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Exposure to ambient particulate matter increases blood count parameters with potential to mediate a cardiovascular event: results from a population-based study in Portugal

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Abstract

Variations in blood count parameters are potential mechanisms involved in the occurrence of cardiovascular events caused by particulate matter (PM) exposure. This study aims to estimate the effect of PM_{10} exposure on blood count parameters with potential to mediate a cardiovascular event. We used data from 2211 participants of the 1st Portuguese Health Examination Survey (INSEF, 2015) with available information on blood count parameters and living within a 30-km radius of at least one air quality monitoring station with available PM_{10} measurements. Generalised linear models were used to assess both short (3 days) and long-term effects (1 year) of PM_{10} exposure on blood count parameters. Both short and long-term PM_{10} effects on blood count parameters were found, with males and females affected in a different way. In the short-term scenario, we found a 2.76% (95% CI: 0.65–4.87) increase in white blood cells among females per each 10μg/m^3 PM_{10} increment. Additionally, there was a 2.96% (95% CI: 0.80–5.12) increase in red cell distribution width (RDW), per each 10μg/m^3 PM_{10} increment, among males, when considering the long-term scenario. In conclusion, we detected some sex-differential associations regarding the short and long-term effect of PM_{10} exposure on blood count parameters with potential to mediate a cardiovascular event, namely on the RDW parameter, that were never been described. It is uncertain whether changes in blood count parameters due to PM_{10} exposure constitute an adverse health outcome or it reflects only a normal immunity response. However, due to its potential to trigger cardiovascular events, it is essential to reduce PM_{10} levels exposure to protect the population's cardiovascular health.

Keywords Particulate matter · INSEF 2015 · Blood counts · Leucocytes · Platelets · RDW

Introduction

Ambient particulate matter (PM) is now a well-established risk factor to develop cardiovascular diseases, with more than two thirds of the mortality attributed to PM arising from cardiovascular causes, namely cerebrovascular and ischaemic heart diseases (Cohen et al. 2017; Miller and Newby 2020). Multiple studies have linked PM exposure to both fatal and non-fatal cardiovascular events, but the pathophysiologic mechanisms linking the occurrence of these events with PM exposure are still an area of intensive research and scientific debate (Hamanaka and Mutlu 2018; Pranata et al. 2020; Scheers et al. 2015).

Blood count parameters, namely white blood cells (WBC), red blood cells (RBC) and platelets (PLAT) have a crucial role in atherosclerosis, one of the underlying conditions to trigger a cardiovascular event (Lassale et al. 2018). Consequently, it is plausible to hypothesise that changes in blood count parameters caused by PM exposure are potential mechanisms mediating the effects of PM on cardiovascular health. In fact, evidence from animal studies shows that acute exposure to ambient PM seems to produce cytokines in the lung that will stimulate the bone marrow to release leucocytes and platelets contributing, in conjunction with another proinflammatory

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and prothrombotic markers, to destabilisation of atherosclerotic plaques, making them more vulnerable to rupture and thrombosis (Mukae et al. 2001; Peters et al. 2001; Van Eeden and Hogg 2002). Additionally, the cytokines produced in the lung due to the deposition of PM can potentially interact with erythropoietin in the bone marrow, lowering the RBC cells production and suppress RBC maturation. This will lead to an immature RBC increase and, thus higher red cell distribution width (RDW) values (Lassale et al. 2018; Van Eeden and Hogg 2002), originating an anaemic condition with increased cardiovascular risk in proatheroscleroctic situations (Mozos 2015).

Some epidemiologic studies already found associations between both short and long-term PM exposure and blood count parameters, namely WBC (Gondalia et al. 2020; Lee et al. 2018), RBC (Elbarbary et al. 2020; Poursafa et al. 2011) or platelet count (Hou et al. 2020; Zhang et al. 2018) but results remain controversial (Dabass et al. 2016; Liao et al. 2005) and studies on this topic are still scarce. Consequently, the present study aims to estimate the short and long-term effects of PM_{10} exposure (PM_{10}: particles with an aerodynamic equivalent diameter ≤10μm) on blood count parameters potentially related to cardiovascular risk (WBC, white blood cells count; PLAT, platelet count; RBC, red blood cells count; HEMOG, haemoglobin; and RDW, red cell distribution width) in the adult Portuguese mainland population.

Material and methods

Study population

This study was conducted using data from the 1st Portuguese National Health Examination Survey (INSEF), collected between February and December 2015 (Nunes et al. 2019). INSEF was a cross-sectional population-based survey led by the National Health Institute Doutor Ricardo Jorge (INSA) in partnership with the five Regional Health Administrations from mainland Portugal, the two Regional Health Secretariats from the Autonomous Regions of Azores and Madeira and the Norwegian Institute of Public Health. This survey included a physical examination, a blood collection and an interview using a structured health questionnaire. The INSEF target population was non-institutionalised individuals aged between 25 and 74 years old, living in Portugal for more than 12 months and who were able to follow an interview in Portuguese. The INSEF sample (n=4911) was selected through complex multistage probabilistic design to be representative of the Portuguese population at national and regional levels (Nunes et al. 2019). For this study, the analysis was restricted to the subsample of INSEF participants from mainland Portugal with informed consent to link data, available data on zip code address number, living within a 30-km radius of an air quality monitoring station with available PM_{10} concentration values and available data on blood count parameters (WBC, PLAT, RBC, HEMOG and RDW) (n=2211). The flow diagram of the participants' selection can be found in Figure S1 (available in the Supplementary information section).

The INSEF survey received approval from the Ethics Committee of the Portuguese National Health Institute Doutor Ricardo Jorge, the National Data Protection Authority (Authorization n° 9348/2010) and from the regional Ethics Committees. Moreover, Ethics Committee of the Portuguese National Health Institute Doutor Ricardo Jorge approved the study protocol of this particular research. All participants provided informed consent before data collection.

Health and sociodemographic data

Health data collection occurred at primary care level venues and was performed by trained health professionals. It included core physical measurements (blood pressure, height, weight and waist and hip circumference), a blood collection to perform blood tests, including blood count parameters (WBC, units/μL; PLAT, units/μL; RBC, units/μL; HEMOG, g/dL and RDW, %) and a computer assisted personal interview (CAPI), according to the European Health Examination Survey (EHES) procedures (Tolonen 2013).

Blood count was performed in fresh non-fasting whole blood samples in the 12 regional collaborating laboratories that participated in the National Program for External Quality Assessment (PNAEQ) to assure comparability and reliability of blood tests results.

Using the WHO criteria, anaemia was defined as the haemoglobin concentrations below 13 g/dL in men and below 12 g/dL in women (WHO 2011)

Sociodemographic (age, sex, educational level and occupation) and lifestyles variables (smoking, excessive alcohol consumption, sedentary and unhealthy diet) were obtained by self-report through the interview.

Regarding educational level, we considered the highest level of education completed, grouped into 3 categories, according to the aggregate levels of education presented in International Labour Organization (ILOSTAT): low education (levels 0–2 of the ISCED 2011), medium education (levels 3–4 of the ISCED 2011) and high education (levels 5–8 of the ISCED 2011) (UNESCO 2012; ILOSTAT 2020). Occupation was grouped according to the International Standard Classification of Occupations (ISCO-08) (International Labour Office 2012) into 2 categories: white-collar occupation (Managers, Professionals, Technicians and Associate Professional, Clerical Support Workers and Services and Sales Workers) and blue-collar occupation (Skilled Agricultural Workers, Craft and Related trades Workers, Plant and Machine Operators and Elementary occupations).

Regarding the lifestyles related variables, smokers include current daily and occasional smokers, and excessive alcohol consumption was defined as reporting 3 or more days/week of consumption of at least one of the following alcoholic beverages: wine, beer, brandy/bagasse, port wine/martini/liqueur, whisky/gin/vodka. Self-reported unhealthy diet was based on the question: "How often do you eat fruit/vegetables (excluding juice and potatoes)?" Individuals who reported eating fruit and vegetables less than once a day were considered to have an unhealthy diet. Self-reported sedentary was based on the question: "Which of these situations best describes your leisure time activities during the last 12 months?" Individuals who answered "Reading, watching TV and other sedentary activities" were considered to be sedentary.

Environmental exposure assessment

PM_{10} values were obtained from the QualAr database, available online at the Portuguese Environment Agency (APA) website (https://qualar.apambiente.pt/). APA provides hourly observation data for different atmospheric pollutants, measured by 68 air quality monitoring stations that are classified according to the type of environment (demographic area) they represent (rural, urban and suburban) and the influence in terms of dominant atmospheric emission sources (background, traffic and industrial). The PM_{10} hourly data collected from the air quality monitoring stations reported to the period between February 2014 and December 2015, to cover the previous year of exposure before the INSEF examination day to all participants (INSEF fieldwork occurred between February and December 2015).

We assumed the exposure window period of 1 year as being representative of the long-term PM_{10} exposure for all study participants as they reported to live in the same place (same zip code number) at least 1 year before the INSEF examination day. Moreover, taking into account the published scientific evidence suggesting that acute particulate matter effects on the occurrence of cardiovascular events are generally larger at very shorter periods of time (few days) (Kim et al. 2012), we also considered the exposure window period of the 3 previous days before the examination date in order to assess the short-term PM_{10} exposure effects.

To reduce the exposure misclassification, only participants living within a 30-km radius of at least one air quality monitoring station with available PM_{10} values collected during the study exposure window periods (1-year average and 24-h average in the previous 3 days) were included. Moreover, only background stations with data collection efficiency of at least 75% (with at least 75% of the hourly values regarding the 24-h averages and at least 75% of the daily values regarding the 1-year average) were considered. The geographic distribution of the participants (zip code address number) and the 33 background air quality monitoring stations used to assess the individual allocated PM_{10} concentrations are shown in Fig. 1.

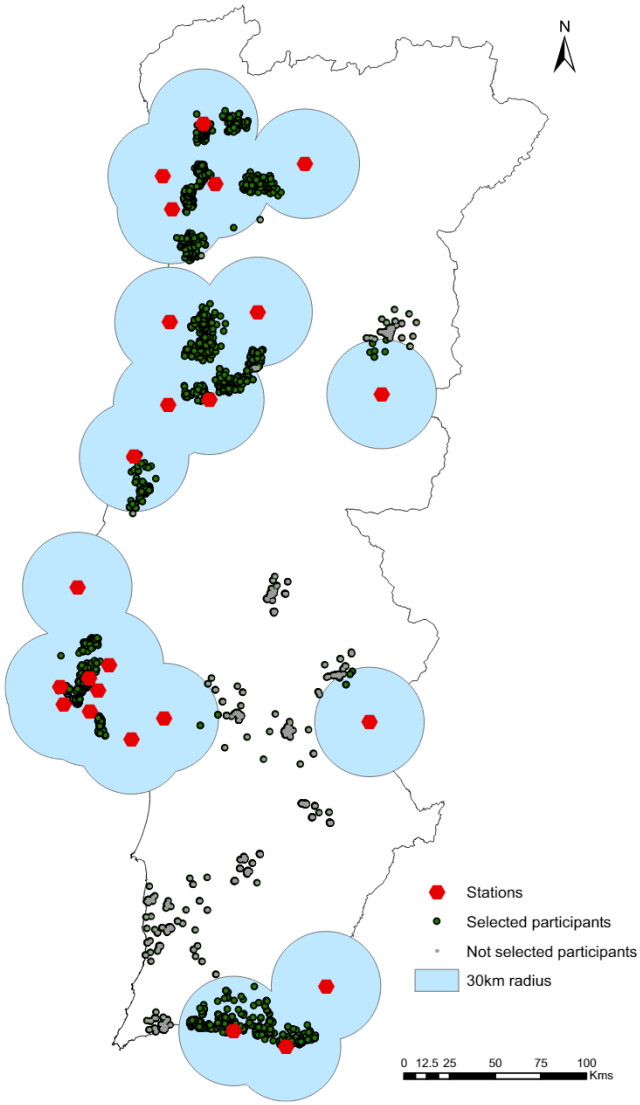


Fig. 1 Geographic distribution of the participants and the 33 background air quality monitoring stations with available PM_{10} data during the study period. Red points represent the air quality monitoring stations, green points represent the INSEF Portuguese mainland participants and blue circles represent the 30 km radius from each station. The grey points not covered by the blue circles are the excluded participants (names of the air quality monitoring stations: Alverca, Anta-Espinho, Arcos, Avintes, Burgães-Santo Tirso, Cerro, Custóias-Matosinhos, Douro Norte, Ermesinde-Valongo, Ervedeira, Fernando Pó, Fidalguinhos, Fornelo do Monte, Frossos-Braga, Fundão, Ílhavo, Instituto Geofísico de Coimbra, Joaquim Magalhães, Laranjeiro, Leça do Balio-Matosinhos, Loures-Centro, Lourinhã, Malpique, Mem Martins, Mindelo-Vila do Conde, Montemor-o-Velho, Olivais, Paços de Ferreira, Quinta do Marquês, Reboleira, Sobreiras-Lordelo do Ouro, Terena and VNTelha-Maia)

Daily (24 h) average PM_{10} concentrations were calculated, in all INSEF fieldwork days, using the hourly observation values from each station. One-year average PM_{10} concentrations were estimated for each station, in all INSEF fieldwork days, using the preceding 365-daily average PM_{10} concentrations values.

For each individual the allocated average PM_{10} concentrations (3-day average, 1-year average) was the weighted average of PM_{10} concentrations from all stations within 30 km from that participant's residence. This average was weighted by the inverse of the squared distance between the residence and the air quality monitoring stations. The location of the measurement stations and participant's residences (zip code number) were identified and managed by geographic information system (ArcGIS version 10.4) (ESRI 2019).

For each individual, the allocated ambient temperatures (3-day average, 1-year average) were obtained using data from the National Oceanic and Atmospheric Administration (NOAA) database (www.ncdc.noaa.gov). We assumed the value of the closest temperature monitoring station as being representative of the Individual allocated temperature exposure.

Statistical analysis

The statistical analysis was performed using the R program (version 3.6.3) (R Core Team 2020). The significance level for all analysis was set at 5%. Sampling weights were used in data analysis. All estimates were weighted to account for different selection probabilities resulting from complex sample design and to match the population distribution in terms of geographic region, age group and sex, in 2015.

Regarding the general characteristic's description, the t-test and the Wilcoxon test were used to access differences of quantitative variables according to their adherence to the normal distribution or not. Proportions were compared using Pearson's chi-square test.

We constructed a directed acyclic graph (DAG) shown in Fig. 2 based on literature review to select a minimal sufficient adjustment set of variables needed to account for confounding of the exposure-outcome relationship. This analysis was performed using the "DAGitty" R package (Textor et al. 2016). Accordingly, the minimal sufficient adjustment set of variables were age, sex, socioeconomic status (educational level and occupation), lifestyles (smoking, excessive alcohol consumption, unhealthy diet and sedentary) and ambient air temperature.

Primary analysis

Regression coefficients (β) regarding the effect of PM_{10} on WBC, PLAT, RBC, HEMOG and RDW with the corresponding 95% confidence intervals (CI) were obtained by generalised linear regression models analyses for each 10-$\mu g/m^3$ increment of PM_{10}. Then, percent change with corresponding 95% CIs were calculated by using the formula $100 \times [\exp(\beta*10)-1]$. We used the svyglm function from the "survey" R package to run each Gaussian family model with a link function log (family = gaussian(link = "log")).

First, an unadjusted exposure-outcome model was fitted for each outcome (WBC, PLAT, RBC, HEMOG and RDW) in both short and long-term exposure periods, considering respectively the 3 previous days' average of PM_{10} concentrations and 1 previous year average of PM_{10} concentrations as exposure variables. Then, a second model confounder-adjusted for sex (2 categories: Male/Female), age group (2

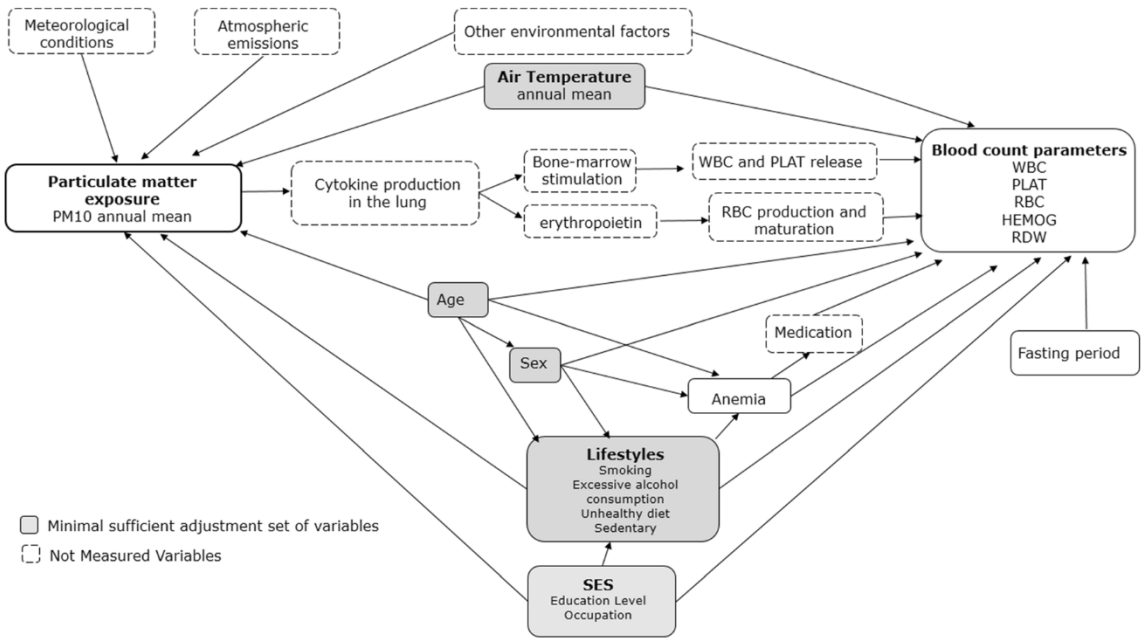


Fig. 2 A Directed Acyclic Graph (DAG) for the association between particulate matter exposure and blood count parameters. Abbreviations: WBC, white blood cells count; PLAT, platelet count; RBC, red blood cells count; HEMOG, haemoglobin; and RDW, red cell distribution width; PM, particulate matter

categories: < 50 years old; ≥50 years old), educational level (3 categories: Low education/Medium education/High education), occupation (2 categories: white-collar occupation/blue-collar occupation), smoking (2 categories: smoker/no smoker), excessive alcohol consumption (2 categories: Yes/No), sedentary (2 categories: Yes/No), unhealthy diet (2 categories: Yes/No) and individual allocated temperature (continuous) was performed for each outcome in both short and long-term exposure periods. Additionally, in the models assessing the short-term effects of PM_{10} exposure, an adjustment for the long-term effect of PM_{10} was also performed by adding the variable 1 previous year average of PM_{10} concentrations.

Moreover, taking into account the published scientific evidence suggesting sex-related differences regarding the PM endocrine-disrupting effects on blood elements, due probably to different hormones levels such as estrogens involved in blood cells formation at bone marrow level (Nagata et al. 2003; Rudel and Perovich 2009; Zhang et al. 2018), we also fitted the same models in a sex-stratified analysis (males/females).

Sensitivity analysis

We assess the sensitivity of our analysis to the assumption that PM_{10} concentrations obtained from the air quality monitoring stations within a 30 km from the participant's residence were representative of their exposure. For that, we fit the models for each outcome and for each exposure window period considering only participants living within a 20 km radius of an air quality monitoring station with available PM_{10} measurements.

Additionally, to evaluate the sensitivity of our analysis regarding the exposure assessment method, we also fit the models considering the modelled PM_{10} concentrations obtained by the application of an air quality modelling system composed by the Weather Research and Forecasting (WRF, version 3.7.1) (Skamarock 2008) and Comprehensive Air Quality Model with Extensions (CAMx, version 6.40) (ENVIRON 2018). The WRF-CAMx system has been extensively applied for Portugal and worldwide and it is described in more detail elsewhere (Ferreira et al. 2020; Sá et al. 2016; Wang et al. 2018). Briefly, in our study, CAMx was applied to the whole years of 2014 and 2015 following a downscaling approach, using two nested domains, the first domain covering the European region with 25×25 km^2 grid spacing and the second domain over Portugal with a dimension of 475 km by 625 km, gridded as 95 by 125 cells of 5×5 km^2 horizontal spatial resolution. To initialize and drive the WRF meteorological simulation (ENVIRON 2018; Skamarock 2008) ERA Interim reanalysis data was used, including three dimensional (3D) fields of wind, temperature, and relative humidity and 2D field of surface pressure, among others, from ECMWF (European Centre for Medium Range Weather Forecast) at 6 h and 0.75 degrees temporal and spatial resolution, respectively. Other inputs comprise anthropogenic emissions of atmospheric pollutants and initial and boundary conditions for the CAMx European domain taken from the outputs (3D concentration fields of gaseous and particulate species) of the global chemical model MOZART (NCAR 2010) at every 6 h. CAMx returns surface hourly average concentrations of simulated species by grid cell that were used to compute PM_{10} daily averages in 2014 and 2015. Participants living within a 30-km radius of at least one air quality monitoring station (zip code address number) were linked to the correspondent grid cell and PM_{10} daily averages of each grid cell were considered being representative of the individual exposure. The preceding 365-daily average PM_{10} concentrations at the INSEF examination day were considered to obtain the individual allocated 1-year average PM_{10} concentrations. The preceding 24-h average on the 3 days before the INSEF examination day was considered to obtain the individual allocated 3-day average PM_{10} concentrations.

Finally, we also repeat the primary analysis after excluding the participants with anaemia to confirm our results in the participants with normal haemoglobin levels.

Additionally, in the models assessing the short-term effects of PM_{10} exposure we also repeat the analysis considering the 2 and 5 previous days' average PM_{10} concentrations instead of the 3 previous day's average PM_{10} concentrations considered in the primary analysis.

Results

General characteristics of participants

A comparison of the INSEF mainland participants included and excluded from our study is presented in Table S1 of the supplementary material. Included and excluded participants were similar regarding all of the analysed characteristics (Table S1 of the Supplementary Material).

General characteristics of the included participants, in both males and females, are presented in Table 1. Among the 2211 participants in our study, 53.4 % aged between 25 and 49 years old, 58.2% had low education level and 63.0% had a white-collar occupation. Regarding the lifestyles variables, 21.1% of the participants were smokers, 36.1% were excessive alcohol consumers, 36.1% reported to had an unhealthy diet and 45.1% reported to have a sedentary lifestyle. The prevalence of anaemia was 5.2%, being higher in females (7.5%) when compared to males (2.7%). Sex differences were also found regarding level of education, occupation, percentage of smokers, excessive alcohol consumers and of those reporting to have an unhealthy diet (Table 1). Individual allocated 1-year average temperature was 15.9 °C and individual allocated 3-day average was 16.0 °C.

Table 1 General characteristics of the study participants, according to sex

Characteristics	Females (*n*=1195)	Males (*n*=1016)	Total participants (*n*=2211)
Age (*n*=2211) (%)			
25–49 years old	52.8	54.0	53.4
50–74 years old	47.2	46.0	46.6
[a]Level of education (*n*=2210) (%)			
Low education	**54.6**	**62.2**	**58.2**
Medium education	**21.7**	**21.5**	**21.6**
High education	**23.7**	**16.3**	**20.2**
[b]Occupation (*n*=2047) (%)			
White-collar occupation	**69.6**	**56.1**	**63.0**
Blue-collar occupation	**30.4**	**43.9**	**37.0**
Lifestyles variables (%)			
[c]Smokers (*n*=2211)	**16.2**	**26.5**	**21.1**
[d]Excessive alcohol consumers (*n*=2210)	**20.3**	**53.4**	**36.1**
[e]Unhealthy diet (*n*=2210)	**27.0**	**46.1**	**36.1**
[f]Sedentary (*n*=2198)	41.7	48.1	45.1
Anaemia (*n*=2191) (%)	**7.5**	**2.7**	**5.2**
Individual allocated temperature (*n*=2211) (°C (mean ± sd))			
1-year average	15.9±4.1	16.0±4.0	15.9±4.0
3-day average	16.1±4.0	16.1±4.0	16.0±4.0

[a] Low education: levels 0–2 of the ISCED 2011; medium education: levels 3–4 of the ISCED 2011; high education: levels 5–8 of the ISCED 2011

[b] White-collar occupation: Managers, Professionals, Technicians and Associate Professional, Clerical Support Workers and Services and Sales Workers; Blue-collar occupation: Skilled Agricultural Workers, Craft and Related trades Workers, Plant and Machine Operators and Elementary occupations

[c] Smokers include current daily and occasional smokers

[d] 3 or more days/week of consumption of at least one of the following alcoholic beverages (wine, beer, brandy/bagasse, port wine/martini/liqueur, whisky/gin/vodka)

[e] No consumption of fruit and vegetables at least once a day

[f] Reading, watching TV or other sedentary activities declared as the best description of the leisure time activities during the last 12 months

Results in bold are those with statistically significant difference between females versus males, according to the Pearson's chi-square test ($p<0.05$)

The distribution of the individual allocated PM_{10} concentrations in the different analysed exposure windows is described in Table 2. The mean value of the individual allocated 1-year average PM_{10} concentration was 17.5 μg/m^3 (median = 18.4 μg/m^3, IQR=15.2–19.2 μg/m^3). The mean value of the individual allocated 3-day average PM_{10} concentration was 18.6 μg/m^3 (median = 17.2 μg/m^3, IQR=12.0–24.3 μg/m^3) and there were no differences between females and males (Table 2). The mean values of RBC, HEMOG, RDW, WBC and PLAT were 4.7x10^{6}units/μL, 14.1 g/dL, 13.2%, 7.3 × 10^{3}units /μL and 233 × 10^{3}units/μL, respectively. Sex differences were found regarding RBC, HEMOG, RDW and PLAT values (Table 2).

Short-term effects of PM on blood count parameters

Results concerning the association of short-term exposure to PM_{10} with blood count parameters are shown in Fig. 3. There was an association between PM_{10} and WBC values (2.08% WBC increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 0.42%; 3.73%) after adjustment for age, sex, educational level, occupation, lifestyle variables and individual allocated 3-day average mean temperature, respectively. In the sex-stratified analysis, this association maintains only among females (2.76% WBC increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 0.65%; 4.87). The estimates and respective 95% confidence intervals presented in Fig. 3 are available in Table S2 of the supplementary material.

Table 2 Distribution of the individual allocated PM_{10} values and blood count parameters, according to sex

	Total		Females		Males	
	Mean ± sd	Median (Q1–Q3)	Mean ± sd	Median (Q1–Q3)	Mean ± sd	Median (Q1–Q3)
Individual allocated PM_{10}						
1-year average	17.5±3.0	18.4 (15.2–19.2)	17.5±3.0	18.4 (15.2–19.2)	17.5±3.0	18.4 (15.2–19.2)
3-day average	18.6±8.3	17.2 (12.0–24.3)	18.6±8.4	17.2 (12.0–24.4)	18.6±8.3	17.2 (12.0–24.1)
Blood count parameters						
RBC (10^6 units/μL)	**4.7±0.4**	**4.7 (4.4–5.0)**	**4.5±0.3**	**4.5 (4.2–4.7)**	**4.9±0.4**	**5.0 (4.7–5.2)**
HEMOG (g/dL)	**14.1±1.3**	**14.1 (13.2–15.1)**	**13.3±1.0**	**13.3 (12.7–13.9)**	**15.1±1.0**	**15.1 (14.4–15.7)**
RDW (%)	**13.2±0.9**	**13.1 (12.7–13.6)**	**13.3±1.1**	**13.1 (12.7–13.7)**	**13.2±0.8**	**13.1 (12.7–13.5)**
WBC (10^3 units/μL)	7.3±2.0	7.0 (5.9–8.4)	7.3±2.0	7.0 (5.9–8.5)	7.3±1.9	7.0 (6.0–8.3)
PLAT(10^3 units/μL)	**233±56**	**227 (195–266)**	**246±57**	**240 (207–281)**	**219±52**	**215 (184–249)**

Results in bold are those with statistically significant difference between females versus males, according to the Wilcoxon test ($p<0.05$)

Abbreviations: *PM*, particulate matter; *sd*, standard deviation; *RBC*, red blood cells count; *HEMOG*, haemoglobin; *RDW*, red cell distribution width; *WBC*, white blood cells count; *PLT*, platelet count

Regarding the sensitivity analysis, when we restricted our analysis to participants without anaemia (Fig. 4), similar results were found. Per each 10 μg/m^3 PM_{10} increment, there was a 2.34% (95% CI: 0.69; 3.99) increase in the WBC values after confounding adjustment, when considering the total sample, and a 3.38% (95% CI: 1.15; 5.63) increase in the WBC values, when considering only females.

When we restricted our sample to the participants living within a 20 km radius of an air quality monitoring station with available PM_{10} values, similar results were found when considering the total sample and also when considering only females. Per each 10 μg/m^3 PM_{10} increment, there was a 3.56% (95% CI: 0.72–6.48) increase in the WBC values.

When we considered a different exposure period of time (2 previous days instead of 3 previous days), similar results were found but only among females. Per each 10 μg/m^3 PM_{10} increment, there was a 3.07% (95% CI: 0.96–5.18) increase in the WBC values. On the other hand, when we considered the 5 previous days as the exposure period of time, no associations were found. Additionally, when we considered the individual allocated PM_{10} concentrations obtained by the air quality modelling system (WRF-CAMx), no associations were also found. The estimates and respective 95% confidence intervals presented in Fig. 4 are available in Tables S3 to S7 of the supplementary material.

Long-term effects of PM on blood count parameters

Results concerning the association of long-term exposure to PM_{10} with blood count parameters are shown in Fig. 5. We found an association between individual allocated 1-year average PM_{10} concentrations and RDW (2.82% RDW increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 0.62%; 5.02%)

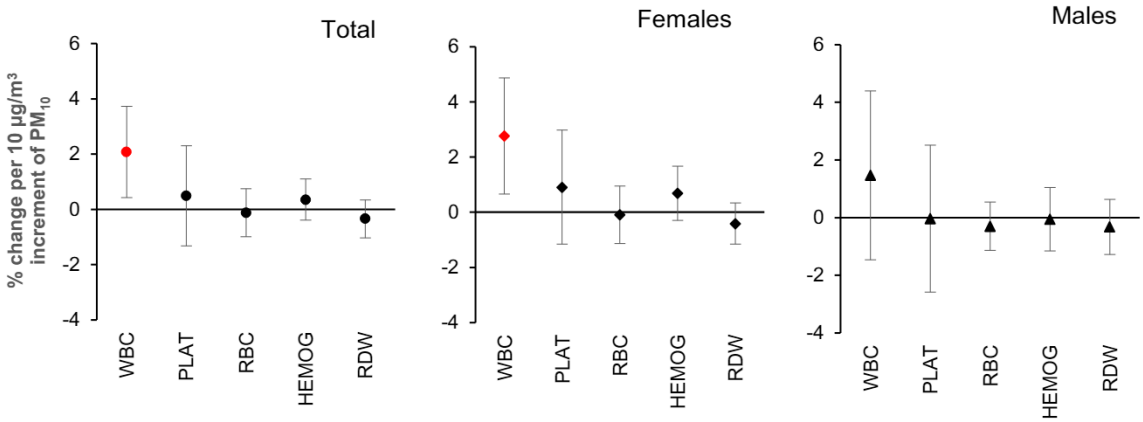
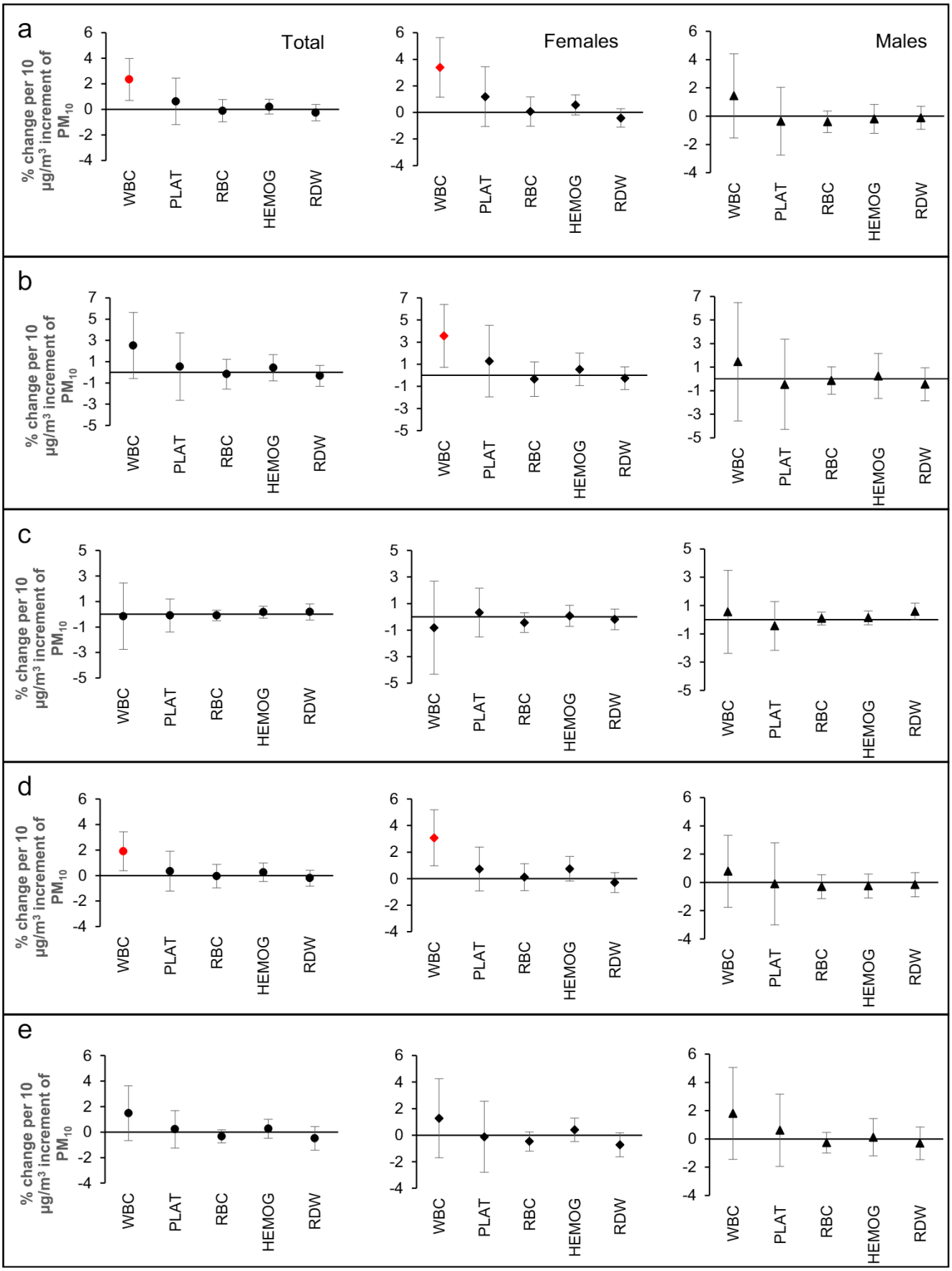


Fig. 3 Percent changes in WBC, PLAT, RBC, HEMOG and RDW per 10 μg/m^3 increment of PM_{10} according to sex in the short-term exposure scenario (3 previous day average PM_{10} concentrations). Estimates in red are those statistically significant ($p<0.05$). Abbreviations: PM, particulate matter; WBC, white blood cells count; PLT, platelet count; RBC, red blood cells count; HEMOG, haemoglobin; RDW, red cell distribution width


a
Total
Females
Males
b
c
d
e
% change per 10 µg/m³ increment of PM10
WBC
PLAT
RBC
HEMOG
RDW

◀ **Fig. 4** Percent changes in WBC, PLAT, RBC, HEMOG and RDW per 10 μg/m^3 increment of PM10 according to sex in the short-term exposure scenario (3 previous days' average PM10 concentrations) **a** after exclusion of participants with anaemia, **b** after restricting participants to those living within a 20-km radius of at least one air quality monitoring station with available PM_{10} measurements, **c** considering the PM_{10} obtained by the air quality modelling system (WRF-CAMx), **d** considering the 2 previous days' average PM_{10} concentrations, **e** considering the 5 previous days' average PM_{10} concentrations. Estimates in red are those statistically significant (p<0.05). Abbreviations: PM, particulate matter; WBC, white blood cells count; PLT, platelet count; RBC, red blood cells count; HEMOG, haemoglobin; RDW, red cell distribution width

and PLAT (3.31% PLAT increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 0.61%; 6.01%) after adjustment for confounding, when considering all participants.

In the sex-stratified analysis, the association between PM_{10} and RDW was only present among males (2.96% RDW increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 0.80%; 5.12%). In this sex category, we additionally found an association between PM_{10} and WBC (5.78% WBC increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 1.46%; 10.13%). The estimates and respective 95% confidence intervals presented in Fig. 5 are available in Table S8 of the supplementary material.

Regarding the sensitivity analysis, when we restricted our analysis to participants without anaemia (Fig. 6), similar results were found. There is an association between individual allocated 1-year average PM_{10} concentrations and RDW (2.99% RDW increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 0.81%; 5.18%) and PLAT (4.01% PLAT increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 1.26%; 6.76%) after adjustment for confounding, when considering all participants. In the sex-stratified results, both associations remains among males (2.82% RDW increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 0.69%; 4.97%; and 3.63% PLAT increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 0.44%; 6.82%) but not among females. Additionally, among males, there is an association between PM_{10} and WBC (5.67% WBC increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 0.87%; 10.49%).

When we restricted our sample to the participants living within a 20 km radius of an air quality monitoring station with available PM_{10} values, we only found an association between PM_{10} and RDW (3.08% RDW increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 1.63%; 4.53%). Through sex-stratified analysis, this association remains among both females (3.09% RDW increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 0.18%; 6.02%) and males (3.38% RDW increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 1.02%; 5.76%).

Similarly, when we considered the individual allocated PM_{10} concentrations obtained by the air quality modelling system (WRF-CAMx), we only found an association between PM_{10} and RDW (1.59% RDW increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 0.17%; 3.01%) that only persists among males in the stratified analysis (1.58% RDW increase per each 10 μg/m^3 PM_{10} increment, 95% CI: 0.10%; 3.06%). The estimates and respective 95% confidence intervals presented in Fig. 6 are available in Tables S9 to S11 of the supplementary material.

Discussion

Key findings

Concerning the short-term effect of PM_{10} exposure on blood count parameters with potential to mediate a cardiovascular event, our study showed an association between PM_{10} concentrations and WBC, mainly among females. This result was supported by the sensitivity analysis when considering only participants without anaemia, when considering a more

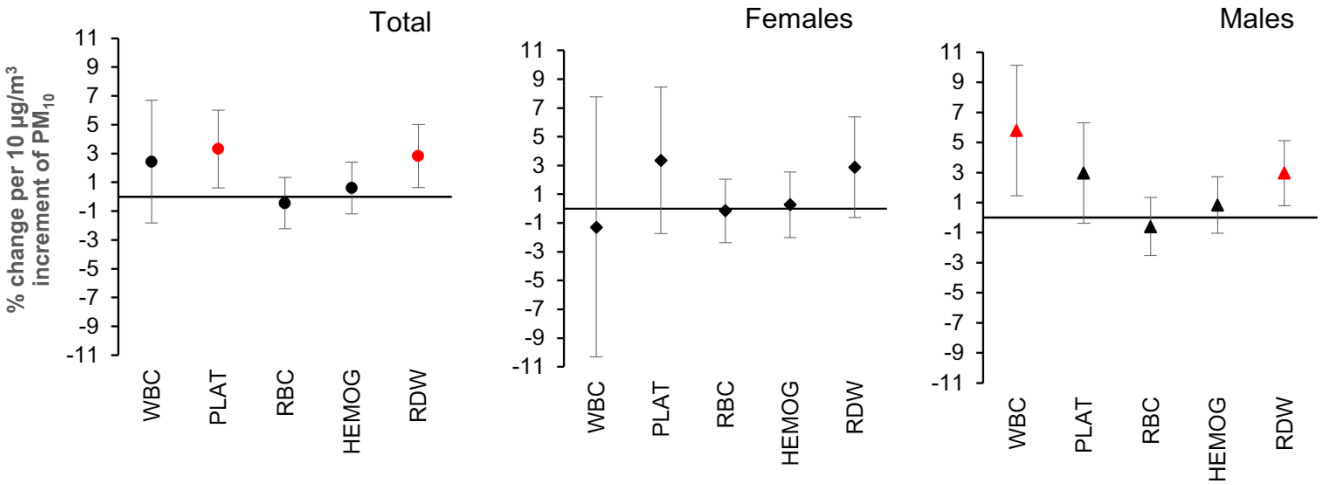


Fig. 5 Percent changes in WBC, PLAT, RBC, HEMOG and RDW per 10 μg/m^3 increment of PM_{10} according to sex in the long-term exposure scenario (1-year average PM_{10} concentrations). Estimates in red are those statistically significant (p<0.05). Abbreviations: PM, particulate matter; WBC, white blood cells count; PLT, platelet count; RBC, red blood cells count; HEMOG, haemoglobin; RDW, red cell distribution width

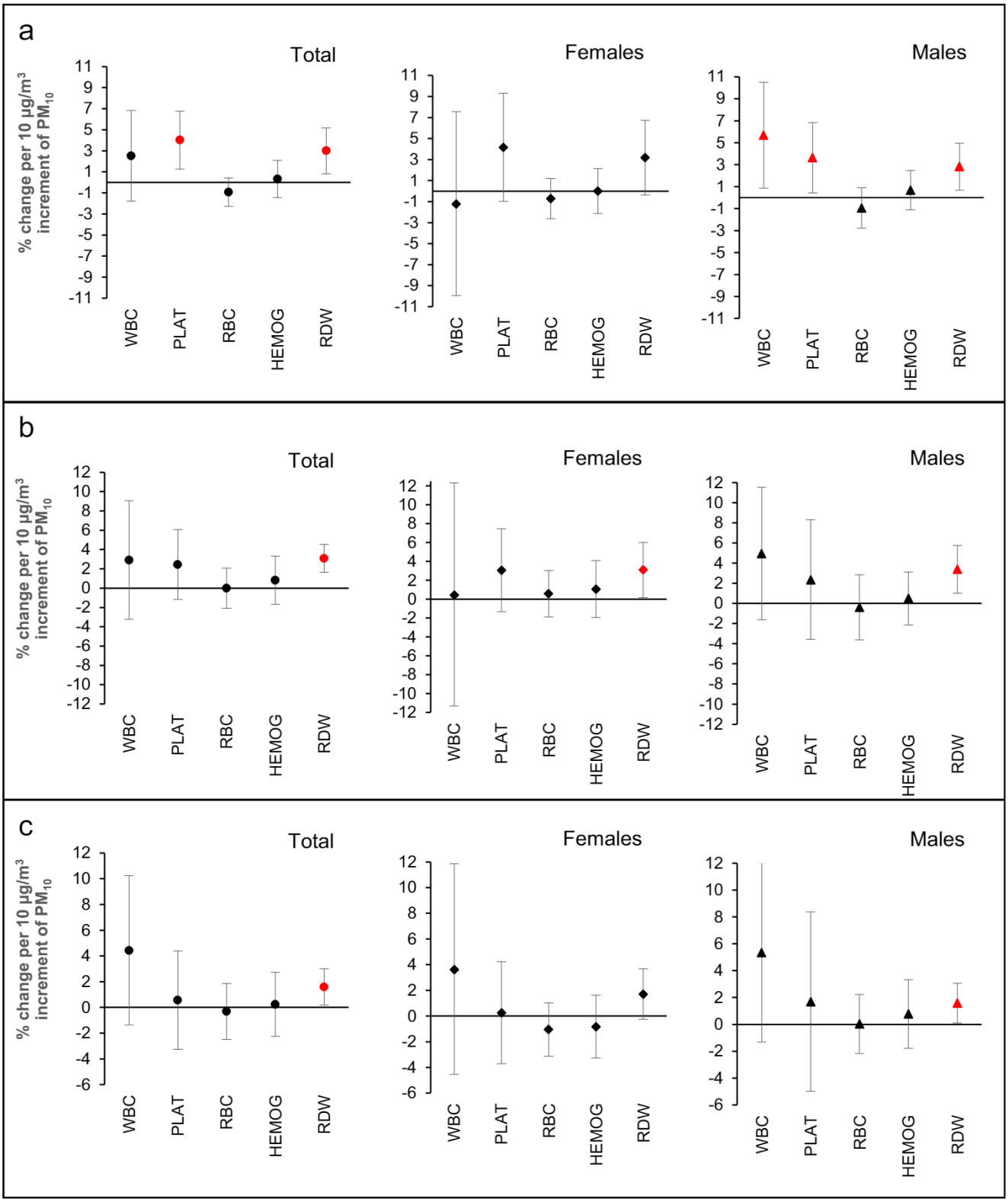


Fig. 6 Percent changes in WBC, PLAT, RBC, HEMOG and RDW per 10 µg/m^3 increment of PM_{10} according to sex in the long-term exposure scenario (1-year average PM_{10} concentrations) **a** after exclusion of participants with anaemia, **b** after restricting participants to those living within a 20-km radius of at least one air quality monitoring station with available PM_{10} measurements, **c** considering the PM_{10} obtained by the air quality modelling system (WRF-CAMx). Estimates in red are those statistically significant ($p<0.05$). Abbreviations: PM, particulate matter; WBC, white blood cells count; PLT, platelet count; RBC, red blood cells count; HEMOG, haemoglobin; RDW, red cell distribution width

restrictive criteria to the exposure assessment (participants living within a 20 km radius of an air quality monitoring station with available PM_{10} values) and when considering the 2 previous days instead of 3 previous days as the exposure period of time.

Regarding the long-term effect of PM_{10} exposure on blood count parameters, we found an association between PM_{10} concentrations and RDW values, but mainly among males, and this result was supported to all the performed sensitivity analysis. The associations between PM_{10} and WBC and PLAT, in the long-term scenario, were found only among males and they disappear on the sensitivity approach, when considering a more restrictive criteria to the exposure assessment (participants living within a 20 km radius of an air quality monitoring station with available PM_{10} values) and when considering the PM_{10} obtained by the air quality modelling system (WRF-CAMx).

Comparison with other published studies and interpretations

Despite the few number of epidemiologic studies reporting associations between both short and long-term PM_{10} exposure and blood count parameters, our results are in agreement with some of them. Lee and her colleagues (Lee et al. 2018), in 2018, found that increased WBC counts were associated with the long-term (1-year average) PM_{10} exposure (0.76% WBC increase per each 4.4 $\mu g/m^3$ PM_{10} increment, 95% CI: 0.42%; 1.10%) but not with the short-term (3-day average) PM_{10} exposure. In our study, we also found an association between the long-term (1-year average) PM_{10} exposure and WBC values, but only in males (5.78% WBC increase per each 10 $\mu g/m^3$ PM_{10} increment (95% CI: 1.46%; 10.13%). Additionally, we also found that increased WBC counts were significantly associated with the short-term exposure (3-day average) to PM_{10} but only among females (2.76% WBC increase per each 10 $\mu g/m^3$ PM_{10} increment, 95% CI: 0.65%; 4.87%). However, some methodological differences between the two studies could also explain the different obtained results (a hospital-based cohort study in South Korea versus a Health Examination Survey-based study in Portugal).

Taking into account the biological mechanism hypothesised to be the most contributor to the PM_{10} effect on WBC, it makes sense that the PM_{10} effects occurs soon in a short-term exposure period. Due to the PM_{10} deposition on lung, cytokines will be produced and will stimulate the bone marrow to produce and release WBC that have a crucial role on the inflammatory process (Van Eeden and Hogg 2002). In fact, experimental studies show that after an acute exposure to PM_{10} levels, the WBC elevation is a rapid mechanism, being detectable 24 h after exposure (Cozzi et al. 2007; Emmerechts et al. 2010). However, this process will depend on the dose to which individuals are exposed and, in the Portuguese context, it is expected that the most frequent exposure will be less acute and possibly more prolonged over time (Gama et al. 2018). Consequently, the PM_{10} exposure effect on the real context of the population will be different and comparison with experimental studies should be done with caution. Additionally, there are already some studies that support the importance of the long-term exposure effect of PM_{10} in blood parameters (Cozzi et al. 2007; Emmerechts et al. 2010; Hou et al. 2020) and other biological mechanisms must be considered in addition to the one described in our study.

Regarding our findings on the RDW parameter, we found an association between long-term exposure to PM_{10} and this blood parameter, mainly among males, which is well supported by the sensitivity analysis. To the best of our knowledge, this is the first study describing this association, although being biologically expected because cytokines produced in the lung due to the deposition of PM can potentially interact with erythropoietin in the bone marrow, suppressing RBC maturation and, thus, increase immature RBC which is reflected in the RDW parameter values (Lassale et al. 2018; Van Eeden and Hogg 2002). RDW has been identified as an independent prognostic biomarker of multiple cardiovascular diseases (Fava et al. 2019; Haybar et al. 2019; Parizadeh et al. 2019), therefore we consider this result to be of special relevance in particular to explain the effect of PM_{10} in triggering cardiovascular events.

Another very interesting result of our study was the sex differences not only regarding the type of blood element affected by the PM_{10} exposure but also regarding the temporal pattern of the effects. Actually, our results suggest that females are the most affected in the short-term exposure scenario, being WBC the most affected blood parameters. On the other hand, in the long-term scenario, males seem to be the most affected, mainly at the RDW parameter. A recent study (Ding et al. 2020) reported that PM_{10} have a significant effect on human eosinophils, a WBC subtype, for both women and men, but with different temporal patterns, with women showing a lag of 0–5 days and men showing a lag of 20–28 days. Consequently, we must consider the hypothesis that, among males, the PM_{10} short-term effect on WBC, that we were not able to detect, occurs in a later lag day, which was not the target of our study. These results suggest a sex-differential response to PM_{10} exposure whose underlying biological mechanism, to the best of our knowledge, is unknown. However, previous studies already detected some of these sex-related differences and authors argue that it was possibly due to the effects of different hormones levels, such as estrogens (Biino et al. 2013; Nagata et al. 2003; Zhang et al. 2018). Moreover, the endocrine-disrupting potential of the PM might also interfere with hormone signalling with expected different effect on males and females (Rudel and Perovich 2009; Zhang et al. 2018).

Concerning our results on sensitivity analysis, when we restricted our analysis to participants without anaemia, results were confirmed and, in some cases, estimates were more robust after this restriction. When considering a more restrictive criteria to the exposure assessment (participants living within a 20 km radius of an air quality monitoring station with available PM_{10} values), results on the association between short-term PM_{10} exposure and WBC was reinforced but only among females. It also supports the results on the association between long-term PM_{10} exposure and RDW in both sexes. This result, suggest us that exposure misclassification could be present and could be the reason for not detecting associations between PM_{10} and the RBC or even HEMOG, in our principal analysis, when considering all participants living within a 30 km radius of an air quality monitoring station. Consequently, we think that if we restricted more this distance criteria, assessing the PM_{10} exposure in a more personalised way, which was not possible due to the huge sample reduction, associations will be probably found regarding the remaining blood count parameters.

When considering the modelled PM_{10} concentrations obtained by the air quality modelling system (WRF-CAMx), in the sensitivity analysis, only results on the association between long-term PM_{10} exposure and RDW, among males, were supported. One possible explanation for this result is that modelled PM_{10} concentrations, when compared with measured PM_{10} concentrations, could be less representative of the real participants PM_{10} exposure because they are a mathematical representation of the reality with a certain degree of uncertainty of the input data, namely in the atmospheric emissions data. Consequently, it is expected that modelled PM_{10} concentrations are associated with a higher degree of individual exposure misclassification (and not representative of high spatial detail) and only the strong association with the RDW was detected when considering this PM_{10} exposure assessment methodology.

Strengths and limitations

In the present study we detect multiple associations regarding the short and long-term effect of PM_{10} exposure on blood count parameters with potential to mediate a cardiovascular event and also sex differences were reported regarding these associations, which have not been described/identified before, to the best of our knowledge. We were careful to perform an extensive bibliographic review and construct a conceptual model before the statistical analysis, in order to guarantee that the main confounding variables on the relationship between PM_{10} and blood count parameters were considered. Moreover, due to the diversity observed regarding the air pollution exposure assessment methodology (Gaio et al. 2019), we tried to consider multiple methodologies to obtain PM_{10} concentrations, by using both measurements and numerical modelling (WRF-CAMx) approaches, as presented in the sensitivity analysis.

One of the main limitations of our study is related to the exposure assessment method, due the high distance considered between participant's residence and the air quality monitoring stations (30 km) in the inclusion criteria. In fact, as the sensitivity analysis indicates, exposure misclassification could be present in our study. However, the number and the spatial distribution of air quality monitoring stations in the Portuguese mainland does not allow us to apply a more restrictive distance due to a substantial sample reduction that could compromise the power of the estimates. Even with a more restrictive distance, the air quality data available (both monitoring and modelled-based PM_{10} concentrations) are limited to assess the real individual exposure. A better assessment of this exposure could be possible through the use of new technology, with Global Position Systems (GPS) and mobile devices with low-cost air pollution sensors (Hoek 2017) that would capture the unique activity-patterns of the real individual exposure.

Finally, even with the adjustment for several potential confounders, there is still a possibility of the observed estimates to have been affected by residual confounding due to other unmeasured confounders. Moreover, effect estimates presented in this study were based on a single-pollutant model, due the scarce available air quality monitoring data for the remaining air pollutants. However, it is known that there are important interactions between the atmospheric pollutants, namely the potential additive effects of multiple pollutants and they should be considered in future studies (Davalos et al. 2017; Oakes et al. 2014).

Conclusions

In the present study we detected some associations regarding the short and long-term effect of PM_{10} exposure on blood count parameters with potential to mediate a cardiovascular event and also we report sex-differences regarding these associations that, to the best of our knowledge, were never been described. It is uncertain whether changes in blood count parameters due to PM_{10} exposure constitute an adverse health outcome or it reflect only a normal immunity response in healthy individuals. However, due to its potential to trigger cardiovascular events, more studies are essential to better understand the effects of PM_{10} on these parameters.

Finally, even at relatively low levels of PM_{10} concentrations, in Portugal, it was possible to detect the PM_{10} exposure effect on blood count parameters with potential to mediate a cardiovascular event, suggesting

that there is no safe level of air pollutants. Our findings suggest that reducing PM_{10} levels would result in additional benefits concerning the cardiovascular health of the population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11869-021-01007-9.

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Declarations

Ethics approval and consent to participate The INSEF survey received approval from the Ethics Committee of the Portuguese National Health Institute Doutor Ricardo Jorge, the National Data Protection Authority (Authorization n° 9348/2010) and from the regional Ethics Committees. Moreover, Ethics Committee of the Portuguese National Health Institute Doutor Ricardo Jorge approved the study protocol of this particular research. All participants provided informed consent before data collection.

Conflict of interest The authors declare no competing interests.

References

Biino G, Santimone I, Minelli C, Sorice R, Frongia B, Traglia M, Ulivi S, di Castelnuovo A, Gögele M, Nutile T, Francavilla M, Sala C, Pirastu N, Cerletti C, Iacoviello L, Gasparini P, Toniolo D, Ciullo M, Pramstaller P, Pirastu M, de Gaetano G, Balduini CL (2013) Age- and sex-related variations in platelet count in Italy: a proposal of reference ranges based on 40987 subjects' data. PLoS One 8(1): e54289. https://doi.org/10.1371/journal.pone.0054289

Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, Balakrishnan K, Brunekreef B, Dandona L, Dandona R, Feigin V, Freedman G, Hubbell B, Jobling A, Kan H, Knibbs L, Liu Y, Martin R, Morawska L, Pope CA III, Shin H, Straif K, Shaddick G, Thomas M, van Dingenen R, van Donkelaar A, Vos T, Murray CJL, Forouzanfar MH (2017) Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 389: 1907–1918. https://doi.org/10.1016/S0140-6736(17)30505-6

Cozzi E, Wingard CJ, Cascio WE, Devlin RB, Miles JJ, Bofferding AR, Lust RM, van Scott MR, Henriksen RA (2007) Effect of ambient particulate matter exposure on hemostasis. Transl Res 149:324–332. https://doi.org/10.1016/j.trsl.2006.12.009

Dabass A, Talbott EO, Venkat A, Rager J, Marsh GM, Sharma RK, Holguin F (2016) Association of exposure to particulate matter (PM2.5) air pollution and biomarkers of cardiovascular disease risk in adult NHANES participants (2001-2008). Int J Hyg Environ Health 219:301–310. https://doi.org/10.1016/j.ijheh.2015.12.002

Davalos AD, Luben TJ, Herring AH, Sacks JD (2017) Current approaches used in epidemiologic studies to examine short-term multipollutant air pollution exposures. Ann Epidemiol 27(2):145–153. https://doi.org/10.1016/j.annepidem.2016.11.016

Ding Z, Xie Z, Su Y et al (2020) The lagged effect of air pollution on human eosinophils: a distributed lag non-linear model. Int J Occup Med Environ Health 33:299–310. https://doi.org/10.13075/ijomeh.1896.01528

Elbarbary M, Honda T, Morgan G, Guo Y, Guo Y, Kowal P, Negin J (2020) Ambient air pollution exposure association with anaemia prevalence and haemoglobin levels in Chinese older adults. Int J Environ Res Public Health 17(9):3209. https://doi.org/10.3390/ijerph17093209

Emmerechts J, Alfaro-Moreno E, Vanaudenaerde BM et al (2010) Short-term exposure to particulate matter induces arterial but not venous thrombosis in healthy mice. J Thromb Haemost 8:2651–2661. https://doi.org/10.1111/j.1538-7836.2010.04081.x

ENVIRON (2018) User's guide on Comprehensive Air Quality Model with Extensions (CAMx), version 6.50. report

ESRI (2019) https://www.esri.com/en-us/arcgis/about-arcgis/overview

Fava C, Cattazzo F, Hu ZD et al (2019) The role of red blood cell distribution width (RDW) in cardiovascular risk assessment: useful or hype? Ann Transl Med 7:581–581. https://doi.org/10.21037/atm.2019.09.58

Ferreira J, Lopes D, Rafael S, Relvas H, Almeida SM, Miranda AI (2020) Modelling air quality levels of regulated metals: limitations and challenges. Environ Sci Pollut Res 27(27):33916–33928. https://doi.org/10.1007/s11356-020-09645-9

Gaio V, Roquette R, Dias CM, Nunes B (2019) Ambient air pollution and lipid profile: systematic review and meta-analysis. Environ Pollut 254:113036. https://doi.org/10.1016/j.envpol.2019.113036

Gama C, Monteiro A, Pio C, Miranda AI, Baldasano JM, Tchepel O (2018) Temporal patterns and trends of particulate matter over Portugal: a long-term analysis of background concentrations. Air Qual Atmos Health 11:397–407. https://doi.org/10.1007/s11869-018-0546-8

Gondalia R, Holliday KM, Baldassari A, Justice AE, Stewart JD, Liao D, Yanosky JD, Engel SM, Jordahl KM, Bhatti P, Horvath S, Assimes TL, Pankow JS, Demerath EW, Guan W, Fornage M, Bressler J, North KE, Conneely KN, Li Y, Hou L, Baccarelli AA, Whitsel EA (2020) Leukocyte traits and exposure to ambient particulate matter air pollution in the women's health initiative and atherosclerosis risk in communities study. Environ Health Perspect 128(1):017004. https://doi.org/10.1289/EHP5360

Hamanaka RB, Mutlu GM (2018) Particulate matter air pollution: effects on the cardiovascular system. Front Endocrinol 9:680. https://doi.org/10.3389/fendo.2018.00680

Haybar H, Pezeshki SMS, Saki N (2019) Evaluation of complete blood count parameters in cardiovascular diseases: an early indicator of prognosis? Exp Mol Pathol 110:104267. https://doi.org/10.1016/j.yexmp.2019.104267

Hoek G (2017) Methods for assessing long-term exposures to outdoor air pollutants. Curr Environ Health Rep 4(4):450–462. https://doi.org/10.1007/s40572-017-0169-5

Hou J, Duan Y, Liu X, Li R, Tu R, Pan M, Dong X, Mao Z, Huo W, Chen G, Guo Y, Li S, Wang C (2020) Associations of long-term exposure to air pollutants, physical activity and platelet traits of cardiovascular risk in a rural Chinese population. Sci Total Environ 738:140182. https://doi.org/10.1016/j.scitotenv.2020.140182

ILOSTAT (2020) International Standard Classification of Education (ISCED): Aggregate levels of education. Available from: https://ilostat.ilo.org/resources/concepts-and-definitions/classification-education/

International Labour Office (2012) International Standard Classification of Occupations: ISCO-08. Available from: https://www.ilo.org/wcmsp5/groups/public/—dgreports/—dcomm/—publ/documents/publication/wcms_172572.pdf

Kim SY, Peel JL, Hannigan MP, Dutton SJ, Sheppard L, Clark ML, Vedal S (2012) The temporal lag structure of short-term associations of fine particulate matter chemical constituents and cardiovascular and respiratory hospitalizations. Environ Health Perspect 120:1094–1099. https://doi.org/10.1289/ehp.1104721

Lassale C, Curtis A, Abete I, van der Schouw YT, Verschuren WMM, Lu Y, Bueno-de-Mesquita HB() (2018) Elements of the complete blood count associated with cardiovascular disease incidence: findings from the EPIC-NL cohort study. Sci Rep 8(1):1–11. https://doi.org/10.1038/s41598-018-21661-x

Lee H, Myung W, Jeong BH, Choi H, Jhun BW, Kim H (2018) Short- and long-term exposure to ambient air pollution and circulating biomarkers of inflammation in non-smokers: a hospital-based cohort study in South Korea. Environ Int 119:264–273. https://doi.org/10.1016/j.envint.2018.06.041

Liao D, Heiss G, Chinchilli VM, Duan Y, Folsom AR, Lin HM, Salomaa V (2005) Association of criteria pollutants with plasma hemostatic/inflammatory markers: a population-based study. J Expo Anal Environ Epidemiol 15:319–328. https://doi.org/10.1038/sj.jea.7500408

Miller MR, Newby DE (2020) Air pollution and cardiovascular disease: car sick. Cardiovasc Res 116(2):279–294. https://doi.org/10.1093/cvr/cvz228

Mozos I (2015) Mechanisms linking red blood cell disorders and cardiovascular diseases. Biomed Res Int 2015:1–12. https://doi.org/10.1155/2015/682054

Mukae H, Vincent R, Quinlan K et al (2001) The effect of repeated exposure to particulate air pollution (PM10) on the bone marrow. Am J Respir Crit Care Med 163:201–209. https://doi.org/10.1164/ajrccm.163.1.2002039

Nagata Y, Yoshikawa J, Hashimoto A, Yamamoto M, Payne AH, Todokoro K (2003) Proplatelet formation of megakaryocytes is triggered by autocrine-synthesized estradiol. Genes Dev 17:2864–2869. https://doi.org/10.1101/gad.1128003

NCAR (2010) Model for Ozone and Related chemical Tracers, version 4 (MOZART-4). National Center of Atmosferic Research

Nunes B, Barreto M, Gil AP, Kislaya I, Namorado S, Antunes L, Gaio V, Santos AJ, Rodrigues AP, Santos J, Roquette R, Alves-Alves C, Castilho E, Cordeiro E, Dinis A, Prokopenko T, Silva AC, Vargas P, Lyshol H, Dias CM (2019) The first Portuguese National Health Examination Survey 2015: design, planning and implementation. J Public Health (Bangkok) 41:511–517. https://doi.org/10.1093/pubmed/fdy150

Oakes M, Baxter L, Long TC (2014) Evaluating the application of multipollutant exposure metrics in air pollution health studies. Environ Int 69:90–99. https://doi.org/10.1016/j.envint.2014.03.030

Parizadeh SM, Jafarzadeh-Esfehani R, Bahreyni A, Ghandehari M, Shafiee M, Rahmani F, Parizadeh MR, Seifi S, Ghayour-Mobarhan M, Ferns GA, Avan A, Hassanian SM (2019) The diagnostic and prognostic value of red cell distribution width in cardiovascular disease; current status and prospective. BioFactors 45(4):507–516. https://doi.org/10.1002/biof.1518

Peters A, Dockery DW, Muller JE, Mittleman MA (2001) Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103:2810–2815. https://doi.org/10.1161/01.CIR.103.23.2810

Poursafa P, Kelishadi R, Amini A, Amini A, Amin MM, Lahijanzadeh M, Modaresi M (2011) Association of air pollution and hematologic parameters in children and adolescents. J Pediatr 87:350–356. https://doi.org/10.2223/jped.2115

Pranata R, Vania R, Tondas AE, Setianto B, Santoso A (2020) A time-to-event analysis on air pollutants with the risk of cardiovascular disease and mortality: a systematic review and meta-analysis of 84 cohort studies. J Evid Based Med 13:102–115. https://doi.org/10.1111/jebm.12380

R Core Team (2020) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria

Rudel RA, Perovich LJ (2009) Endocrine disrupting chemicals in indoor and outdoor air. Atmos Environ 43:170–181. https://doi.org/10.1016/j.atmosenv.2008.09.025

Sá E, Martins H, Ferreira J, Marta-Almeida M, Rocha A, Carvalho A, Freitas S, Borrego C (2016) Climate change and pollutant emissions impacts on air quality in 2050 over Portugal. Atmos Environ 131:209–224. https://doi.org/10.1016/j.atmosenv.(2016).01.040

Scheers H, Jacobs L, Casas L, Nemery B, Nawrot TS (2015) Long-term exposure to particulate matter air pollution is a risk factor for stroke: meta-analytical evidence. Stroke 46:3058–3066. https://doi.org/10.1161/STROKEAHA.115.009913

Skamarock W (2008) A description of the advanced research WRF version 3, NCAR Tech. Note, NCAR/TN-468+STR. Natl Cent Atmos Res Boulder, Color. https://doi.org/10.5065/D68S4MVH

Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GTH (2016) Robust causal inference using directed acyclic graphs: the R package "dagitty". Int J Epidemiol 45:1887–1894. https://doi.org/10.1093/ije/dyw341

Tolonen H (2013) EHES manual. Part B. Fieldwork procedures. Helsinki

UNESCO (2012) The international standard classification of education 2011, Comparative Social Research. https://ilostat.ilo.org/resources/concepts-and-definitions/classification-education/

Van Eeden SF, Hogg JC (2002) Systemic inflammatory response induced by particulate matter air pollution: the importance of bone-marrow stimulation. J Toxicol Environ Health 65:1597–1613. https://doi.org/10.1080/00984100290071685

Wang X, Wei W, Cheng S, Li J, Zhang H, Lv Z (2018) Characteristics and classification of PM2.5 pollution episodes in Beijing from 2013 to 2015. Sci Total Environ 612:170–179. https://doi.org/10.1016/j.scitotenv.2017.08.206

WHO (2011) Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. World Health Organization, Geneva

Zhang Z, Chan TC, Guo C, Chang LY, Lin C, Chuang YC, Jiang WK, Ho KF, Tam T, Woo KS, Lau AKH, Lao XQ (2018) Long-term exposure to ambient particulate matter (PM2.5) is associated with platelet counts in adults. Environ Pollut 240:432–439. https://doi.org/10.1016/j.envpol.2018.04.123