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Association of long-term exposure to traffic-related PM_{10} with heart rate variability and heart rate dynamics in healthy subjects

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ABSTRACT

Background: Epidemiological evidence on the influence of long-term exposure to traffic-related particulate matter (TPM_{10}) on heart rate variability (HRV) is weak.
Objective: To evaluate the association of long-term exposure (10 years) with TPM_{10} on the regulation of the autonomic cardiovascular system and heart rate dynamics (HRD) in an aging general population, as well as potential modifying effects by the a priori selected factors sex, smoking status, obesity, and gene variation in selected glutathione S-transferases (GSTs).
Methods: We analyzed data from 1593 SAPALDIA cohort participants aged ≥ 50 years. For each participant, various HRV and HRD parameters were derived from 24-hour electrocardiogram recordings. Each parameter obtained was then used as the outcome variable in multivariable mixed linear regression models in order to evaluate the association with TPM_{10}. Potential modifying effects were assessed using interaction terms.
Results: No association between long-term exposure to TPM_{10} and HRV/HRD was observed in the entire study population. However, HRD changes were found in subjects without cardiovascular morbidity and both HRD and HRV changes in non-obese subjects without cardiovascular morbidity. Subjects without cardiovascular morbidity with homozygous *GSTM1* gene deletion appeared to be more susceptible to the effects of TPM_{10}.
Conclusion: This study suggests that long-term exposure to TPM_{10} triggers adverse changes in the regulation of the cardiovascular system. These adverse effects were more visible in the subjects without cardiovascular disease, in whom the overall relationship between TPM_{10} and HRV/HRD could not be masked by underlying morbidities and the potential counteracting effects of related drug treatments.

1. Introduction

Short- and long-term exposure to particulate matter (PM) air pollution has been associated with increased cardiovascular morbidity and mortality. Investigations of short-term effects have shown greater risks in susceptible populations, such as the elderly, individuals with diabetes, patients with preexisting coronary heart disease, chronic lung disease, or heart failure, and individuals with low education or socioeconomic status (Brook et al., 2010; Pieters et al., 2012; Pope III et al., 2004). Current or former smokers, obese subjects, and women could also be susceptible populations (Brook et al., 2010).

Possible mechanisms underlying these associations include effects on the autonomic nervous system. Heart rate variability (HRV) is a useful non-invasive measure to assess the autonomic regulation of cardiac rhythm (Task Force, 1996). Lower HRV is associated with higher cardiovascular morbidity and mortality, and has proved itself as an important prognostic tool for several cardiovascular conditions (Bigger Jr. et al., 1992; Kleiger et al., 1987; Task Force, 1996; Tsuji et al., 1996). There is strong epidemiological evidence that short-term PM exposure (in days) is associated with reductions in most indices of

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HRV, and the association might be more pronounced among the elderly, patients with preexisting cardiovascular disease or diabetes, or people with reduced antioxidative defenses (Brook et al., 2010; Mordukhovich et al., 2015; Park et al., 2005; Pieters et al., 2012). Indeed, response to air pollutants has been shown to be modified by genes that modulate endogenous oxidative stress (Bergamaschi et al., 2001; Schwartz et al., 2005b). In particular, recent observations have shown strong modifications of the relationships of HRV with PM, second-hand smoke, and BMI, by glutathione S-transferase (GST) (Adam et al., 2017; Baccarelli et al., 2008; Park et al., 2006; Probst-Hensch et al., 2008; Schwartz et al., 2005b), a family of enzymes involved in the metabolism of reactive oxygen species and xenobiotic compounds, and showing common genetic variations (Schwartz et al., 2005b).

Although long-term PM exposure is known to have a stronger effect on cardiovascular morbidity and mortality than acute exposure, there is limited or weak epidemiological evidence that HRV is altered by low-level, but long-term exposure (in years) to PM (Brook et al., 2010), and whether there is a greater risk in susceptible populations. Indeed, studies on the chronic impact of PM air pollution on HRV are scarce (Adam et al., 2012; Adam et al., 2014; Mordukhovich et al., 2015) and the American Heart Association has stated that there is a lack of evidence regarding long-term effects of air pollution on HRV (Brook et al., 2010). It is conceivable that the stronger effect of long-term air pollution exposure, compared to short-term exposure, reflects the accumulation of molecular damage in the cardiovascular system in response to long-term air pollution exposure. This molecular damage may be visible in lowered HRV in part. Accumulated molecular damage may also predispose the heart to acute effects of air pollution at a later stage.

Finally, there is increasing evidence that the regulation of the cardiovascular system involves nonlinear control mechanisms (Rajendra Acharya et al., 2006; Task Force, 1996) which can be best characterized using nonlinear time series analysis techniques (Goldberger and West, 1987; Meyer and Stiedl, 2003; Pikkujamsa et al., 2001; Pincus, 1991; Rajendra Acharya et al., 2006; Vandeput et al., 2012). The recent implementation of such methods to evaluate the influence of current smoking and smoking cessation on heart rate dynamics in the large epidemiological dataset of SAPALDIA (Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults), which allowed for the control of most known potential confounders, enabled us to unveil long-term alterations in former heavy smokers who might need up to 15–25 years to fully recover (Girard et al., 2015).

By applying the same kind of approach, the present study aimed first at evaluating the influence of low-level, but long-term exposure (i.e. over a 10-year period) to traffic-related particulate matter (TPM_{10}) on the regulation of the autonomic cardiovascular system and heart rate dynamics in an aging general population. In a further analysis, we used ambient NO_2 concentrations, as well as ambient PM_{10} concentrations, as an alternative proxy for exposure to traffic-related pollutants. Second, we focused our investigation on the subgroups with or without cardiovascular morbidity (i.e., cardiovascular disease and/or hypertension). Finally, we investigated potential modifications of these effects by the a priori selected factors sex, smoking status, obesity, and gene variation in selected glutathione S-transferases (GSTs) in the entire study population and in the subgroups with or without cardiovascular morbidity.

2. Methods

2.1. Ethics statement

The study was approved by the Central Ethics Committee of the Swiss Academy of Medical Sciences and the Cantonal Ethics Committees for each of the study areas. Each subject was informed in detail about the health examinations and signed a written informed consent form before any of the health examinations were conducted.

2.2. Study population

This study is part of the SAPALDIA study which was designed to assess the health effects of long-term exposure to air pollutants in the Swiss adult population. The study design has been described in detail elsewhere (Ackermann-Liebrich et al., 2005; Martin et al., 1997). In brief, the SAPALDIA cohort (n = 9651) was enrolled in 1991, and consisted of a random sample of the Swiss population aged 18 to 60 years, recruited from the local registries of inhabitants in eight areas featuring distinct geographical and environmental conditions.

In 2002, the follow-up study included 8047 (83.4%) participants. A random sample of 1846 out of 4417 participants, aged ≥ 50 years underwent a 24-hour electrocardiogram (ECG) Holter recording to assess HRV, as previously described in detail (Felber Dietrich et al., 2006). Exclusion criteria were general or spinal anaesthesia within 8 days before the ECG recording (n = 5), a myocardial infarction within 3 months prior to the examination (n = 2), taking digitalis (n = 6), and an artificial internal pacemaker (n = 0). Participants with recordings showing atrial fibrillation (n = 12), ECG duration lower than 18 h (n = 73), ECG of insufficient quality (n = 6), or non-valid data on HRV (n = 96) were also excluded (Felber Dietrich et al., 2006). By comparing the 1607 remaining participants with SAPALDIA follow-up participants above age 50, but without HRV measurements (N = 2810), it was noted the study participants to be less likely ever smokers (56.8% vs. 59.8%), physically active (41.3% vs. 47.9%), or diagnosed with diabetes (3.8% vs. 6.9%), but more likely to be hypertensive (47.5% vs. 44.1%), or take heart medication (24.5% vs. 21.5%) (Adam et al., 2012). This current analysis is restricted to 1593 participants with valid data on HRV, cardiovascular risk factors, and TPM_{10} exposure.

2.3. Questionnaires and measurements

Extensive health examinations and a detailed assessment of personal risk factors were conducted in 1991 and repeated in 2002 in the 8047 (83.4%) participants of the follow-up study (Ackermann-Liebrich et al., 2005). Information about questionnaires and biological measurements performed at these two time points has been reported elsewhere (Ackermann-Liebrich et al., 2005; Felber Dietrich et al., 2006; Martin et al., 1997). The 24-hour ECG and measurements such as blood pressure, heart rate, uric acid, and high-sensitivity C-reactive protein were performed only in 2002.

2.3.1. Measures of heart rate variability and heart rate dynamics

Time series analysis parameters of heart rate variability were calculated for each individual time series of inter-beat intervals (RR series) generated from the 24-hour ECG recordings performed in 2002.

The traditional time domain measure used was the standard deviation of normal interbeat intervals (SDNN) (Task Force, 1996). Additionally, a power-law relationship between the power spectral density (PSD) of the interbeat interval time series and frequency was determined by estimating the slope β of the linear best-fit of the PSD as a function of the frequency on a double logarithmic scale. In our previous study, related to heart rate dynamics and smoking exposure, we found a positive association between this slope β and smoking exposure (Girard et al., 2015).

We used nonlinear time series analysis methods to quantify and characterize the heart rate dynamics. Several nonlinear analysis methods of heart rate behaviour have been developed to obtain a more comprehensive quantification of the heart rate dynamic fluctuations (Anonymous, 1996; Goldberger, 1996). Characterization of the complexity in the fluctuation behaviour of system signals holds enormous promise for providing new understandings of the regulatory mechanisms of physiological systems and how they change with diseases. However, the translation of such involved mathematical concepts into the clinical and epidemiological fields is challenging and is still exploratory. Furthermore, to the best of authors5 knowledge, associations

between air pollutants exposure and heart rate dynamic fluctuations have not been investigated yet. Consequently, we calculated several heart rate dynamics (HRD) parameters (Goldberger and West, 1987; Meyer and Stiedl, 2003; Pikkujamsa et al., 2001; Pincus, 1991; Rajendra Acharya et al., 2006; Vandeput et al., 2012), and report on the results for those parameters which appeared to best capture the association of long-term exposure to TPM_{10} with heart rate dynamic fluctuations. Description of the other parameters is provided in the Supplemental Material.

- Exponent α: we used detrended fluctuation analysis (DFA) to measure the presence or absence of fractal correlation properties in signals. This method has been validated for interbeat intervals time series (Peng et al., 1995). The fractal long-range correlations are characterized by a scaling exponent α. A fractal-like signal results in $\alpha = 1$. White Gaussian noise (totally random signal) results in a value of 0.5. In healthy young subjects, it is closer to 1, and this value falls within different ranges for various types of cardiac abnormalities (Pikkujamsa et al., 2001; Rajendra Acharya et al., 2006). In our previous study, related to heart rate dynamics and smoking exposure, we found an inverse association between α and smoking exposure (Girard et al., 2015).
- Largest Lyapunov exponent: detection of chaos in a time series can be done by measuring the largest Lyapunov exponent in the appropriate phase space embedding (Rosenstein et al., 1993). It quantifies the exponential divergence of initially close state-space trajectories and estimates the amount of chaos in a system. The extent to which chaos relates to physiological or pathological dynamics is a subject of active investigation and some controversy (Goldberger et al., 2000). In our previous study, related to heart rate dynamics and smoking exposure, we found an inverse association between the largest Lyapunov exponent and smoking exposure (Girard et al., 2015).

More details about the choice, implementation, and properties of the aforementioned time series analysis methods are described in the Supplemental Material.

2.3.2. Air pollutant exposure estimation

Monitoring of air pollutants was conducted between 1991 and 2002. Consequently, individual estimates of home outdoor exposure to TPM_{10} could be obtained for each of the 10 years preceding the respective subject's ECG recording (i.e., for the period 1991–2002) using a dispersion modeling and temporal interpolation approach (Liu et al., 2007) and taking into account residential moves. The dispersion model made use of different source-specific emissions, thus, it was possible to derive spatial distributions of source-specific PM_{10} such as TPM_{10} (Adam et al., 2012; Kunzli et al., 2009). The 10 annual means were then averaged to obtain estimates of mean residential home-outdoor exposure to TPM_{10} over the 10 years preceding the ECG recording.

The description of the modeling of residential exposure has been described in detail elsewhere (Liu et al., 2007). Briefly, estimates of residential PM_{10} exposure were obtained for each of the years 1991 to 2002 using a dispersion modeling and temporal interpolation approach (Liu et al., 2007). As for traffic-related $PM_{10,}$ these annual values were used to obtain estimates of average residential exposure to PM_{10} over 10 years. Estimates of residential NO_2 exposure were derived from land-use regression models of NO_2-passive sampler measurements conducted in 1993 and 2003 across the eight study areas. These models involved dispersion model predictions, land-use and meteorological variables. Annual estimates for the years 1991 to 2002 were obtained by temporal inter- and extrapolation based on fixed-site monitor measurements. As for $PM_{10,}$ these annual values were used to obtain estimates of average residential home-outdoor exposure to NO_2 over 10 years.

2.3.3. Definition of cardiovascular morbidity

There was no cardiovascular morbidity if there was no evidence for cardiovascular disease or hypertension (i.e., the subject had no physician diagnosed heart disease, no major cardiovascular medication intake, and no hypertension). Major cardiovascular medication included beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor antagonists, calcium channel blockers, diuretic medications, antiarrhythmic drugs class I + III, sympathomimetic medications. Absence of hypertension was defined as absence of a physician diagnosis of hypertension, blood pressure in the hypertensive range, and antihypertensive medication.

2.3.4. Genotyping

GSTM1 and GSTT1 genotypes are commonly investigated in studies assessing the interactions between gene variation in GST and air pollution because these genes are expressed in the respiratory tract, are involved in detoxification of chemicals present in diesel exhaust particles or environmental carcinogens, and have common functional variant alleles (Gilliland et al., 2004). GSTM1 and GSTT1 genes have both a common allele that results in a lack of the respective protein. The GSTM1 gene is deleted in approximately half of the white population, and lack to the GSTM1 protein has been associated with an enhanced nasal allergic response to PM air pollution (Schwartz et al., 2005b).

The genotyping has been described in detail elsewhere (Probst-Hensch et al., 2008). In brief, all subjects were genotyped for *GSTM1* (UniGene ID Hs.301961; UniGene 2008a) and *GSTT1* (UniGene Hs.268573; UniGene 2008b) gene deletions.

2.4. Statistical analysis

2.4.1. Descriptive analysis

Results are expressed as numbers and percentages for categorical variables and as a mean ± standard deviation or median [25th percentile; 75th percentile] for continuous variables, according to their distribution.

2.4.2. Multivariable analysis

Each parameter describing the HRV, or heart rate dynamics, was used as the outcome variable in multivariable linear mixed effects regression models in order to evaluate the association with long-term exposure to TPM_{10}. Estimates were expressed (1) for a one interquartile range-increment in TPM_{10}, in order to enable comparison of effect size with other air pollutants; (2) for an increase of 1 $\mu g/m^3$ in TPM_{10}, in order to facilitate comparisons with other studies. Initial inspection of the outcome variables showed a skewed distribution of the residuals for some of them, which were therefore log-transformed. Estimated effects on these variables are presented as percentage changes in geometric means. All the models included random intercepts for the study areas and were adjusted for established and potential confounding factors (Adam et al., 2012; Adam et al., 2014; Felber Dietrich et al., 2006), i.e., sex (male as reference), age (for an increase of 1 year), age^2, body mass index (BMI, for an increase of 1 kg/m^2), BMI^2, alcohol consumption (< 1 glass/day as reference, ≥ 1 glass/day), duration of weekly physical activity to the point of getting out of breath or sweating (never as reference, between 0.5 h and 2 h, ≥ 2 h/week), daily exposure to environmental tobacco smoke (none as reference, between 0 h and 3 h, ≥ 3 h/day), diabetes (no as reference, yes), smoking group (lifelong non-smoker as reference, former light smoker (< 20 pack-years), former heavy smoker (≥ 20 pack-years), current light smoker, current heavy smoker), uric acid concentration (μmol/L), high-sensitivity C-reactive protein (hsCRP) (mg/L), street and railway noise exposure (mean dB(A) per night), sine and cosine functions of the day of examination with a period of 1 year (to model potential seasonal patterns), education level (high as reference, middle, low), employment category (employed as reference, unemployed, homemaker, pensioner), occupational exposure (no as reference, yes if currently exposed to

dust/gas/smoke/aerosols/fumes/vapors at the working place), cardiovascular morbidity (no as reference, yes).

2.4.3. Investigation of susceptible groups

Potential modifying effects of cardiovascular morbidity, sex, as well as of inflammation and oxidative stress related parameters such as smoking status (defined as ever smoker or lifelong non-smoker), obesity (defined as BMI ≥ 30 kg/m^2), and known whole gene deletion polymorphisms of *GSTM1* and *GSTT1* previously found to modify the smoking-HRV association in the SAPALDIA cohort study (Probst-Hensch et al., 2008) were assessed for each outcome using interaction terms.

2.4.4. Sensitivity analyses

Given the small number of participants with diabetes in the subpopulation without cardiovascular morbidity, the potential modifying effect of diabetes could not be assessed using an interaction term. Instead, participants with a physician diagnosis of diabetes were excluded in a sensitivity analysis.

As previous work on the SAPALDIA cohort had found stronger adverse effects of TPM_{10} on the traditional parameters of HRV among participants under angiotensin-converting-enzyme (ACE) inhibitor therapy (Adam et al., 2012), the potential modifying effect of ACE inhibitor therapy was also assessed for each of the present outcomes using a respective interaction term.

As the effects observed may have consisted of longer term and acute components, multivariable models were adjusted for short-term exposure to PM_{10} (i.e., level of PM_{10} on the day preceding the HRV-measurement) in another sensitivity analysis (short-term exposure to TPM_{10} was not available). Data related to short-term PM_{10} exposure were available at ambient air pollution monitoring stations (NABEL, Cantons).

Finally, it might be hypothesized that hsCRP is on the causal pathway and/or an effect of air pollution as well. In this case, adjusting for hsCRP might results in "over-adjustments". Consequently, effects of TPM_{10} were assessed without adjusting for hsCRP and estimated effect sizes were compared with those observed when adjusting for hsCRP.

2.4.5. Associations with other air pollutants

In addition, we investigated the relationship of HRV/HRD-variables with the 10-year means of PM_{10} and NO_2. Methods are provided in the Supplemental Material. Correlation between TPM10 and PM10, as well as between TPM10 and NO2, were assessed using Spearman correlation coefficient (ρ).

All tests were two-sided with a significance level of 0.05. Statistical analysis was performed using R, Version 3.3.1 (Computing R Foundation for Statistical Computing, 2008.

3. Results

3.1. Study population

The study population consisted of 1593 subjects. The mean age of the subjects was 60.5 ± 6.2 years. Demographic characteristics, lifestyle factors, cardiovascular health and diabetes, long-term exposure to air pollution, and GST genotypes are summarized in Table 1. A more detailed description has been reported elsewhere (Adam et al., 2012; Girard et al., 2015).

3.2. Relationship between long-term exposure to TPM_{10} and HRV/HRD

Neither in the entire study population nor in any of the subgroups defined according to sex, smoking status, obesity and GST genotypes, did we observe any significant association between long-term exposure to TPM_{10} and HRV/HRD parameters (Tables 2, 4, 5 and Tables S1–S3).

However, stratification by cardiovascular morbidity revealed significant associations between TPM_{10} and the HRD parameters slope β (0.2 [0.03, 0.3], p = 0.01) and largest Lyapunov exponent (−0.01 [−0.02, −0.001], p = 0.03) in subjects without cardiovascular morbidity, while the corresponding associations in subjects with

Table 1
Characteristics of the study population and subpopulations investigated.

Characteristic	Entire study population (n = 1593)	MD	Subpopulation without cardiovascular morbidity (n = 510)	MD
Demographic characteristics				
Age, years	60.5 ± 6.2	–	59.6 ± 6.01	–
Sex, men	773 (48.5%)	–	200 (39.2%)	–
BMI, kg/m^2	26.7 ± 4.34	3	25.1 ± 3.78	–
Education		–		–
Low	144 (9.0%)		48 (9.4%)	
Middle	1048 (65.8%)		325 (63.7%)	
High	401 (25.2%)		137 (26.9%)	
Employment		10		6
Employed	862 (54.5%)		291 (57.7%)	
Homemaker	352 (22.2%)		121 (24%)	
Unemployed	81 (5.1%)		21 (4.2%)	
Pensioner	288 (18.2%)		71 (14.1%)	
Lifestyle factors				
Smoking status		60		12
Lifelong non-smoker	692 (45.1%)		230 (46.2%)	
Current light smoker	65 (4.2%)		28 (5.6%)	
Current heavy smoker	222 (14.5%)		71 (14.3%)	
Former light smoker	314 (20.5%)		112 (22.5%)	
Former heavy smoker	240 (15.7%)		57 (11.4%)	
Time elapsed since cessation, years		7		3
< 15	154/547 (28.2%)		46/166 (27.7%)	
15–25	150/547 (27.4%)		44/166 (26.5%)	
≥25	243/547 (44.4%)		76/166 (45.8%)	
Daily ETS exposure, hours		2		2
None	1253 (78.8%)		407 (80.1%)	
< 3	216 (13.6%)		63 (12.4%)	
≥3	122 (7.7%)		38 (7.5%)	
Alcohol, ≥1 glass/day	731 (45.9%)	2	211 (41.5%)	2
Weekly physical activity		14		5
None	666 (42.2%)		203 (40.2%)	
30 min–1 h	516 (32.7%)		183 (36.2%)	
2 h or more	397 (25.1%)		119 (23.6%)	
Noise exposure, dB(A)	56.6 ± 7.31	7	57 ± 7.11	3
Cardiovascular health and diabetes				
Diabetes	80 (5.0%)	–	9 (1.8%)	–
Heart disease diagnosed by a doctor	126 (7.9%)	–	0 (0%)	–
Hypertension	861 (54.0%)	–	0 (0%)	–
Major cardiovascular medication (≥1)	403 (31.7%)	321	0 (0%)	–
ACE inhibitor therapy	102 (8.0%)	321	0 (0%)	–
Uric acid, μmol/L	326 ± 85.93	56	300 ± 77.01	15
hs-CRP, mg/L	1.2 [0.6;2.6]	56	1 [0.5;2]	15
Heart rate (bpm)	74.2 ± 9.1	1	74.6 ± 7.85	1
SDNN (ms)	136.5 ± 35.22	–	140.5 ± 34.49	–
α	2.5 ± 0.4	–	2.5 ± 0.3	–
Slope β	−2.6 ± 1.0	–	−2.7 ± 0.9	–
Largest Lyapunov exponent	0.2 ± 0.09	–	0.2 ± 0.08	–
Air pollutants exposure				
Occupational exposure	400 (25.2%)	3	131 (25.8%)	2
Long-term PM_{10} exposure, $\mu g/m^3$	20.9 [17.8;25.1]	9	20.2 [17.1;24.7]	5
Long-term traffic-related PM_{10} exposure, $\mu g/m^3$	1.9 [1.2;3.1]	9	1.5 [1.1;2.9]	5
Long-term NO_2 exposure, $\mu g/m^3$	24.0 [17.4;34.6]	7	21.6 [16.2;35.3]	4
GST genotypes				
GSTM1 deletion	781 (52.3%)	100	240 (50.3%)	33

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Entire study population (n = 1593)	MD	Subpopulation without cardiovascular morbidity (n = 510)	MD
GSTT1 deletion	261 (17.5%)	100	79 (16.6%)	33
GSTM1 and *GSTT1* deletions	145 (9.7%)	100	41 (8.6%)	33

ACE inhibitor, angiotensin-converting-enzyme inhibitor; BMI, body mass index; ETS, Environmental Tobacco Smoke; hs-CRP, high-sensitivity C-reactive protein; GST, glutathione S-transferase; MD, missing data; PM, particulate matter; SDNN, standard deviation of all NN intervals.
Long-term traffic-related PM_{10}, PM_{10}, and NO_2 exposure correspond to the average of the 10 estimates of annual mean residential exposure to traffic-related PM_{10}, PM_{10}, and NO_2, respectively, over the 10 years preceding the ECG recording (i.e., for the period 1992–2002).
Values shown are mean ± standard deviation, median [25th percentile; 75th percentile] and numbers (percentages).
GST genotypes correspond to homozygous gene deletions of *GSTM1* or *GSTT1*.
Smokers were defined as heavy smokers if they had smoked ≥ 20 pack-years.

Table 2
Association between HRV and heart rate dynamics parameters (outcome variable) and traffic-related PM_{10} in linear mixed effects regression models.

	Entire study population (n = 1237[a])	
	% ΔGM, 95%CI or ΔAM, 95%CI	p-Value
SDNN	−1.3% [−3.7%, 1.1%]	0.27
α	−0.7% [−2.5%, 1.0%]	0.42
Slope β	−0.005 [−0.08, 0.07]	0.89
Largest Lyapunov exponent	−0.002 [−0.01, 0.006]	0.63

All the models include random intercepts for the study areas and are adjusted for gender, age, BMI, smoking status, environmental tobacco smoke exposure, alcohol consumption, physical activity, uric acid, high-sensitivity C-reactive protein, noise exposure, seasonal effect, education level, employment category, occupational exposure, diabetes, and cardiovascular morbidity. Estimates are expressed for a one interquartile range-increment in traffic-related PM_{10} (i.e., 2 μg/m^3). Values shown are percentage change in the geometric mean (% ΔGM) and 95% confidence interval (95%CI), or change in arithmetic mean (ΔAM) (i.e., regression coefficient) and 95%CI.
SDNN, standard deviation of all NN intervals.
[a] Number of subjects included in the regression models (i.e., with no missing values on variables included in the regression models).

cardiovascular morbidity were not statistically significant (Table 3, Fig. 1). Effect modification was statistically significant in the case of β (p = 0.04) and marginally significant in the case of largest Lyapunov exponent (p = 0.08).

Estimates for an increase in TPM_{10} of 1 μg/m^3, instead of an interquartile range, are provided in the Tables S4–S10.

3.3. Investigation of the subgroup without cardiovascular morbidity

In the subgroup of subjects without cardiovascular morbidity, TPM_{10} effects became particularly visible in non-obese subjects both in the HRV parameter (SDNN: −4.4% [−7.9%, 0.04%], p = 0.05) and in the HRD parameters (α: −2.3% [−4.8%, 0.01%], p = 0.05; slope β: 0.2 [0.02, 0.3], p = 0.02; largest Lyapunov exponent: −0.02 [−0.03, −0.004], p = 0.01), while the corresponding associations in obese subjects were not statistically significant. For SDNN, the respective difference was statistically significant (p = 0.01) (Table 4, Fig. 1).

There was no evidence of effect modification by sex (Table S1) and by smoking status (Table S2).

We found strongly significant associations between TPM_{10} and HRV/HRD parameters (SDNN: −5.7% [−10.6%, −0.6%], p = 0.03; slope β: 0.2 [0.08, 0.4], p < 0.001) in subjects with homozygous *GSTM1* gene deletion, i.e., in subjects with a weakened oxidative stress defense (Table 5, Fig. 1). Note that slope β is indeed expected to be increased in case of deleterious effects on heart rate dynamics. Conversely, the HRD parameter α was significantly decreased (−3.4% [−6.1%, −0.8%], p = 0.01) in subjects without *GSTM1* deficiency.

When stratifying by *GSTT1* genotype, we observed significant associations in subjects without GSTT1 deficiency (Table S3). However, coefficients in subjects with homozygous *GSTT1* gene deletion were similar to those in subjects without *GSTT1* deficiency, and confidence intervals were very broad. The small sample size of the subgroup of subjects with homozygous *GSTT1* gene deletion (n = 69) might have limited the statistical power of these analyses. Consequently, there is no evidence of effect modification by *GSTT1* genotype.

Estimates, provided above for an interquartile range, are additionally provided for an increase of 1 μg/m^3 in TPM_{10} in the Supplemental Material (Tables S5–S10).

3.4. Sensitivity analyses

As previously shown in the SAPALDIA cohort study, there was a strong decrease in SDNN (−12.9% [−23.9%, −1.4%], p = 0.03) in subjects under ACE inhibitor therapy (Table S11). In contrast, we found no evidence that the effects of TPM_{10} on the HRD parameters were modified by ACE inhibitor intake.

Exclusion of subjects with diabetes made associations even stronger

Table 3
Association between HRV and heart rate dynamics parameters (outcome variable) and traffic-related PM_{10} in linear mixed effects regression models stratified by cardiovascular morbidity.

	Cardiovascular morbidity (n = 775[a])		No cardiovascular morbidity (n = 462[a])		Interaction[b]
	% ΔGM, 95%CI or ΔAM, 95%CI	p-Value	% ΔGM, 95%CI or ΔAM, 95%CI	p-Value	p-Value
SDNN	−0.5% [−3.5%, 2.4%]	0.76	−3.0% [−6.6%, 1.2%]	0.15	0.36
α	−0.06% [−2.5%, 2.4%]	0.96	−1.8% [−4.4%, 0.4%]	0.11	0.24
Slope β	−0.06 [−0.2, 0.06]	0.36	0.2 [0.03, 0.3]	0.01	0.04
Largest Lyapunov exponent	0.003 [−0.005, 0.01]	0.47	−0.01 [−0.02, −0.001]	0.03	0.08

All the models include random intercepts for the study areas and are adjusted for gender, age, BMI, smoking status, environmental tobacco smoke exposure, alcohol consumption, physical activity, uric acid, high-sensitivity C-reactive protein, noise exposure, seasonal effect, education level, employment category, occupational exposure, and diabetes. Estimates are expressed for a one interquartile range-increment in traffic-related PM_{10} (i.e., 2 μg/m^3). Values shown are percentage change in the geometric mean (% ΔGM) and 95% confidence interval (95%CI), or change in arithmetic mean (ΔAM) (i.e., regression coefficient) and 95%CI.
SDNN, standard deviation of all NN intervals.
[a] Number of subjects included in the regression models (i.e., with no missing values on variables included in the regression models).
[b] Interaction between TPM_{10} and cardiovascular morbidity.

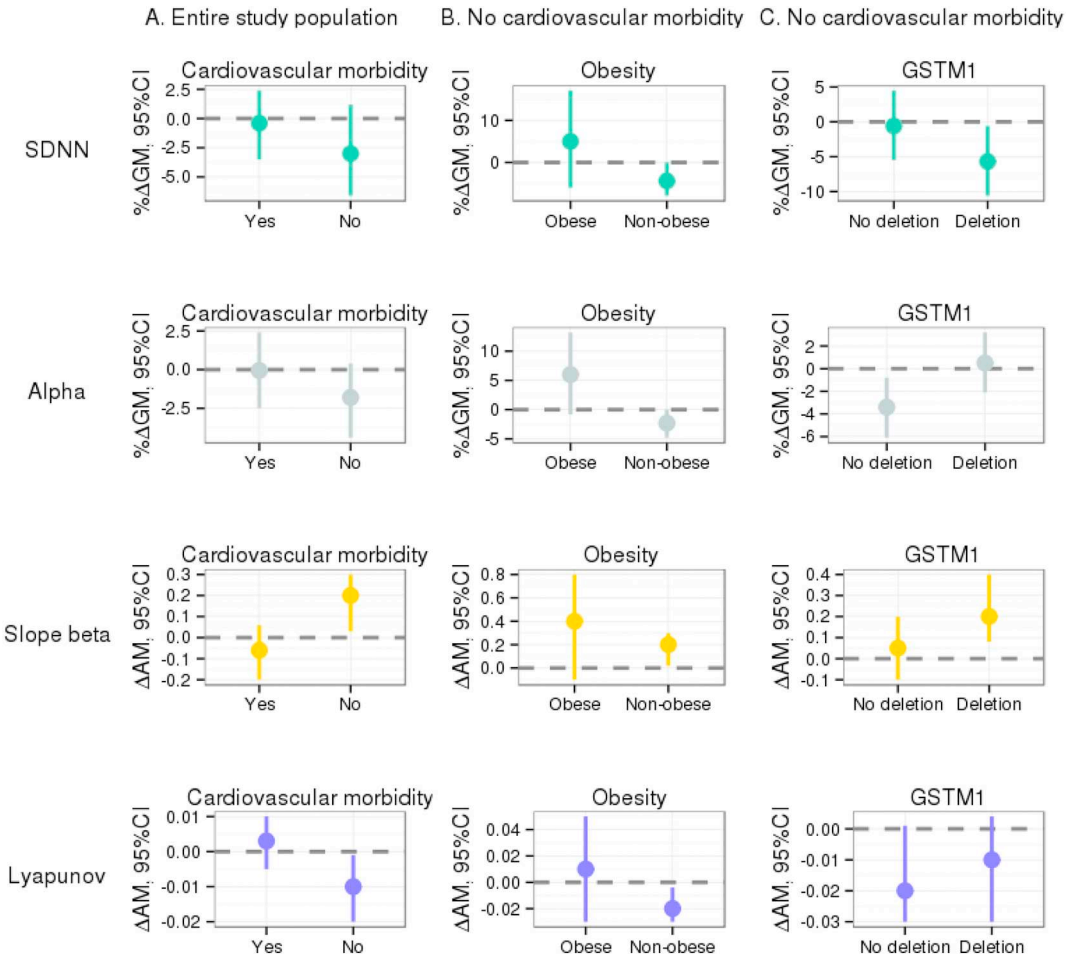

Fig. 1. Percentage change in geometric mean (% ΔGM) and 95% confidence interval (95%CI) of SDNN and alpha, or change in arithmetic mean (ΔAM) (i.e., regression coefficient) and 95%CI of slope beta and largest Lyapunov exponent, for a one interquartile range-increment in traffic-related PM_{10} (i.e., 2 μg/m^3), in models stratified by cardiovascular morbidity in the entire study population (A), and by obesity (B) and *GSTM1* (C) in the subpopulation without cardiovascular morbidity.
GST, glutathione S-transferase; SDNN, standard deviation of all NN intervals.

in non-obese subjects for SDNN (−4.6% [−8.1%, −0.9%], p = 0.04) and α (−2.4% [−4.9%, −0.1%], p = 0.04) (Table S12), as well as in subjects without *GSTT1* deletion for α (−2.4% [−4.9%, −0.02%], p = 0.05) and slope β (0.2 [0.0007, 0.3], p = 0.05) (Table S13).

Adjustment for short-term exposure to PM_{10} led only to minor changes in the results (data not shown) and did not alter conclusions.

Estimated effect sizes observed from models with or without adjustment for hsCRP were very similar (data not shown), excluding potential issues related to eventual over-adjustments.

3.5. Relationship between other air pollutants and HRV/HRD

Results for long-term exposure to PM_{10} and NO_2 were very similar to those found for TPM_{10} (Figs. S1–S2, Tables S14–S41), which is consistent with medium to high correlations between these pollutants ($\rho_{TPM10/PM10}$ = 0.86, p < 0.001; $\rho_{TPM10/NO2}$ = 0.76, p < 0.001). The effects sizes of long-term exposure to PM_{10} and NO_2 were smaller though. More detailed comparisons of NO_2 and PM_{10} findings with TPM_{10} findings are provided in the Supplemental Material.

4. Discussion

4.1. Main findings

This study evaluated the influence of long-term exposure to TPM_{10} on HRV and heart rate dynamics. While we did not find any significant associations in the entire study population, we observed significant associations of long-term exposure to TPM_{10} with the HRD parameters slope β and largest Lyapunov exponent in subjects without cardiovascular morbidity. Findings for PM_{10} and NO_2 were similar, though the effect sizes were smaller.

The null findings in the subgroup with diseases is no proof of no effect in this population. Not only is statistical power reduced but the pathophysiologic heterogeneity of this sub-population is certainly larger, with a range of other factors (including in particular various drugs) possibly intervening with the relevant pathways related to air pollution. If this is the case, statistical signals in this subgroup are expected to be much “noisier” than in the more homogeneous group of health people. In particular, effects of TPM_{10} may have been counteracted by drug treatments in subjects with cardiovascular disease, which would explain why the TPM_{10}–HRV/HRD relationship became more visible in subjects without cardiovascular disease and related drug treatments. Moreover, a damaged heart may no longer react well to both positive and negative influences, in which case HRV/HRD might thus be decoupled from external influences. Finally, the TPM_{10} effects became even more visible in the subgroup of non-obese subjects without cardiovascular morbidity, as shown by both HRV and HRD parameters, while the underlying health conditions and the counteracting effects of drug treatments (e.g., statins) might have weakened the TPM_{10}–HRV/HRD relationship in obese subjects.

Table 4
Association between HRV and heart rate dynamics parameters (outcome variable) and traffic-related PM_{10} in linear mixed effects regression models stratified by obesity.

Entire study population	Non-obese (n = 974[a])		Obese (n = 263[a])		Interaction[b]
	% ΔGM, 95%CI or ΔAM, 95%CI	p-Value	% ΔGM, 95%CI or ΔAM, 95%CI	p-Value	p-Value
SDNN	−1.4% [−4.0%, 1.7%]	0.33	−1.3% [−6.2%, 3.8%]	0.61	0.72
α	−0.6% [−2.3%, 1.2%]	0.53	−0.6% [−4.5%, 3.2%]	0.76	0.88
Slope β	−0.01 [−0.1, 0.08]	0.82	0.05 [−0.1, 0.2]	0.54	0.34
Largest Lyapunov exponent	0.0001 [−0.008, 0.008]	0.98	−0.006 [−0.02, 0.009]	0.41	0.21
Subpopulation without cardiovascular morbidity	**Non-obese (n = 415[a])**		**Obese (n = 47[a])**		**Interaction[b]**
	% ΔGM, 95%CI or ΔAM, 95%CI	p-Value	% ΔGM, 95%CI or ΔAM, 95%CI	p-Value	p-Value
SDNN	−4.4% [−7.9%, 0.04%]	0.05	5.0% [−6.0%, 17.2%]	0.38	0.01
α	−2.3% [−4.8%, 0.01%]	0.05	6.0% [−0.8%, 13.2%]	0.08	0.13
Slope β	0.2 [0.02, 0.3]	0.02	0.4 [−0.1, 0.8]	0.14	0.56
Largest Lyapunov exponent	−0.02 [−0.03, −0.004]	0.01	0.01 [−0.03, 0.05]	0.60	0.11

All the models include random intercepts for the study areas and are adjusted for gender, age, BMI, smoking status, environmental tobacco smoke exposure, alcohol consumption, physical activity, uric acid, high-sensitivity C-reactive protein, noise exposure, seasonal effect, education level, employment category, occupational exposure, diabetes, and cardiovascular morbidity (except for the subpopulation without cardiovascular morbidity). Estimates are expressed for a one interquartile range-increment in traffic-related PM_{10} (i.e., 2 μg/m^3). Values shown are percentage change in the geometric mean (% ΔGM) and 95% confidence interval (95%CI), or change in arithmetic mean (ΔAM) (i.e., regression coefficient) and 95%CI.
SDNN, standard deviation of all NN intervals.
[a] Number of subjects included in the regression models (i.e., with no missing values on variables included in the regression models).
[b] Interaction between TPM_{10} and obesity.

Table 5
Association between HRV and heart rate dynamics parameters (outcome variable) and traffic-related PM_{10} in linear mixed effects regression models stratified by *GSTM1* genotype.

Entire study population	Deletion in *GSTM1* (n = 620[a])		No deletion in *GSTM1* (n = 572[a])		Interaction[b]
	% ΔGM, 95%CI or ΔAM, 95%CI	p-Value	% ΔGM, 95%CI or ΔAM, 95%CI	p-Value	p-Value
SDNN	−2.2% [−5.3, 1.1]	0.19	−0.6% [−3.5%, 2.4%]	0.69	0.38
α	0.5% [−1.9, 3.1]	0.68	−1.7% [−4.0%, 0.4%]	0.12	0.23
Slope β	0.04 [−0.08, 0.2]	0.48	−0.01 [−0.1, 0.1]	0.82	0.65
Largest Lyapunov exponent	−0.002 [−0.01, 0.01]	0.76	−0.002 [−0.01, 0.007]	0.66	0.79
Subpopulation without cardiovascular morbidity	**Deletion in *GSTM1* (n = 227[a])**		**No deletion in *GSTM1* (n = 217[a])**		**Interaction[b]**
	% ΔGM, 95%CI or ΔAM, 95%CI	p-Value	% ΔGM, 95%CI or ΔAM, 95%CI	p-Value	p-Value
SDNN	−5.7% [−10.6%, −0.6%]	0.03	−0.6% [−5.5%, 4.6%]	0.82	0.11
α	0.5% [−2.1%, 3.2%]	0.72	−3.4% [−6.1%, −0.8%]	0.01	0.21
Slope β	0.2 [0.08, 0.4]	< 0.001	0.05 [−0.1, 0.2]	0.59	0.29
Largest Lyapunov exponent	−0.01 [−0.03, 0.005]	0.16	−0.02 [−0.03, 0.001]	0.08	0.57

All the models include random intercepts for the study areas and are adjusted for gender, age, BMI, smoking status, environmental tobacco smoke exposure, alcohol consumption, physical activity, uric acid, high-sensitivity C-reactive protein, noise exposure, seasonal effect, education level, employment category, occupational exposure, diabetes, and cardiovascular morbidity (except for the subpopulation without cardiovascular morbidity). Estimates are expressed for a one interquartile range-increment in traffic-related PM_{10} (i.e., 2 μg/m^3). Values shown are percentage change in the geometric mean (% ΔGM) and 95% confidence interval (95%CI), or change in arithmetic mean (ΔAM) (i.e., regression coefficient) and 95%CI.
GST, glutathione S-transferase; SDNN, standard deviation of all NN intervals.
[a] Number of subjects included in the regression models (i.e., with no missing values on variables included in the regression models).
[b] Interaction between TPM_{10} and *GSTM1* genotype.

Additionally, our findings support the hypothesis that TPM_{10} might impact in part through oxidative stress pathways. We found significant associations between TPM_{10} and HRV/HRD parameters in subjects with homozygous *GSTM1* gene deletion (as shown by SDNN and slope β), in accordance with a previous oxidative stress gene pathway analysis conducted in SAPALDIA on smoking, air pollution and lung function (Curjuric et al., 2012).

Finally, the fact that significant adverse effects of TPM_{10} were revealed in subjects without cardiovascular morbidity only for HRD parameters suggests that measuring changes in the complexity of heart rate dynamics in response to environmental exposures, might unveil subtle but important changes in the regulatory mechanisms of the cardiovascular system not detectable by traditional parameters of heart rate variability.

4.2. Strengths and weaknesses of the study

To the best of our knowledge, this is the first study examining the influence of low-level, but long-term, particulate matter air pollution exposure on parameters describing the HRV and heart rate dynamics (using nonlinear time series analysis methods). Additional strengths of the present study include the population-based design, involving a random sample of the Swiss population; the large number of participants; and the detailed information available on participants, allowing for the control of most potential confounders.

A limitation of this study is the absence of a physiological interpretation of the parameters calculated with methods from nonlinear dynamics. The lack of physiological interpretation of such metrics constitutes a major limitation for their use (Francesco et al., 2012; Goldberger et al., 2000; Manor and Lipsitz, 2013). Though it is reasonable to assume that these mathematical concepts could help gain insight into mechanisms underlying systems fluctuation behaviour (e.g., modulations of heart period), efforts are needed to improve our understanding of their physiological correlates. In the present study, this uncertainty, as well as the absence of reference values, limited the interpretation of observed associations. Another limitation is that multiple testing could have led to spurious association with novel HRV parameters. However, the objective of the study was to estimate associations, not to test formal hypotheses. The statistical uncertainty of the estimates is described by their 95% confidence intervals. Finally, the small sample size of some subgroups, as well as the low prevalence of some genotypes, which limited statistical power of the explanatory analyses. The relevance of oxidative stress as a mediating mechanism and susceptibility determinant needs broader exposome approaches in the future (Fiorito et al., 2018).

4.3. Comparison of the study results to other studies

To the best of our knowledge, the association between long-term traffic-related particulate matter exposure and HRV has only been examined in the SAPALDIA cohort study (TPM_{10} levels averaged over a 10 year period) (Adam et al., 2012; Adam et al., 2014), and by Mordukhovich et al., who evaluated sub-chronic (3–84 days) and longer-term (1 year) $PM_{2.5}$ or black carbon (a marker of traffic pollution) exposure in relation to HRV (Mordukhovich et al., 2015). These studies did not observe any consistent overall associations.

Interestingly, in the present study, we observed significant associations between heart rate dynamics and TPM_{10} only in the subgroup of subjects without cardiovascular morbidity (i.e., no hypertension or heart disease). These findings are in line with those from Barclay et al. who did not observe any hematological or electrocardiogram response to ambient air pollution in patients with cardiac failure, thought to be a susceptible group (Barclay et al., 2009), while, in contrast to their earlier findings, they observed such associations in healthy elderly people (Seaton et al., 1999). They concluded that modern cardiac therapy was likely to give a measure of protection against the adverse cardiac effects of air pollution.

Several studies have provided evidence that the relation between HRV and cardiovascular drug therapies varies and depends on the type of therapy. Adam et al. observed that the adjusted HRV of subjects treated with ACE inhibitors or beta blockers was generally increased, while the HRV of subjects treated with angiotensin receptor blockers, calcium channel blockers, or diuretics, was decreased when compared with the average HRV levels of participants without any heart medication intake (Adam et al., 2012). Furthermore, they provided suggestive evidence that participants under ACE inhibitor treatment may represent a specific subgroup susceptible to the adverse effects of TPM_{10} on HRV. In some other studies, beta blockers (Gold et al., 2000; Park et al., 2005), calcium channel blockers (Park et al., 2005) and statins (Schwartz et al., 2005b) were shown to attenuate the effects of air pollutants; while another study found no evidence of effect modification by beta blockers (Schwartz et al., 2005a). These findings suggest that response to long-term TPM_{10} exposure might result from the relative contribution of both the underlying cardiovascular condition and the counteracting effects of drug treatments, which might in turn explain the heterogeneous effects of short- and long-term exposure to PM air pollution found in subjects with a cardiovascular morbidity (Buteau and Goldberg, 2016; Chuang et al., 2005; Holguin et al., 2003; Park et al., 2005; Pieters et al., 2012; Schwartz et al., 2005a).

The TPM_{10}-HRV/HRD relationship became even more visible when we focused on healthier subjects in the subgroup of subjects without cardiovascular morbidity (i.e., non-obese subjects, and subjects without diabetes). These findings are consistent with those from Yingying et al., who found greater reductions in HRV in relation to PM_{10} exposure in subjects with low Framingham risk score (i.e., low global cardiac risks) (Feng et al., 2015).

We found significant associations in subjects with homozygous *GSTM1* gene deletion, which is in line with previous studies having indicated that air pollutants might impact in part through oxidative stress pathways (Pieters et al., 2012; Probst-Hensch et al., 2008; Schwartz et al., 2005b). Conversely, the HRD parameter α was significantly decreased in subjects without *GSTM1* deficiency. This observation might be explained by the fact that those subjects are likely to be healthier than the subjects with homozygous *GSTM1* gene deletion (i.e., not likely to have systemic inflammation and oxidative stress) and thus, similarly to our findings in non-obese subjects, TPM_{10} effects might be visible in such subjects while being masked in the others.

Our findings support the hypothesis that long-term air pollution effects may lead the accumulation of molecular damage in the cardiovascular system, while short-term air pollution exposure might lead to increased risk of acute cardiovascular disease events in persons with a cardiovascular diagnosis. This hypothesis is supported by a) sensitivity analyses that showed that short-term exposure effects do not confound long-term exposure effects, b) stronger long-term than short-term effects on cardiovascular disease mortality (Brook et al., 2010), and c) our observation that long-term effects were more pronounced in healthier persons, while short-term effects are generally seen to be stronger in persons with a cardiovascular diagnosis (Brook et al., 2010; Pieters et al., 2012; Pope III et al., 2004). The joint influence of short- and long-term influence in persons with and without existing disease should be further evaluated in future studies.

Finally, we found very similar results for long-term exposure to PM_{10} and NO_2 to those found for TPM_{10}, though the effects sizes of long-term exposure to PM_{10} and NO_2 were smaller. These findings are in line with those from Sanyal et al., who confirmed that PM has a long-term impact on mortality and morbidity and who observed that exposure to NO_2 could also lead to increased health risks (Sanyal et al., 2018).

4.4. Relevance of the study and implications for policymakers

First, this study provides evidence of the adverse effects of long-term exposure to TPM_{10} on HRV and heart rate dynamics in subjects without cardiovascular disease, which are believed to be less susceptible than specific subpopulations with morbidities (e.g., the elderly, patients with preexisting cardiovascular disease or diabetes, obese subjects) though. However, further studies are needed to see whether these alterations in HRV/HRD in healthy people are in part on the pathologic pathway of the many studies confirming a causal role of air pollution in shortening life expectancy.

Second, this study provides evidence that the TPM_{10}-HRV/HRD relationship in subjects with cardiovascular morbidity might be modified by both the underlying cardiovascular condition and the related treatments. Thus, some cardiac therapies, for a given underlying cardiovascular condition, might be protective against the adverse cardiac effects of air pollution, whereas some other cardiac therapies/conditions might render subjects particularly susceptible to those effects.

Alternatively, effects of treatments not controlled in our analyses could result in stronger and possibly heterogeneous effects on the same outcomes, thus, the detection of subtle effects of air pollution may be possible only in much larger populations of patients. Further studies investigating the TPM_{10}-HRV/HRD relationship in subjects with cardiovascular morbidity are therefore necessary.

5. Conclusions

In conclusion, findings from the present study indicate that long-term exposure to TPM_{10}, even at low levels, may trigger adverse changes in the regulation of the cardiovascular system and in the heart rate dynamics. These adverse effects were more visible in healthier subjects, in whom the overall TPM_{10}-HRV/HRD relationship could not be not modified by an underlying cardiovascular condition, obesity, or weakened oxidative stress defense, and the potential counteracting effects of related drug treatments. Future studies need to evaluate the predictive value of the observed heart rate dynamics differences for all cause and cardiovascular morbidity and mortality.

Declarations of interest

None.

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Appendix A. Supplementary data

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