.82	1.67	1.83	2.15	2.36	15	28	34	36	40	48
9	ND	1.61	1.7	1.79	2.24	2.22	ND	48	53	55	60	70
10	0.79	2.22	2.25	2.53	2.6	2.93	15	29	29	34	37	43
11	0.59	1.83	1.91	1.9	1.9	2.1	13	27	28	34	36	42
12	0.87	2.35	3.1	2.93	2.59	3.01	13	16	13	18	31	35
13	0.79	1.76	1.8	1.9	2.11	2.44	22	46	46	52	53	57
14	1.26	1.62	1.45	1.43	1.52	1.92	10	36	52	62	78	77
15	0.65	1.88	1.73	1.8	1.88	1.72	21	27	34	36	47	69
16	0.76	1.09	1.82	1.94	1.89	2.19	13	18	29	36	40	46
17	0.59	1.69	1.6	1.91	2.15	2.26	16	30	39	42	45	50
18	0.99	1.88	1.83	1.98	2.5	2.59	14	33	39	41	44	58
19	0.65	2.15	2.31	2.44	2.23	2.8	17	25	28	31	42	53
20	1.25	1.68	1.74	1.75	2.03	2.31	19	33	37	41	48	53
21	1.13	2.03	2.09	2.17	1.97	2.09	10	30	29	32	38	51
22	1.46	2.31	2.12	2.06	2.44	2.5	14	24	29	31	32	42
23	0.89	0.59	1.79	1.77	1.79	2.04	16	32	27	37	46	52
24	0.44	1.65	1.78	1.83	1.9	1.97	21	26	39	45	49	50
25	0.65	1.58	1.6	1.75	1.81	1.92	15	27	35	40	46	50
26	1.08	2.49	2.63	2.49	2.64	2.51	13	31	31	37	40	53

Note: Subject #9 had no recorded resting breathing parameters. ND = no data.

One may ask whether a greater impact on individual athletic performance decrement may be attributed to local airway response to PM exposure or to a more systemic response producing cardiopulmonary and inflammatory effects. While acute effects may be expected to be more clinically prominent, at least initially in the tracheobronchial region due to bronchoconstriction and local inflammation, it is also possible that a significant clinical impact on performance in some athletes may result from the early systemic responses generated by deep lung deposition in the pulmonary/alveolar region. In any case, detailed modeling of airway deposition during PM exposure at various levels of exertion is indicated.

2. Methods

To assess regional airway deposition of inhaled particles at increasing levels of exertion in athletes, Multiple-Path Particle Dosimetry (MPPD) modeling was utilized (Ashgarian, Hofmann, & Bergmann, 2001). The model focuses on mechanisms of sedimentation, diffusion, impaction, and interception that cause particles to deposit as they sequentially traverse a series of structures representing the nasopharyngeal, tracheobronchial and pulmonary airway regions (Ashgarian et al., 2001; Hofmann, 2011).

A nomogram for the assessment of breathing patterns in athletes during treadmill exercise utilizing data collected from trained athletes in Europe was published by Naranjo, Centeno, Galiano, and Beaus (2005). In their treadmill ramp protocol for progressive exertion, breathing data including tidal volume (V_t) and breathing frequency (f_b) were collected from 26 male athletes. Their previously unpublished individual breathing data from the original study were utilized (Table 1) (Naranjo, personal communication, 2013).

Using the MPPD Model (v 2.11), deposition fractions of inhaled particles measuring 10.0 μm, 2.5 μm, 1.0 μm, 0.1 μm, and 0.05 μm in diameter (spherical with unit density 1.0 g/cm^3) were modeled in this study for each athlete according to their individual breathing parameters at the six levels of exertion from rest to maximum exertion used in the original Naranjo

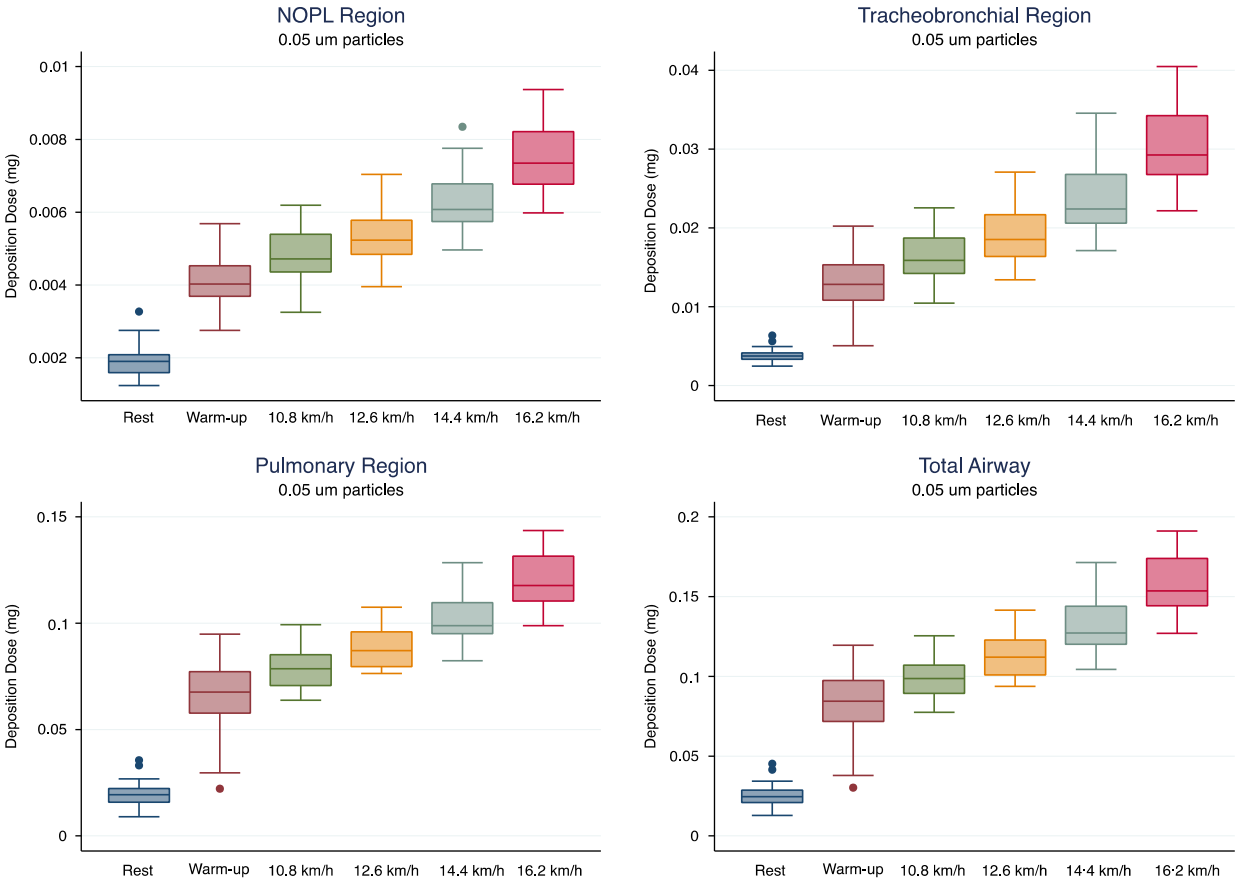

Fig. 2. Modeled deposition dose of 0.05 μm aerodynamic diameter particles by airway region in 26 male athletes during three-minute intervals at increasing treadmill speeds.

*Abbreviation: NOPL – naso-oro-pharyngo-laryngeal region. Results indicate non-cumulative deposition dose at each exertion level.

Note: Boxes indicate the lower and upper quartiles of the deposition dose, defining the interquartile range. The horizontal line within each box represents the median deposition dose. Whiskers span 1.5 times above the upper quartile and 1.5 times below the lower quartile.

treadmill protocol. The breathing parameters of the subjects were measured starting at rest, during a three-minute warm-up at 8.0 km/h, and then every 3 min (with speed increasing by 0.2 km/h every 20 s, keeping the incline steady at 1.0%) until a final maximum speed of 16.2 km/h was reached.

The modeled particle diameters were selected in order to provide a range of sizes representing a broad spectrum of typical particles in urban areas and locations common to athletic competition and training, ranging from ultrafine particles to larger particles, generated by various sources including combustion engine exhaust, industrial processes, etc.

Modeling was performed in each case using the MPPD selectable human airway morphometry data for the age-specific 5-lobe model (for a 21 year-old) with uniform expansion, a default functional residual capacity of 2123.75 mL, and an upper respiratory tract default volume of 42.27 mL. The use of this single, age-specific 21 year-old lung morphometry modeling selection was based on the mean study population age of 23.5 years.

The exposure scenario in each case assumed a normal acceleration of gravity (981.0 cm/s^2), upright body orientation, aerosol concentration of 1.0 mg/m^3, and oronasal-normal-augmenter breathing. Breathing frequencies and tidal volumes were entered into the MPPD software by individual athlete for each level of exertion. Deposition fractions by airway region were computed for each individual athlete at each level of exertion, and deposited dose for each respective airway region was calculated from the deposition model.

2.1. Statistical analysis

For each particle diameter, mean values of a three-minute deposition dose (mg) in each airway region (NOPL, TB, P, and total airway) at each level of exertion from rest to a maximum speed of 16.2 km/h were compared by repeated measures ANOVA testing using STATA 12.1. (Stata Corp., College Station, TX).

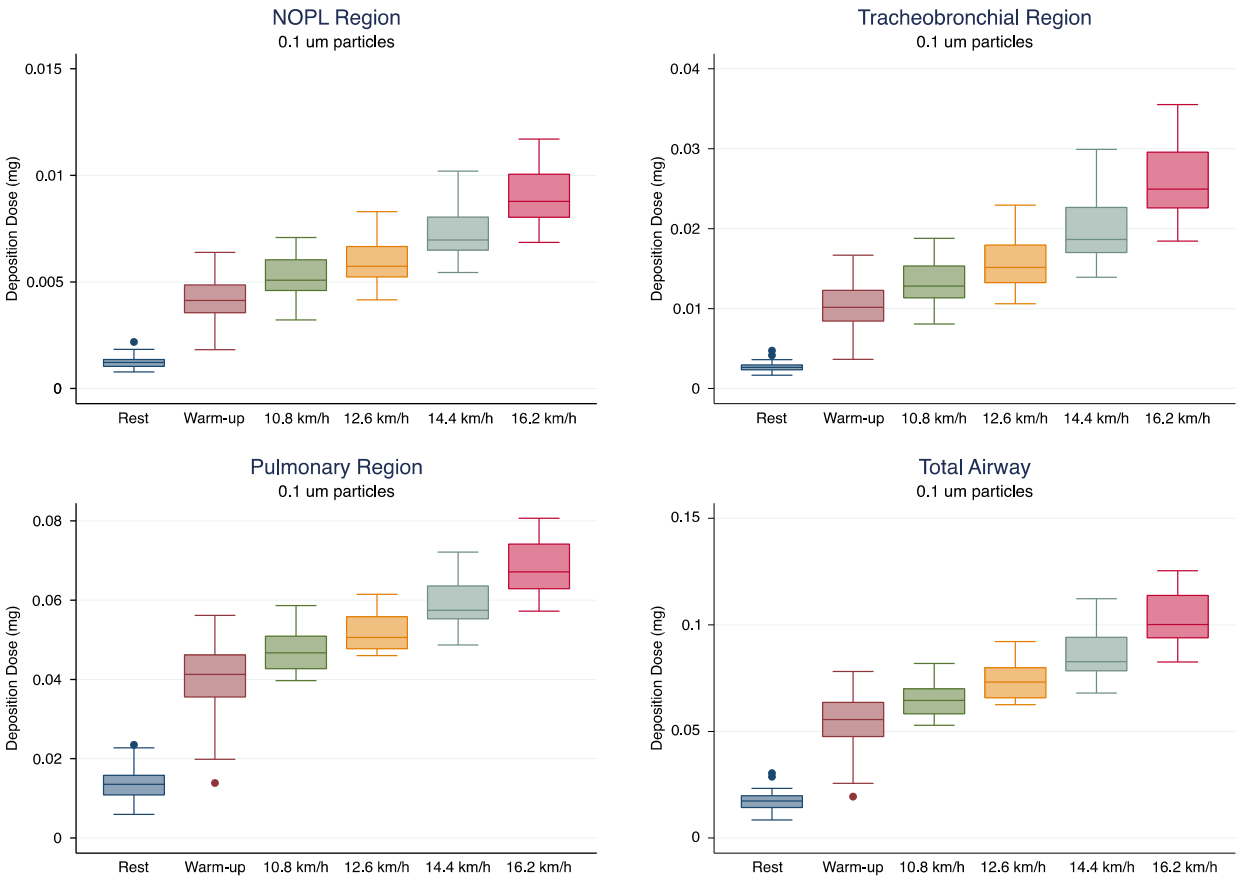

Fig. 3. Modeled deposition dose of 0.1 μm aerodynamic diameter particles by airway region in 26 male athletes during three-minute intervals at increasing treadmill speeds.
*Abbreviation: NOPL – naso-oro-pharyngo-laryngeal region. Results indicate non-cumulative deposition dose at each exertion level.
Note: Boxes indicate the lower and upper quartiles of the deposition dose, defining the interquartile range. The horizontal line within each box represents the median deposition dose. Whiskers span 1.5 times above the upper quartile and 1.5 times below the lower quartile.

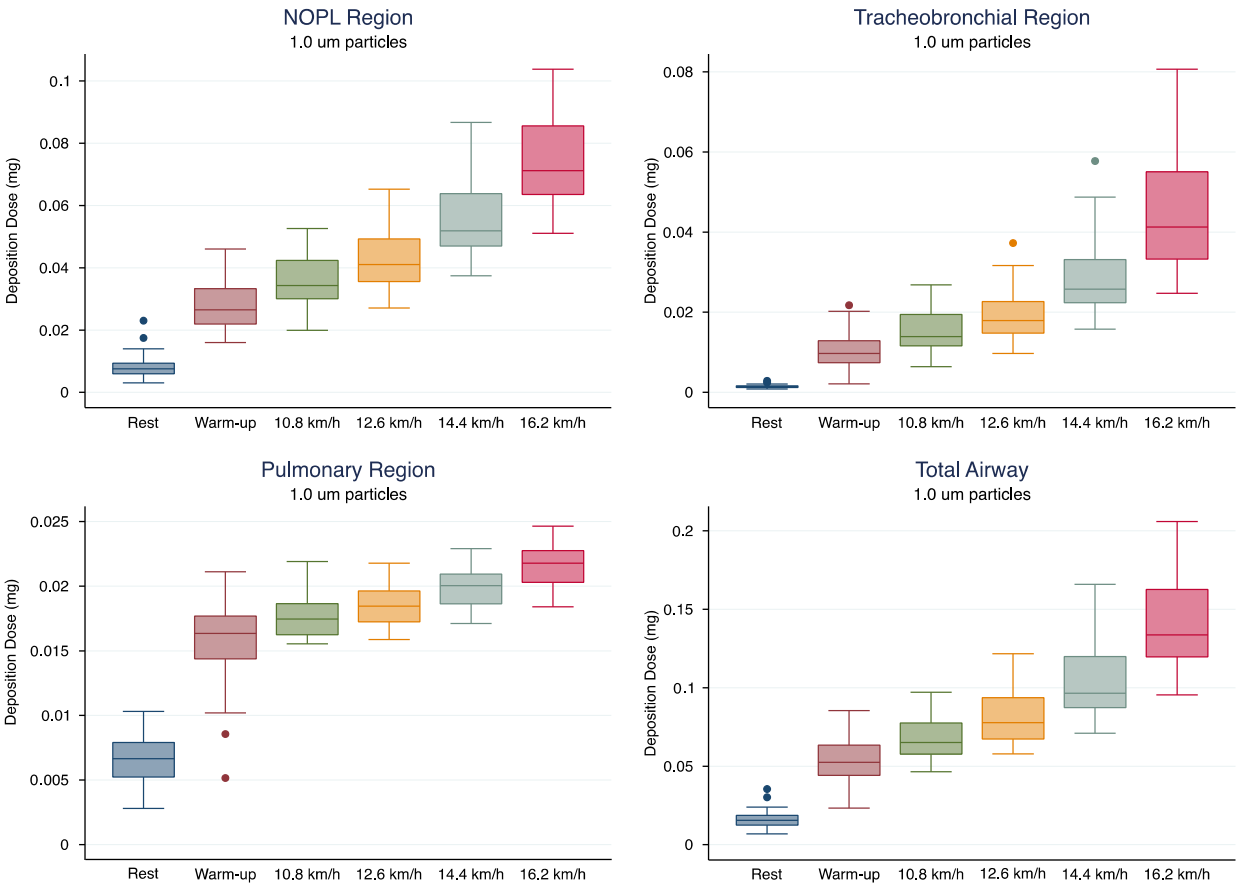

Fig. 4. Modeled deposition dose of 1.0 μm aerodynamic diameter particles by airway region in 26 male athletes during three-minute intervals at increasing treadmill speeds.
**Abbreviation: NOPL – naso-oro-pharyngo-laryngeal region. Results indicate non-cumulative deposition dose at each exertion level.*
Note: Boxes indicate the lower and upper quartiles of the deposition dose, defining the interquartile range. The horizontal line within each box represents the median deposition dose. Whiskers span 1.5 times above the upper quartile and 1.5 times below the lower quartile.

3. Results

There is a statistically significant effect ($p < 0.01$) of exertion on the mean particle dose deposited in each airway region (NOPL, TB, P, and total airway). Box plots of regional and total deposition for all particle sizes and levels of exertion are available (Figs. 2–7). Depending on particle size and maintaining constant environmental aerosol exposure concentration of 1 mg/m^3, the regional breakdown of deposition doses does not necessarily parallel the typical overall rise in that of the total airway. In fact, it appears that as particles increase in size, increasing exertion may lead to an overall increased dose when considering the entirety of the respiratory tract, but in the deep lung (pulmonary) region, increasing exertion appears to be negatively associated with dose after an initial spike from rest to warm-up. This phenomenon is most apparent with 2.5 and 10.0 μm particles, and while the trend in pulmonary deposition dose of 1.0 μm particles appears to increase with exertion, the rate of increase in deposition dose is less dramatic than seen in smaller particles. Overall, it appears that inhalation of particle diameters greater than 1.0 but less than 2.5 μm begin the trend toward decreased pulmonary deposition with increasing exertion. Figure 7 displays ratios of deposition dose at maximum exertion to rest by particle size and lung region, illustrating the substantial increase in dose ratio noted with 2.5 μm particles in the TB region.

4. Discussion

To the author's knowledge, this study represents the first use of a particle deposition model, in this case MPPD, to assess regional lung deposition of inhaled particles in athletes at exertion. Results indicate possible phenomena that may impact athletic performance. While overall total airway deposition dose of all particle diameters increases as expected with increasing exertion, pulmonary regional deposition dose at exertion tapers off and decreases in the case of larger particles (2.5 and 10.0 μm). The impressive increase in deposition dose ratio from rest to maximum exertion in the case of 2.5 μm

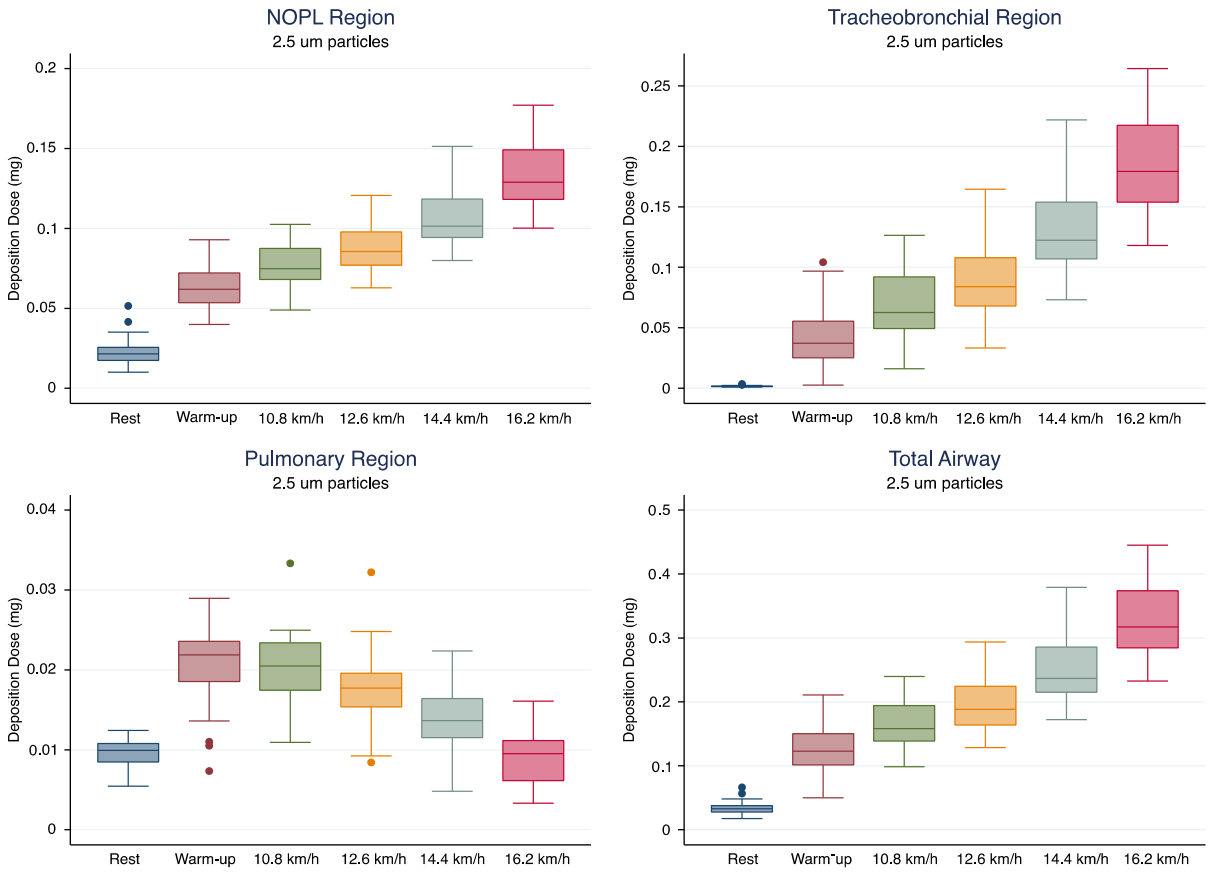

Fig. 5. Modeled deposition dose of 2.5 μm aerodynamic diameter particles by airway region in 26 male athletes during three-minute intervals at increasing treadmill speeds.
**Abbreviation: NOPL – naso-oro-pharyngo-laryngeal region. Results indicate non-cumulative deposition dose at each exertion level.*
Note: Boxes indicate the lower and upper quartiles of the deposition dose, defining the interquartile range. The horizontal line within each box represents the median deposition dose. Whiskers span 1.5 times above the upper quartile and 1.5 times below the lower quartile.

particles in the TB region raises questions as to whether or not current concerns with fine and ultrafine particles in the deep lung at exertion truly carry the same threat to performance as larger particles.

In considering studies based on modeling, the accuracy of the model must be addressed. Daigle and colleagues reported that measured total airway deposition of nanoparticles exceeded model predictions with exercise (Daigle et al., 2003). As Daigle et al. utilized the MPPD software to make predictions of deposition fraction at exertion, the model data in our study could also underestimate the true deposition doses. Therefore our results could underestimate the overall effects of inhaled particle toxicity in athletes at exertion.

The MPPD model is valuable in its ability to analyze specific particle-size related parameters, however, the isolated analyses of single ideal (solid spheres, of unit density) particles of specific sizes does not account for particle composition (including prevalent bioaerosols), other particle sizes, effects of humidity, temperature, and etc. that could also impact inhaled particle deposition in vivo. Therefore our study provides guidance for future studies rather than definitive advice for athletes. Ideally, future studies utilizing tracer (e.g., radiolabeling) techniques could provide in vivo quantitative validity assessments of the MPPD model for prediction of regional deposition at exertion.

Additionally, the MPPD model used in these 26 athletes did not incorporate inhalability adjustments to particle deposition. Inhalability describes the size and wind speed dependent efficiency with which particles in the breathing zone actually enter the respiratory tract via the nose or mouth (Hofmann, 2011). Issues of changes in body position with exertion along with potentially dramatic changes in inhalability factors could contribute to decreased accuracy of the model. Increased air flow demands during exercise may force the turbulence-to-laminar flow transition point distally in the respiratory tract, leading to increased deposition in smaller airways where laminar flow becomes turbulent (Daigle et al., 2003).

Particle diameters were selected for modeling in attempt to broadly cover the range of inhalable particle diameters that are recognized and regulated by the EPA, including those smaller than 2.5 μm. Vehicular emissions are typically considered to be the greatest anthropogenic threat to athletic performance due to elevated levels of combustion-related air pollution

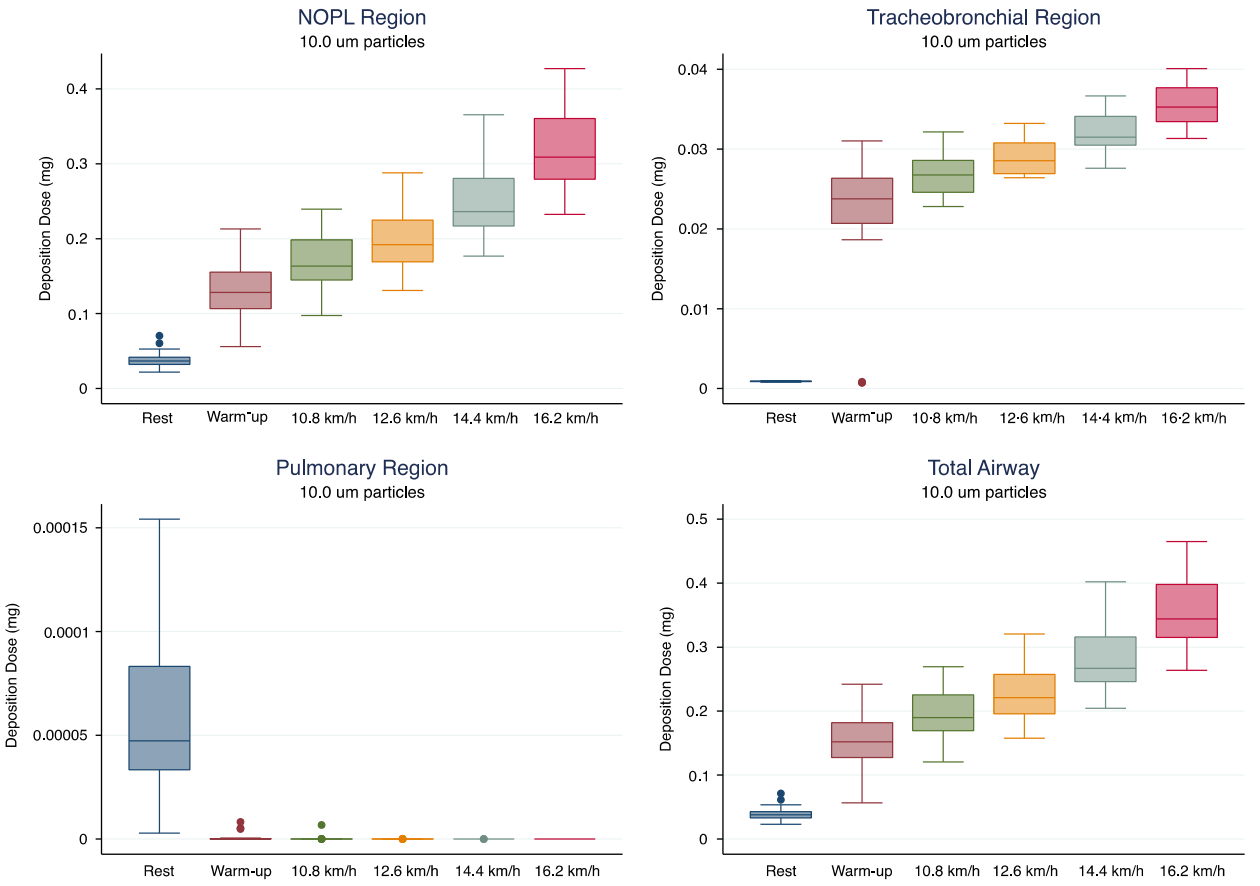

Fig. 6. Modeled deposition dose of 10.0 μm aerodynamic diameter particles by airway region in 26 male athletes during three-minute intervals at increasing treadmill speeds.
*Abbreviation: NOPL – naso-oro-pharyngo-laryngeal region. Results indicate non-cumulative deposition dose at each exertion level.
Note: Boxes indicate the lower and upper quartiles of the deposition dose, defining the interquartile range. The horizontal line within each box represents the median deposition dose. Whiskers span 1.5 times above the upper quartile and 1.5 times below the lower quartile.

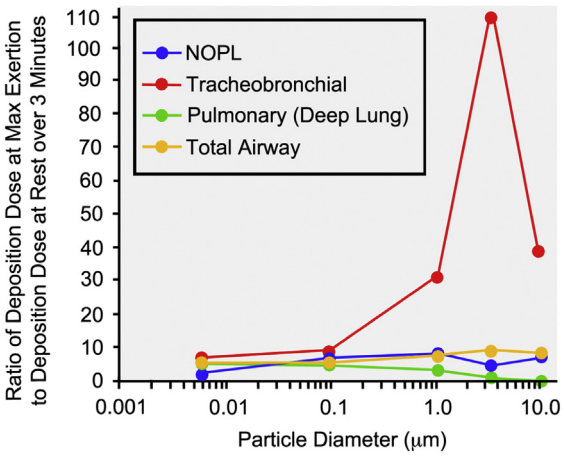

Fig. 7. Ratio of deposition doses at maximum exertion to deposition doses at rest for three-minute periods by particle size and airway region in 26 male athletes.

often found in environments that coincide with training and competition facilities. Particle diameters of 0.05 and 0.1 μm were considered in this study to be suitable representations of freshly generated vehicle exhaust (Rundell, 2012).

Schlesinger and colleagues reported that both epidemiological and toxicological studies indicate that smaller particle size has a closer linkage to adverse health outcomes when compared to outcomes from larger particle exposures (Schlesinger,

Kunzli, Hidy, Gotschi, & Jerrett, 2006). Ultrafine particles, due to their size, are strongly affected by Brownian diffusion and, for some compositions, hygroscopicity. Hygroscopic particles will grow by water vapor condensation, decreasing diffusion rate, and therefore altering the likelihood of deposition (Londahl et al., 2007). The potentially decreased hydration level (relative to resting conditions) in the airway in athletes at exertion could have significant implications in both particle deposition during exercise as well as the validity of the model at progressive levels of exertion.

The mean subject age of 23.46 years indicated that the single age-specific 21-year old lung morphometry model would provide the best estimate of deposition fractions at exertion given the limited age inputs available within the MPPD interface, although use of the coinciding default lung capacity in the model certainly leaves room for error.

It remains to be seen as to whether the threat of oxidative stress and inflammation from deep lung deposition of ultrafine particles outweighs that of larger particle deposition in the more proximal tracheobronchial region from a perspective of impacting performance. Usmani et al. measured regional deposition of radiolabeled albuterol in asthmatics. Distal airway penetration and peripheral lung deposition of albuterol increased with decreased particle size, but the best improvement in forced expiratory volume was observed with the largest particle size at the lowest particle deposition dose, highlighting the key importance of regional particle deposition and subsequent clinical outcome measures (Usmani, Biddiscombe, & Barnes, 2005). A 2012 review of inhalational pharmaceutical deposition by Darquenne reported that total lung deposition alone appears to be a poor predictor of clinical outcome; rather, regional deposition must be assessed to predict therapeutic effectiveness (Darquenne, 2012). It stands to reason that the same level of importance with regard to clinical outcomes based on regional deposition should be placed on potential impacts of inhaled particles on athletic performance.

This study is a step toward understanding how particulate air pollutants may impact athletic performance. Given the anatomic and physiologic diversity of athletes and varied local air pollutant composition by training/competition venue, specific circumstances must undoubtedly be considered, and questions remain as to the accuracy of current dosimetry model capability in high exertion protocols.

In order to assess the effects of inhaled particle exposure on athletic performance, future studies should focus on comparing the acute and chronic effects of regional deposition and subsequent uptake, oxidative stress, and inflammatory responses from exposures resulting in particle deposition both in the deep lung and the more proximal athlete airway.

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