


# BMJ Open Regular running in an air-polluted environment: physiological and anthropometric protocol for a prospective cohort study (Healthy Aging in Industrial Environment Study – Program 4)

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## ABSTRACT

**Introduction** Ambient air pollution is a global environmental problem, which causes adverse health effects and premature deaths worldwide. Although regular exercise and physical activity have evident health benefits, the influence of long-term air pollution exposure during regular outdoor running has not been definitively clarified.

**Methods and analysis** This study protocol describes the physiological and anthropometric perspectives of the ‘Healthy Aging in Industrial Environment’ Study – Programme 4 (4HAIE). The 4HAIE research project is intended to be a single-centre, prospective, longitudinal and multidisciplinary cohort study. The presented study protocol describes the cross-sectional measurements and analyses. Overall, 1500 adult participants (age 18–65 years), runners and inactive individuals, living in a high or low air-polluted area of the Czech Republic will be recruited. We will measure and analyse biomarkers of oxidative stress and inflammation in the blood, exercise capacity (graded exercise test and spirometry), blood pressure, lung function (spirometry), cardiac autonomic regulation and anthropometry (body composition).

**Ethics and dissemination** The 4HAIE study protocol has already been approved by the Ethics Committee of the University of Ostrava (3/2018). A detailed participant information sheet will be provided to each individual prior to obtaining their written informed consent. The study poses little to no risk to participants. The findings of this study will be disseminated at regional and international conferences, in peer-reviewed journals and via social and broadcast media.

## INTRODUCTION

It has been demonstrated that 9 out of 10 people breathe air containing high levels of pollutants. Air pollution (AP) contributes to the premature mortality of an estimated 7 million people worldwide annually (WHO, 2019).<sup>1</sup> For example, fine particulate matter

## Strengths and limitations of this study

- The presented study is part of the multidisciplinary research project with extensive cohorts of runners and inactive individuals (N=1500 in total).
- Participant recruitment into the study cohort is conducted by a professional marketing and social research agency using stratified quota sampling to ensure representation by age, sex and physical activity status, which enables to generalise the study results.
- The first wave of this observational study will provide cross-sectional laboratory data; however, the Healthy Aging in Industrial Environment Study – Program 4 study is intended to become longitudinal and future laboratory follow-up data collection is planned.
- The study focuses on the long-term effect of living and running in a high or low air-polluted region. The acute effects of air pollution are not considered.

<2.5 µm (PM<sub>2.5</sub>) is considered a leading cause of global morbidity and mortality as it promotes the development of chronic cardiometabolic conditions including atherosclerosis, hypertension and diabetes mellitus.<sup>2</sup> In addition, AP has been identified as a contributing factor in inducing epigenetic alterations, along with respiratory, neurological, psychiatric and musculoskeletal diseases.<sup>3,4</sup> Recent evidence suggests that an increased exposure to PM<sub>2.5</sub> is also linked to chronic cardiometabolic comorbidities that have been associated with poor prognosis and death in patients with COVID-19.<sup>5</sup> Furthermore, the cardiorespiratory system is significantly affected by both short-term and



long-term ambient AP exposure.<sup>6</sup> Thus, AP should be considered one of several major modifiable risk factors in the prevention and management of cardiovascular disease.<sup>7</sup>

The underpinning mechanisms of AP on morbidity and mortality are associated with chronic systemic inflammation and oxidative stress,<sup>8,9</sup> as well as genetic and epigenetic pathways.<sup>8</sup> The development of chronic cardiovascular disease can be instigated via three potential pathways: a 'spill over' of proinflammatory or oxidative stress mediators generated in the lungs into the systemic circulation, the incitement of autonomic nervous system imbalance and the penetration of certain particles (ultrafine particles PM<sub>0.1</sub>) or components (soluble metals and organic compounds) directly into the cardiovascular tissues.<sup>10</sup> These three factors can lead to atheroma progression, endothelial dysfunction, impaired fibrinolysis, platelet hyper-reactivity and possibly arrhythmogenesis.<sup>7</sup>

An active lifestyle with regular physical activity and exercise is known to be beneficial to health. However, the most accessible forms of exercise, such as walking, running and cycling, are often performed outdoors, which means an increased exposure to urban AP.<sup>11, 12</sup> Although the beneficial aspects of exercise can be potentially dampened if conducted in AP, exercise recommendations, such as those given by the American College of Sports Medicine, do not take into account the harmful effect of AP.<sup>11</sup> An increased risk of cardiorespiratory function, immune function and exercise performance disruption has been associated with the combination of AP and exercise.<sup>13</sup> Moreover, increased ventilation during exercise causes a greater influx of air and pollutants into the airways and those might even reach systemic circulation.<sup>14, 15</sup> A 12-week aerobic training programme in an urban environment with high traffic-related AP exposure increased markers of respiratory and systemic inflammation (leucocytes count, neutrophil counts and exhaled nitric oxide). These changes positively correlated with personal PM<sub>0.1</sub> exposure during training.<sup>16</sup> Even a short duration of exercise (20 min) near a busy roadway is sufficient to significantly increase blood levels of volatile organic compounds (toluene, ethylbenzene and xylene).<sup>17</sup> Furthermore, 5 days of aerobic outdoor exercise significantly impaired nasal mucociliary clearance in the street runners group when compared with the forest runners group.<sup>18</sup> This suggests that regular outdoor exercise in AP can be potentially harmful to cardiorespiratory health.

The adverse effect of AP on cardiovascular health might also be linked to alterations in autonomic nervous system activity. The relationship between heart rate variability (HRV), as a tool for the cardiac autonomic activity assessment, and increased risk of cardiovascular mortality and morbidity has been recognised.<sup>19</sup> Five consecutive 8-hour days spent in an AP area caused a significant reduction in HRV. However, whether this effect is caused directly by AP or via other factors, such as oxidative stress, is unclear.<sup>20</sup> Furthermore, previous research has observed that several

hours of exposure to increased levels of PM<sub>0.1</sub> and PM<sub>2.5</sub> concentrations may affect HRV and induce acute pathophysiological responses.<sup>21</sup> This fact is primarily evident in individuals with increased risk of cardiovascular diseases.<sup>22, 23</sup> Moreover, a consistent inverse relationship was found for the level of AP and time-domain HRV variables, that is, HRV decreased when pollutant levels increased.<sup>20</sup> In contrast, the associations between ambient concentrations of PM<sub>2.5</sub> and HRV were not definitively confirmed in a separate review study.<sup>24</sup>

Osteoporosis has become a serious disease worldwide. Evidence suggests that there are adverse effects of AP on osteoporosis among the industrial population.<sup>25</sup> By contrast, the total running distance and frequency rank are considered beneficial to body mass density (BMD).<sup>26</sup> However, a high total running distance and frequency has been shown to cause BMD impairment, particularly in the lumbar spine region.<sup>27, 28</sup> Therefore, the effect of AP and regular running on the development of osteoporosis can depend on overall running volume, with a potential U risk curve. Qiao *et al*<sup>25</sup> suggests that physical activity, such as running, may weaken the adverse effects of AP on osteoporosis. However, it is not clear whether regular running is beneficial to bone health, independent of ambient AP.

The aim of the presented physiological and anthropometric perspectives of this multidisciplinary Healthy Aging in Industrial Environment Study – Program 4 (4HAIE) research project is to investigate the long-term influence of AP on health-related variables such as: biochemical markers of inflammation and oxidative stress, cardiorespiratory fitness level, blood pressure (BP), ventilatory (lung) function, cardiac autonomic regulation and body composition in regular runners (>10 km of running per week for more than 6 weeks prior to the tests) and inactive individuals. Both groups are recruited from either the heavy industry area of Silesia (Czech Republic) with high AP or the area of South Bohemia (Czech Republic) with low AP.

## METHODS

### Study design

The presented study protocol describes the physiological and anthropometric perspectives of the 4HAIE. Because of the specific aims and measures, participants recruited for 4HAIE are a separate cohort to programmes 1–3. The 4HAIE study is intended to be a single-centre, prospective, longitudinal and multidisciplinary cohort study investigating the influence of AP on the incidence of sports-related injuries, physical (in)activity, health and quality of life across the lifespan. The presented physiological and anthropometric section describes the first wave of measurement. The main aim of the presented study is a cross-sectional analysis of the health outcome differences between runners living permanently in low versus high air-polluted regions. Additionally, the possible benefits of regular running in a high air-polluted region are considered, which will be compared with inactive individuals in

**Table 1** Overview of 4HAIE study measurements and time points for data collection

Time point	Screening		Laboratory examination		Follow-up		
	Initial contact by telephone and email	Prelaboratory (in situ)	Day 1	Day 2	6 months	12 months	Ongoing
Eligibility	×						
Enrolment	×						
PAR-Q	×	×					
Psychological and behavioural survey	×				×	×	×
Fitbit assessment							×
Blood pressure			×				
GXT			×				
Urine samples				×			
HRV				×			
Blood samples				×			
Anthropometrics				×			
Biomechanics				×			
Cognitive function testing				×			
MRI				×			
Injury incidence				×	×	×	×

GXT, graded exercise test; 4HAIE, Healthy Aging in Industrial Environment Study – Program 4; HRV, heart rate variability; PAR-Q, Physical Activity Readiness Questionnaire.

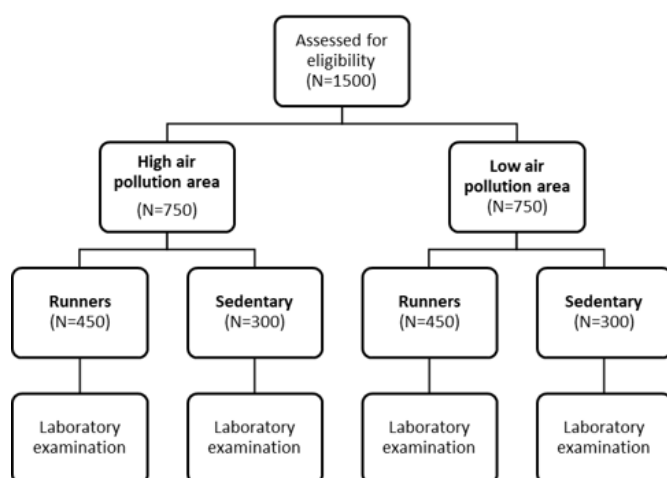
the same region. Overall, the 4HAIE project aims at the following areas of investigation: physiological, anthropometric, biomechanical, behavioural and neurocognitive (table 1). The biomechanical, behavioural and neurocognitive perspectives are beyond the scope of this article and will be presented elsewhere.

### Study population

Participants are adults (age 18–65 years) who live for at least 5 years in a high air-polluted (Moravian-Silesian) or low air-polluted (South Bohemia) region of the Czech Republic. Runners and inactive individuals are recruited from both regions with high and low AP (figure 1). Sociodemographic characteristics of participants are in

accordance with the sociodemographic characteristics of the population. The number of participants for each age decade will be equal.

- ▶ Inclusion criteria – *runners*: running as a main exercise activity, >150 min of moderate or >75 min of strenuous physical activity per week (or an equivalent combination of moderate and strenuous physical activity),<sup>29</sup> >10 km running per week for at least 6 weeks prior to the tests, intending to continue running for next 12 months, permanent (>5 years) whole-year residency in the determined areas, not planning to move away from the determined areas during the next 12 months, with internet access and using a smartphone (with iOS or Android 5.0 or higher).
- ▶ Inclusion criteria – *inactive individuals*: <150 min of moderate or <75 min of strenuous exercise per week, capable of running, but running irregularly and/or less than 6 weeks prior to the tests, no contraindications to exercise, permanent (>5 years) whole-year residency in the determined areas, not planning to move away from the determined areas during the next 12 months, with internet access and using a smartphone (with iOS or Android 5.0 or higher).
- ▶ Exclusion criteria – *runners and inactive individuals*: acute (within 6 weeks) health condition (pain, injury and surgery) preventing from physical activity, any other acute disease, pregnancy, radiological examination within the last 7 days, artificial pacemaker, radioactive, surgical or any other device/implant, insulin pump and smoking.


**Figure 1** Flow chart of the study process.

### Participant and public involvement

This research is conducted without the participants' involvement. Participants are not invited to comment on the study design, nor are they consulted to develop participant relevant outcomes or interpret the results. Furthermore, participants are not invited to contribute to the writing or editing of this document for readability or accuracy. Results that are immediately available are presented to participants with a basic explanation at the conclusion of each measurement. Other results requiring a deeper analysis are available on request.

### High air-polluted versus low air-polluted areas

There are considerable regional differences in terms of air quality within the Czech Republic.<sup>30–33</sup> The Moravian-Silesian region is shown to have the highest long-term values of suspended coarse particulate matter (PM<sub>10</sub>), PM<sub>2.5</sub>, NO<sub>2</sub> and benzo[a]pyrene. However, South Bohemia is considered the region with the lowest AP.<sup>34</sup> For example, the average annual concentrations of PM<sub>10</sub> and PM<sub>2.5</sub> in 2018 in Ostrava-Radvanice (Moravian-Silesian region) were 44.0 and 36.8 µg/m<sup>3</sup>/year, respectively, whereas in Ceske Budejovice (South Bohemia region), they were 19.8 and 16.0 µg/m<sup>3</sup>/year, respectively. Additionally, in 2018, the average annual concentration of NO<sub>2</sub> was substantially higher in Ostrava-Radvanice than in Ceske Budejovice (21.7 vs 14.9 µg/m<sup>3</sup>, respectively), and benzo[a]pyrene concentrations in Ostrava-Radvanice were more than seven times greater than values in Ceske Budejovice (7.7 vs 1.1 ng/m<sup>3</sup>/year).<sup>35</sup>

### Data collection

#### Air pollution

The updated level of AP in both the Moravian-Silesian and South Bohemia regions during the data collection phase will be acquired from the Czech Hydrometeorological Institute.

#### Biochemical analysis

Fasting blood samples (30 mL) are collected from the antecubital vein in the morning hours (06:30–07:00) within the physiology laboratory. Biomarkers previously shown to be associated with chronic diseases are analysed:

- ▶ Basic analysis: erythrocytes, leucocytes, thrombocytes, haemoglobin, haematocrit, total cholesterol, low-density and high-density lipoprotein, triglycerides, free fatty acids, glucose, glycated haemoglobin, fibrinogen and carbohydrate-deficient transferrin.
- ▶ Oxidative stress: total antioxidative capacity, superoxide dismutase, glutathione peroxidase, malondialdehyde, glutathione and glutathione disulphide.
- ▶ Inflammation: high-sensitive C reactive protein, high-sensitive interleukin-6, interleukin-1β, interleukin-10, interleukin-1 receptor antagonist, tumour necrosis factor-α, adiponectin, leptin and brain-derived neurotrophic factor.

The biochemical analysis is provided by an external specialised and certified biochemical laboratory with

long-term experience in clinical analysis and research projects.

### Graded exercise test (GXT)

Participants will perform a laboratory GXT on a motorised treadmill (Rodby RL 2500E) in order to determine maximum aerobic power ( $\dot{V}O_{2max}$ ), the first (VT<sub>1</sub>) and the second ventilatory threshold (VT<sub>2</sub>), total time to exhaustion and respiratory exchange ratio. Prior to the GXT, participants complete 3 min of walking at 5.0 km/hour to familiarise themselves with the treadmill. The GXT protocol then commences at 6.0 km/hour, with speed subsequently increasing by 1.0 km/hour every minute (inclination remaining at 1%) until volitional exhaustion. Expired air is continuously monitored to analyse O<sub>2</sub> and CO<sub>2</sub> concentrations during the GXT with a breath-by-breath system (Blue Cherry, Geratherm Medical AG, Germany). The highest average O<sub>2</sub> consumption measured over a 30 s period is used to determine  $\dot{V}O_{2max}$ . Gas exchange measurements are also used to quantify VT<sub>1</sub> and VT<sub>2</sub>. VT<sub>1</sub> is defined as the first increase in ventilation (VE) accompanied by a minimum of the oxygen equivalent (VE/VO<sub>2</sub>) without an increase in the CO<sub>2</sub> equivalent (VE/VCO<sub>2</sub>). A second sharp increase in ventilation (VE) accompanied by an increase in both VE/VO<sub>2</sub> and VE/VCO<sub>2</sub> is used to define VT<sub>2</sub>.<sup>36</sup> Heart rate (HR) is measured using a chest belt monitor (Polar Electro H9, Kempele, Finland). Perceived effort is measured using the 20-point Borg scale. All sessions are conducted in the afternoon, at least 3 hours after the participants' last meal and in a thermally controlled laboratory (21°C, 40% relative humidity). Each participant is advised not to participate in any vigorous activity 24 hours prior to the test.

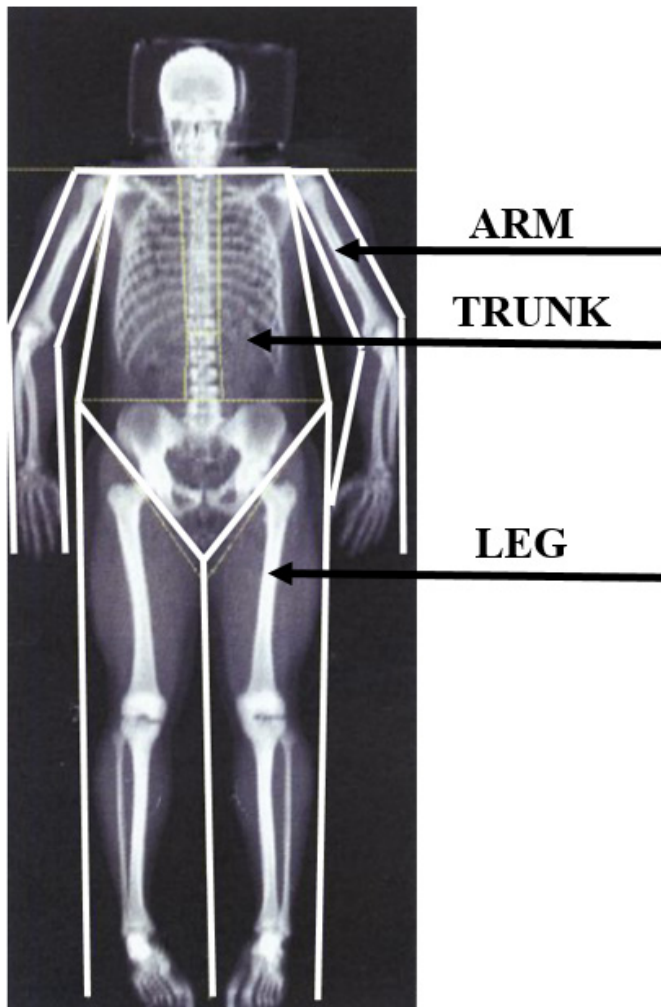
Prior to completing the GXT, if participants do not pass the Physical Activity Readiness Questionnaire, they are not allowed to perform the GXT unless explicit permission (given by a medical doctor) is provided. BP is also checked before the GXT. If the BP values are ≥150/90 mm Hg, the participant is not allowed to perform GXT, but continues in the study protocol.

### Blood pressure

Participants are instructed to avoid caffeinated beverages at least 60 min before BP measurements. The BP measurements commence following ≥10 min of rest in a quiet room. Participants sit with back straight and supported, with feet flat on the floor and legs uncrossed, keeping left arm supported on a table at heart level. The bottom of the cuff is placed directly above the antecubital fossa. BP is recorded repeatedly three times 1–2 min apart. The Nissei DM 3000 device is used for the BP measurement. This procedure is in line with the American College of Cardiology, American Heart Association and European Society of Hypertension recommendations.<sup>37 38</sup>

### Spirometry

Prior to the spirometry test, the spirometer (Blue Cherry, Geratherm Medical AG) is calibrated according to the

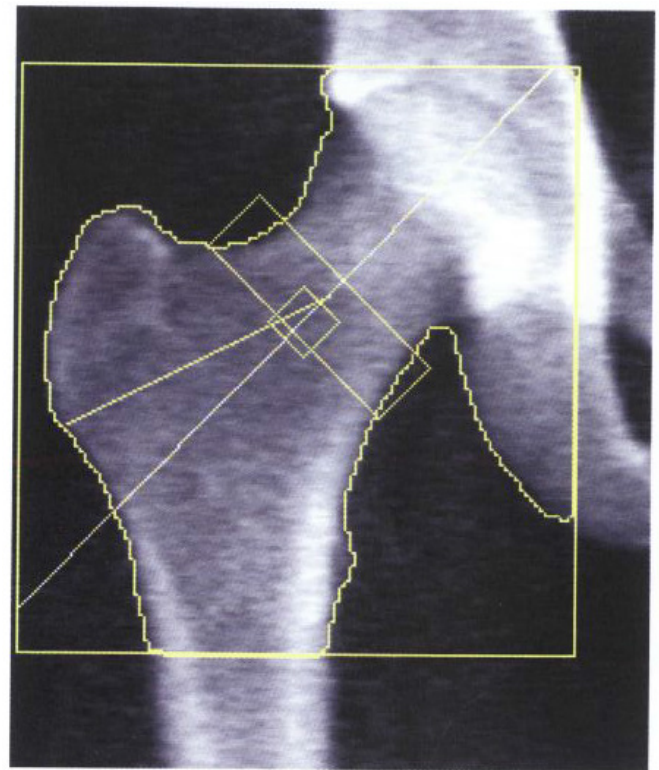


**Figure 2** Whole body scan.

manufacturer instructions. The test is then explained, and the appropriate technique is demonstrated to the participants. Participants are relaxed, seated erect, using a mouthpiece and wearing a nose clip. The vital capacity manoeuvre starts with five tidal breaths, followed by an inspiratory manoeuvre to total lung capacity with no hesitation and then a full expiration to residual volume. The laboratory staff encourages participants to reach maximal inspiratory and expiratory volumes. This procedure is repeated three times with at least 1 min break apart. The spirometry test is performed in line with the American Thoracic Society and European Respiratory Society recommendations.<sup>39</sup> Other lung function variables, such as peak expiratory flow or forced expiratory volume in 1 s, will be evaluated since their adverse relationships to long-term exposure to ambient AP have been observed.<sup>40</sup>

#### Cardiac autonomic regulation

HRV is used to evaluate cardiac autonomic regulation. A Bittium Faros device (Bittium Inc, Oulu, Finland) collects a single-channel ECG from two electrodes placed on a chest belt. The short-term (10 min) ECG is recorded in a quiet room after waking until 07:00. Participants remain resting in a supine position with no external disturbances



**Figure 3** Hip scan.

during the ECG recording. The first half of the ECG recording time is designed to induce steady state conditions and is not included in the HRV analysis (in most participants 5 min). ECG data are imported into Kubios HRV Premium, which automatically detects the R-wave time instants by applying the built-in QRS detection algorithm.<sup>41</sup> Before R-wave time instant extraction, the R-wave is interpolated at 2000 Hz to improve the time resolution of the detection. The standard time/frequency-domain HRV variables are analysed from the 5 min (300 s) long ECG sequence according to the task force recommendations.<sup>42</sup> Prior to the HRV analysis, the ECG records and RR interval time series are visually checked for artefacts, and an automated algorithm<sup>43</sup> for artefact detection is also used through the Kubios software. Artefacts including missing, extra or misaligned beat detections, as well as ectopic beats such as premature ventricular contractions or other arrhythmias, are filtered out from the RR interval time series used for the HRV analysis. Furthermore, slow non-stationary oscillations in RR intervals are detrended with smoothness priors.<sup>44</sup> Main time domain measures of interest include: the SD of all normal-to-normal RR intervals and the root mean square of successive differences of normal-to-normal RR intervals. Main frequency domain components will include the low-frequency, 0.04–0.15 Hz, and high-frequency, 0.15–0.4 Hz, spectral power.<sup>42</sup>

#### Anthropometry

Anthropometric measurements include basic anthropometric parameters (body height and body mass), hydration status and body composition. All measurements are

taken in the morning; the participants are measured in sports clothing (shorts and t-shirt) and barefoot. The standard conditions for the bioelectrical impedance analysis (BIA) method measurements are provided by the specific schedule of the study protocol; that is, the participants are placed in a supervised accommodation at the research centre about 15 hours prior to the BIA measurement. First, body height is measured using the InBody 370 stadiometer (Biospace, South Korea). This is followed by body mass and hydration status (total body water, intracellular and extracellular water), which are measured using the InBody 770 bioimpedance multifrequency scale device (Biospace). Lastly, body composition is measured using the dual-energy X-ray absorptiometry method. The measurement is executed using the Hologic Horizon A bone densitometer (Hologic Discovery A, Waltham, Massachusetts, USA). A whole-body scan is used for the analysis of body composition, including the segmental analysis, hip scans (right and left) and lumbar scan (L1–L4). The measured parameters are body fat, fat free mass, bone mineral content and bone mineral density. The position during measurement is presented in figure 2; figures 3–4 present the scans of the individual areas measured.

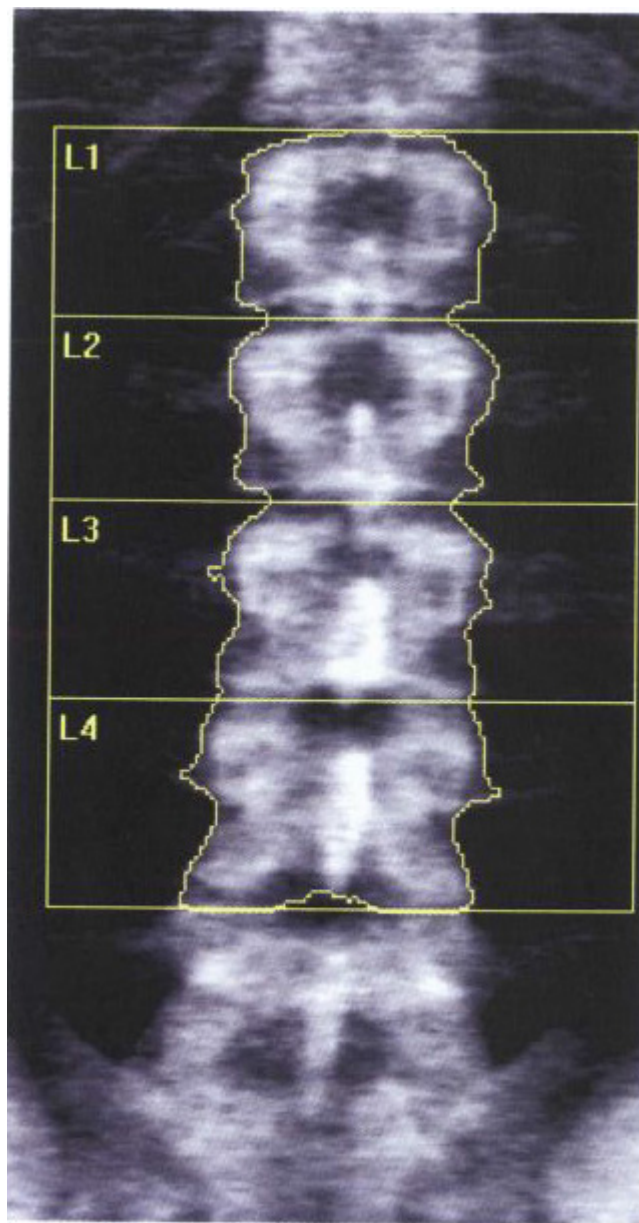
#### Data analysis

Sample size is not calculated since the number of participants in total as well as in each subgroup (figure 1) are considered sufficient to avoid an underpowered study. The number of participants is deliberately high because a follow-up, long-term prospective study is planned and some drop-outs are expected for the second wave of measurements.

The high air-polluted versus low air-polluted group data are assessed for differences in health-related and performance variables using adjusted and unadjusted mixed methods regression, with potential contributing variables such as age, sex and physical activity level. All data are checked for distribution and homoscedasticity. Where these two assumptions are violated, data are analysed using a non-parametric analysis. Analyses are performed using IBM SPSS Statistics 24 and GraphPad Prism 9.0.0 with statistical significance set at  $p < 0.05$ .

#### DISCUSSION

Ambient AP is a global environmental health problem, which caused around 4.2 million premature deaths worldwide in 2016, both in cities and rural areas.<sup>45</sup> Exposure to  $PM_{2.5}$  or less in diameter and ozone has been associated with an increased risk of death, even at levels below the air quality standards annual mean limits for  $PM_{2.5}$ .<sup>46 47</sup> AP exposure may suppress the early immune response to infection, including infectious respiratory diseases such as influenza, pneumonia and severe acute respiratory syndrome. Furthermore, an increase of only  $1 \mu\text{g}/\text{m}^3$  in  $PM_{2.5}$  has been significantly associated with an 8% (95% CI 2% to 15%) increase in the COVID-19 death rate.<sup>5</sup>



**Figure 4** Spine scan (L1–L4).

Regular physical activity and exercise have been proven to produce a number of health and fitness related benefits<sup>48</sup> and are therefore integral to all well-being guidelines within primary and secondary prevention,<sup>29</sup> as well as rehabilitation for patients suffering from chronic diseases.<sup>49 50</sup> Additionally, cardiorespiratory fitness, as well as strength, are strongly related to mortality risk.<sup>51–53</sup> Since physical activity and/or exercise is commonly performed in outdoor conditions, a question arises about the negative health effects of greater long-term exposure to AP from habitual outdoor exercise.<sup>14 15</sup>

This study is unique as it aims to investigate the global environmental problem (ie, AP) in large cohorts of runners and inactive individuals permanently living in areas with high and low AP. It has been suggested that a broader strategy beyond healthcare that includes investments in social services, improved environmental quality

(eg, AP), and health behaviours could improve the health of communities as well as bring substantial economic benefits.<sup>54 55</sup> Additionally, this interdisciplinary research project is intended also to set up a longitudinal prospective study with follow-up waves of measurements. The results might show the real cost–effect ratio of outdoor endurance exercise performed habitually in an air-polluted environment. From the long-term perspective, it can be hypothesised that the health benefits of regular outdoor physical activity will be diminished by adverse environmental factors. However, it can further be hypothesised that regular outdoor physical activity will decrease the adverse health effects of AP. A deeper understanding of the relationship between AP and exercise is important for all physically active individuals, as well as authorities publishing physical activity recommendations for the general population and public services authorities in affected regions.

## ETHICS AND DISSEMINATION

The 4HAIE study is conducted in accordance with the Declaration of Helsinki. The study protocol has already been approved by the Ethics Committee of the University of Ostrava (3/2018). A detailed participant information sheet is provided to each individual prior to them providing written informed consent. The study poses little to no risk to participants.

The findings of this study will be disseminated at regional and international conferences, in peer-reviewed journals and via social and broadcast media.

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**Contributors** LC and PK conceptualised and designed the study, drafted the initial manuscript and critically revised it; TD, MZ, MK, RS and DJ reviewed the manuscript; VJ critically revisited the heart rate variability and methodological part of this manuscript for important intellectual content; PH critically revisited the manuscript for important intellectual content.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

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