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Exposure to Fine Particulate Matter Leads to Rapid Heart Rate Variability Changes

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Introduction: Heart Rate Variability (HRV) reflects the adaptability of the heart to internal and external stimuli. Reduced HRV is a predictor of post-infarction mortality. We previously found in road maintenance workers HRV-increases several hours after exposure to fine particulate matter ($PM_{2.5}$). This seemed to conflict with studies where PM-exposure acutely reduced HRV. We therefore assessed whether time from exposure to HRV-assessment could explain the differences observed.

Methods: On five non-consecutive days, workers carried nephelometers providing 1-min-interval $PM_{2.5}$-exposure. Five-min HRV-intervals of SDNN (Standard Deviation of Normal to Normal beat intervals) and pNN50 (Percentage of the interval differences exceeding 50 ms) were extracted from 24-h electrocardiograms (ECGs). Following 60 min $PM_{2.5}$-exposure, changes in HRV-parameters were assessed during 120-min visually and by regression analysis with control for time at work, at home, and during the night using autoregressive integrating moving average (ARIMA) models to account for autocorrelation of the time-series. Additional controls included changing the time windows and including body mass index (BMI) and age in the models.

Result: Pattern analysis of 12,669 data points showed high modulation of mean, standard deviation (SD), and time trend of HRV (SDNN and pNN50) at low, and much reduced modulation at high $PM_{2.5}$-exposures. The time trend following exposure was highly symmetrical, resembling a funnel plot. Regression analysis showed significant associations of decreasing SDNN and pNN50 (average, SD, and absolute value of time trend) with increasing $PM_{2.5}$-exposure, which remained significant when controlling for activity phases. Changing time windows did not change the pattern of response. Including BMI and age did not change the results.

Conclusions: The reduced modulation of HRV following $PM_{2.5}$-exposure is striking. It suggests strong interference with homeostatic controls. Such an interference would represent a serious bodily burden, and could help explain acute cardiac events. In this model, the increase of HRV several hours later would reflect a recovery response.

Keywords: heart rate variability, fine particulate matter, acute exposure, homeostatic interference, ARIMA methodology

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INTRODUCTION

Heart Rate Variability (HRV) describes the variation of the timing between individual heart beats. It is a consequence of the heart's response to a series of internal and external stimuli such as respiration, baroreceptor feedback loop, and parasympathetic and sympathetic nervous system activity (Billman, 2011; Shaffer et al., 2014). Elevated HRV is a sign for a healthy cardiovascular system, while reduced HRV is a predictor of post-infarct mortality (Billman, 2011), cardiac events in healthy individuals (Tsuji et al., 1996), and incident heart failure in older at-risk adults (Patel et al., 2017). Most commonly assessed are the time- or the frequency-domain of HRV, though a large number of mathematical and statistical approaches are available (Electrophysiology Taskforce Guidelines, 1996; Sassi et al., 2015). Amongst the frequently used time domain parameters are SDNN (Standard Deviation of Normal to Normal beat intervals) and pNN50 (Percentage of the interval differences exceeding 50 ms): SDNN was found to reflect overall autonomic activity and cardiovascular fitness (Electrophysiology Taskforce Guidelines, 1996; Tsuji et al., 1996; Da Silva et al., 2015), While PNN50 is frequently used to assess parasympathetic activity (Ewing et al., 1984; Electrophysiology Taskforce Guidelines, 1996; Tsuji et al., 1996; Mietus et al., 2002).

Fine particulate matter (PM) on roads originates to an important part from traffic and combustion engines which release particles and precursors of secondary aerosols into the air (Riediker et al., 2003; Putaud et al., 2010; Meier et al., 2013). High concentrations occur in particular along busy roads such as highways, which are depending on factors such as traffic counts but also weather and wind (Imhof et al., 2005; Zwack et al., 2011). Workers maintaining the highways will experience exposure to $PM_{2.5}$ that originates from the general background, from the passing traffic and also the different work tasks (Meier et al., 2013). Exposure to airborne PM is a well-established risk for human health (Brook et al., 2010; Landrigan et al., 2017), in particular fine ($PM_{2.5}$) and ultrafine PM increases both short- and long-term cardiovascular risk. PM negatively affects cardiovascular risk factors (reviewed by Brook et al., 2010) such as inflammation (Tsai et al., 2012a), sodium regulation by the kidney (Tsai et al., 2012b), pulse pressure (Tsai et al., 2015), and metabolic syndrome (Brook et al., 2013; Devlin et al., 2014). PM is associated with cardiac arrhythmias (Kowalska and Kocot, 2016; Mordukhovich et al., 2016; Song et al., 2016), arrhythmic events are more frequently detected and treated by implanted cardioverter-defibrillators (Dockery et al., 2005; Metzger et al., 2007; Link et al., 2013), and people spending time in traffic are more likely to suffer a heart attack within the hour (Peters et al., 2004). In line with these ill-health effects of PM was the observation that $PM_{2.5}$ exposure is associated with reduced HRV: in controlled exposure of rats to $PM_{2.5}$, HRV was reduced during ongoing exposure (Wagner et al., 2014). In a series of epidemiological (Pope et al., 2003; Wu et al., 2010; Huang et al., 2014; Nyhan et al., 2014; Mordukhovich et al., 2015; Lee et al., 2016) as well as controlled PM-exposure (Devlin et al., 2003; Weichenthal et al., 2014; Cole-Hunter et al., 2015; Hemmingsen et al., 2015) studies, small reductions in HRV within an hour after PM exposure were observed. However, a recent meta-analysis of panel studies investigating HRV effects of $PM_{2.5}$ (Buteau and Goldberg, 2016) questioned the association between $PM_{2.5}$ and frequently used indices of HRV. Indeed, in our own two studies in healthy workers, we had found increased HRV (SDNN and PNN50) in the morning after exposure to traffic particles (Riediker et al., 2004a,b; Riediker, 2007; Meier et al., 2014). In the study with highway patrol troopers, we had also assessed an intermediary point at the end of the working day, which was well after peak rush hour exposure (Riediker et al., 2004a). At that intermediary point, no associations between $PM_{2.5}$ and HRV were observed. The time from exposure to HRV analysis varies strongly between studies, an aspect that was not further assessed in the aforementioned review (Buteau and Goldberg, 2016). In this study, we aimed to understand if differences in time from exposure until the HRV-response assessment could explain the differences in HRV-association with $PM_{2.5}$. For this purpose, we assessed the immediate HRV response to particles by analyzing the time-series of electrocardiograms (ECGs) and $PM_{2.5}$ obtained in the highway maintenance workers study (Meier et al., 2014) where we had found increases of HRV in the morning after exposure. In addition, we aimed to better understand the way HRV was acutely changed and thus assessed (in addition to changes in average HRV) also the modulation of HRV over a 2-h time window following exposure and the time-trend of the series of 5-min averages of HRV during this time window.

METHODS

We analyzed $PM_{2.5}$-exposure and ECG data collected from a panel of 18 healthy male Swiss highway maintenance workers from 10 different maintenance centers in western Switzerland. The study was approved by the Ethics Committee of the University of Lausanne. All subjects gave written informed consent prior to participation in the study. The here presented analysis focused on the effects of continuously measured $PM_{2.5}$ on HRV. The methodology to collect exposure (Meier et al., 2013) and health (Meier et al., 2014) data was previously described in detail. Briefly, subjects were equipped in the morning before the start of their work with small devices to record ECG and personal $PM_{2.5}$-exposure for 24-h. Twelve ECG leads were attached by a trained researcher, then connected to a. digital ECG Holter monitor recorder (H12+ Digital, Mortara Instrument, Inc., Milwaukee, WI, USA).The high-resolution ECG records were afterwards processed with H-Scribe+ software, and inspected manually by an experienced cardiologist (Wayne E. Cascio, U.S. EPA, Chapel Hill, NC, USA) to remove artifacts and non-normal beats. Processed ECG-derived HRV data was recorded at 5-min resolution. $PM_{2.5}$ was measured at 1-min resolution by light scattering nephelometers (DataRam pDR1000, Thermo Scientific, Waltham, MA, USA). This averaging time gives a precision of $\pm 0.2\%$ of reading or ± 0.005 mg/m^3, whichever is larger (manufacturer specification). We further improved the readout by correcting if for humidity (Richards, 1999). The monitor was attached to the body near the breathing zone while the worker was awake; and placed on the bed side table during

sleep. The 1-min recordings were condensed into 5-min average intervals so that they matched the time intervals of the ECGs. Logbooks were used to identify activity phases at work, at home and at night, defined as the time between 22:00 and 06:00. Subjects participated up to five times on non-consecutive days.

Statistical Analyses

From the time-series of $PM_{2.5}$ recordings, moving average concentrations were calculated for 60-min time-windows. From the HRV-recordings (5-min interval SDNN and pNN50), the following summary variables were calculated for moving time-windows of 120 min: mean HRV-value, Standard Deviation (SD) of the HRV, the time-trend (expressed as the slope over time) of HRV during this time window and the absolute value of the time trend. These HRV summary-variables were compared to the preceding $PM_{2.5}$-exposure (example shown in **Figure 1**). The time intervals were defined based on the hypothesis that effects would occur already within the first 2-h after exposure, and the attempt to have a sufficiently large number of data-points per interval to allow for a robust assessment. The consequences of changing the averaging intervals were tested in a sensitivity analysis. The influence of activity phase at the moment of exposure (at work, home, or night) was assessed both, by stratification and calculation of the effect estimates for each strata, and by including activity phase as a co-factor in the models. The ARIMA methodology was used to account for second-order autocorrelation of the time-series. The models were computed individually for each person and the resulting coefficients were combined using a meta-analysis approach to obtain the population coefficients and variances. To account for the skewed distribution, $PM_{2.5}$ was log-transformed (in basis 2) when fitting the models. To enable a comparison among results involving different cardiac parameters, all these parameters were standardized for each individual by subtracting the mean from the individual observations and dividing the difference by the parameter's SD. The potential influence of age and body mass index (BMI) on the individuals' effect estimates was assessed by using Spearman rank test. Calculations were performed using the basic functions of the R statistical software package Forecast version 7.3.

RESULTS

Data were collected on 50 days from 18 workers, resulting in 88 personal observation-days. On 77 of these days both, valid $PM_{2.5}$ and HRV data were available to calculate HRV and $PM_{2.5}$ parameters. The resulting 12,669 ECG data points and matching exposure data were used for analysis (summarized in **Table 1**). Mean $PM_{2.5}$-exposure at work was about double than that at home and about four times the night values. SDNN during wake phases was slightly smaller than during the night, pNN50 was lowest at work and highest during the night.

Plotting mean and SD of 120 min of SDNN and pNN50 against 60 min of preceding $PM_{2.5}$-exposure (**Figure 2**) showed a wide range of values at low concentrations and a smaller range at higher concentrations, while visually, there was no clear difference in mean value for different exposure levels. The SD of 5-min HRV over the 2-h following exposure showed a similar pattern as the mean (**Figure 2**). However, plotting the time trend of SDNN and pNN50 following the different exposure levels (**Figure 2**) revealed a very symmetrical pattern of time trend-values being highly variable at low exposure and close to zero at elevated exposures, yielding a typical appearance of a funnel plot. This pattern was highly significant, as revealed in the regression analysis below. A similar pattern was observed for all activity phases (work, home, night).

Regression analysis of SDNN and pNN50 parameters (mean, SD and absolute value of the time trend) against exposure (**Table 2**) showed significant negative $PM_{2.5}$ effect estimates for all three parameters of SDNN and pNN50. Control for activity phases at work, at home and during the night reduced the effect estimates but all remained significant at the 5% significance level. Neither age nor BMI were statistically significantly related to the individual effect estimates. Stratified analyses also show significant effect estimates in most strata (**Table 3**).

In a sensitivity analysis, the influence of the averaging times was tested by shortening and increasing the intervals. The visual pattern remained similar at all tested interval lengths and combinations (examples of tested variants shown in **Figure 3**). The effect estimates (all tested combinations shown in **Table 4**) for mean and SD of SDNN and pNN50 remained significant in most tested variants, while the absolute value of the time trends of SDNN and pNN50 were significant only for the longer time windows after control for activity (at least 40 min of exposure, at least 80 min of HRV).

DISCUSSION

Acute exposure to $PM_{2.5}$ was followed by reduced HRV, which is in agreement with previous studies (Pope et al., 2003; Wu et al., 2010; Huang et al., 2014; Nyhan et al., 2014; Mordukhovich et al., 2015; Lee et al., 2016). Different from those studies, we also assessed whether HRV shows a time-trend to increase or decrease after high exposures. The scatterplots showing the time trends of SDNN and pNN50 vs. $PM_{2.5}$ have a remarkable appearance of a "funnel plot": whereas we had approximately as many increasing and decreasing time trends, compensating each other and averaging zero, whatever the value of $PM_{2.5}$, the values of the time trends (whether increasing or decreasing) were consistently distributed over a wide range for low exposures and distributed in a very narrow range for high exposures (**Figure 2**).

The pattern of reduced modulation of HRV at elevated $PM_{2.5}$-levels exists for all three activity phases assessed (work, home, at night), though the pattern is easiest to be recognized visually for the working hours. This is remarkable because the exposure at home and at night is representing what the normal (Swiss) population experiences, which is quite low. In contrast, the working exposure is reflective of the workplace along the highways with occasionally very high exposure levels (Riediker et al., 2003; Meier et al., 2013). In many major cities in low-income countries around the globe similar. Concentrations are at similar or even higher levels than those found at the workplace of these Swiss highway maintenance teams (Landrigan et al., 2017). The here observed striking work-time effects can be expected in

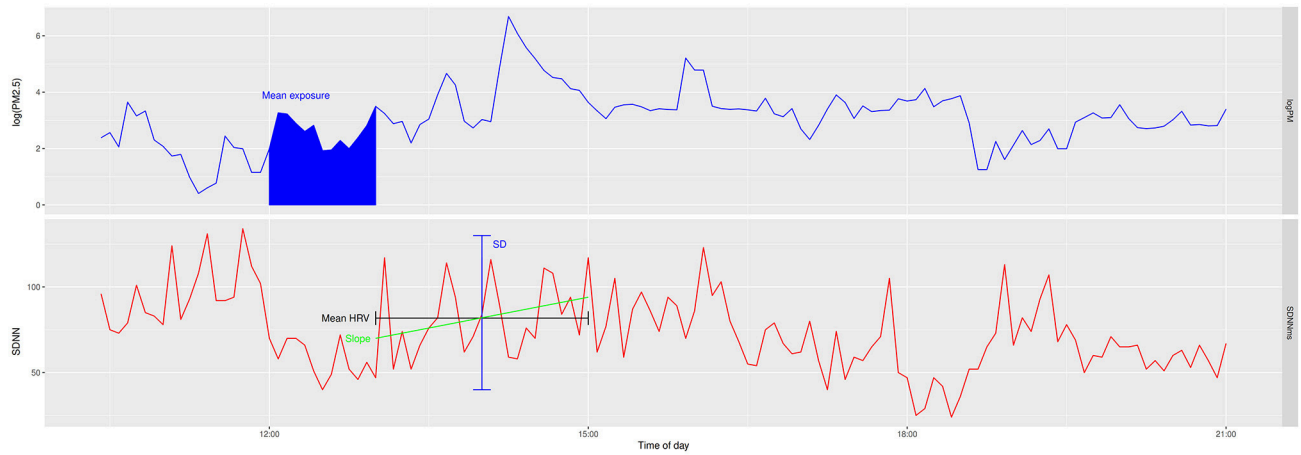

FIGURE 1 | Example of a time series of $PM_{2.5}$ and HRV of one 24-h recording of one subject. **Upper**: $PM_{2.5}$, **Lower**: SDNN. The mean exposure over 1-h was compared to mean, standard deviation (*SD*), and slope of HRV in the 2-h following the exposure.

TABLE 1 | Summary statistics of assessed data.

Parameter	All activity phases mean (range)	Work only mean (range)	Home only mean (range)	Night only mean (range)
n	1,1941	3,887	3,605	4,449
$PM_{2.5}$ (60 min mean) ($\mu g/m^3$)	51.35 (0.026–3333)	88.48 (0.368–3333)	48.17 (0.026–2129)	21.5 (0.026–148.1)
SDNN (120 min mean) (ms)	72.44 (14.91–240.2)	63.28 (22.52–158.30)	63.4 (17.74–205.3)	87.75 (14.91–240.2)
pNN50 (120 min mean) (%)	13.32 (0–86.67)	5.63 (0–56.38)	11.04 (0–77)	21.89 (0–86.67)

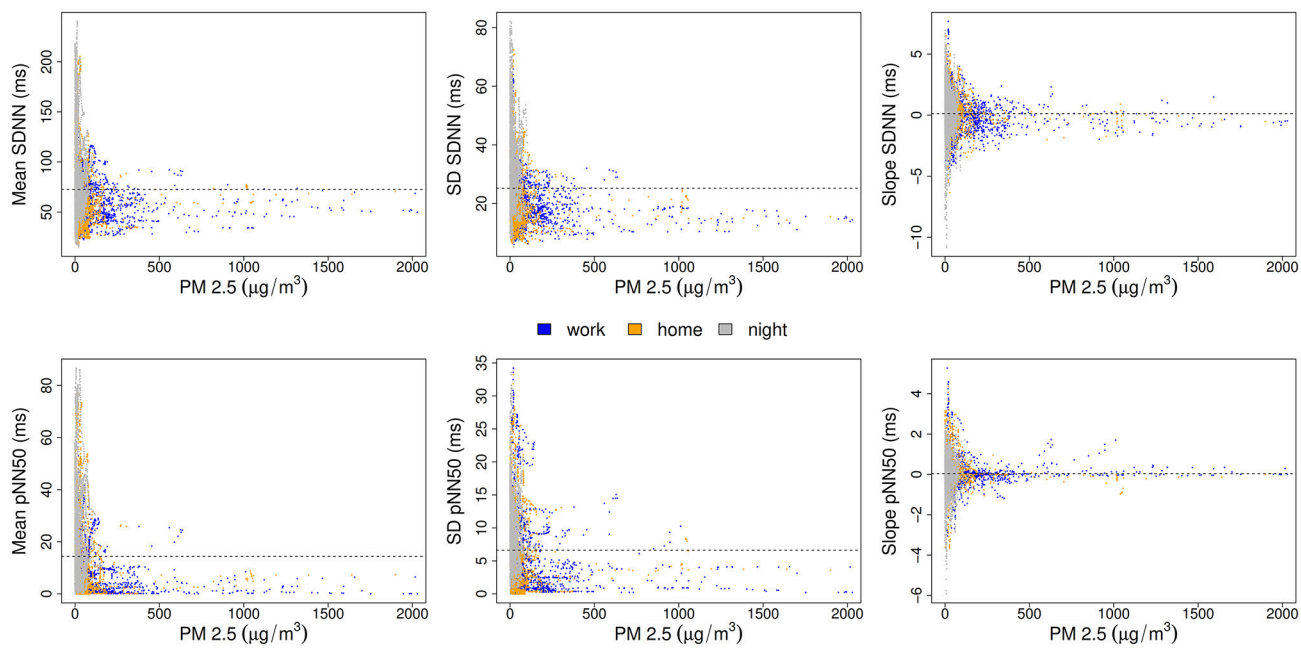

FIGURE 2 | Comparison of HRV parameters SDNN (top) and pNN50 (bottom) after $PM_{2.5}$-exposure: Average HRV **(Left)**, the standard deviation of HRV **(Middle)**, and the time trend of HRV following exposure **(Right)**. A dotted line shows the arithmetic average of the HRV variable, colors code the different activity phases.

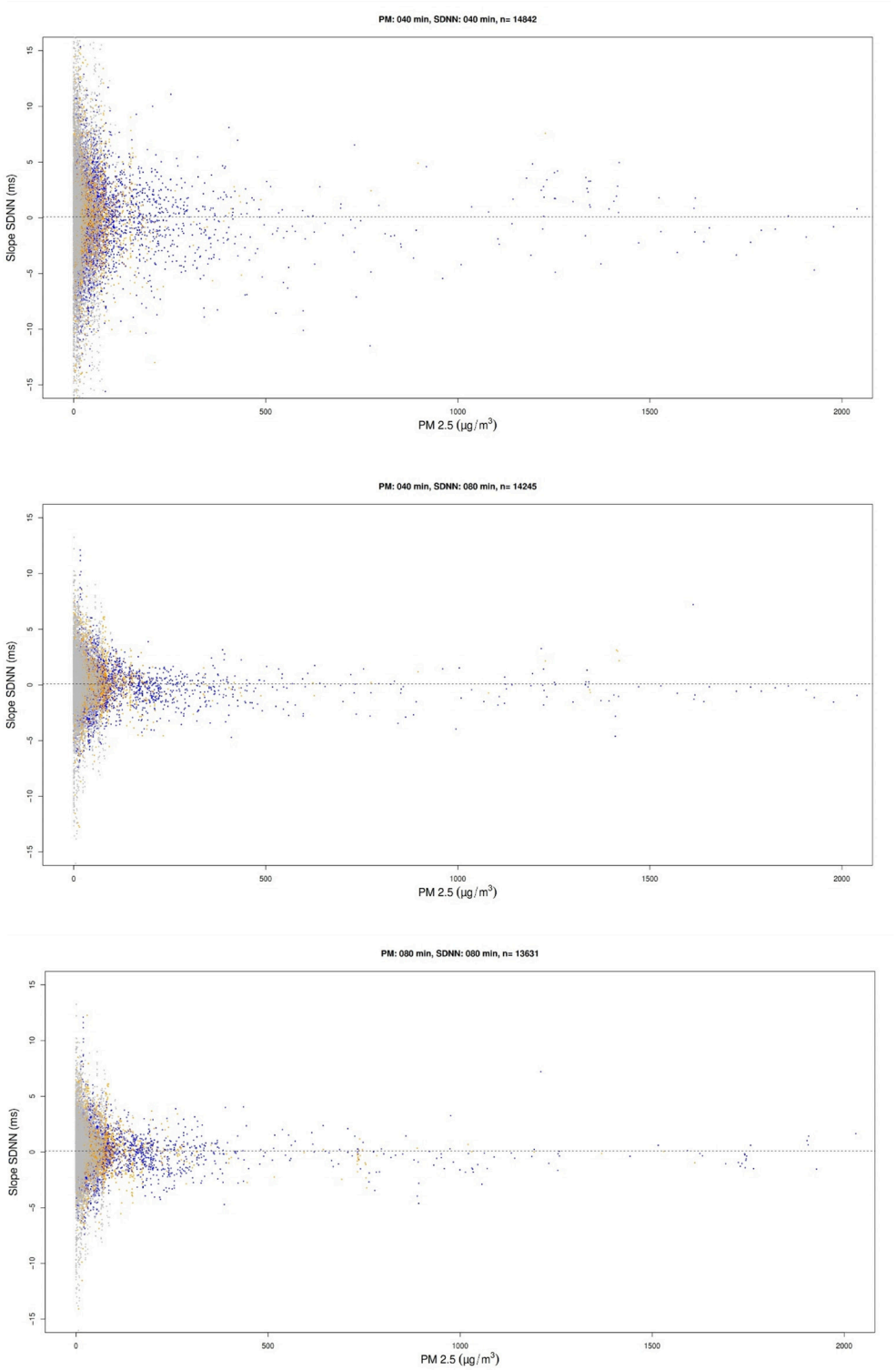

FIGURE 3 | Examples of the scatterplots comparing exposure and time trend (slope over time) for other averaging time windows for the absolute values of the time trend of SDNN, created as part of the sensitivity analysis.

TABLE 2 | Association of 1-h exposure to $PM_{2.5}$ with mean, *SD*, and absolute value of the time trend of SDNN and pNN50 (controlled for activity phase) in the following 2-h.

Model	Standardized SDNN effect estimates per $log_2(PM_{2.5})$	*p*-value	Standardized pNN50 effect estimates per $log_2(PM_{2.5})$	*p*-value
Crude: mean ~ $PM_{2.5}$	−1.449	<0.001	−0.997	0.008
Controlled: mean ~ $PM_{2.5}$	−1.026	<0.001	−0.829	0.012
Crude: SD ~ $PM_{2.5}$	−1.158	<0.001	−0.977	<0.001
Controlled: SD ~ $PM_{2.5}$	−0.685	<0.001	−0.800	<0.001
Crude: abs(time trend) ~ $PM_{2.5}$	−0.279	0.003	−0.347	0.001
Controlled: abs(time trend) ~ $PM_{2.5}$	−0.149	0.047	−0.284	0.002

Coefficients are standardized effect estimates per $log_2(PM_{2.5})$.

TABLE 3 | Stratification by activity phase of the analysis of the association of short-term exposure to $PM_{2.5}$ for mean, *SD*, and absolute value of the slope of SDNN and pNN50.

Model	SDNN coefficient	Variance	*p*-value	pNN50 coefficient	Variance	*p*-value
WORK ONLY						
Mean—$PM_{2.5}$	−0.592	0.440	0.028	0.139	0.015	0.356
SD—$PM_{2.5}$	−0.438	0.083	0.013	−0.478	0.010	0.002
Absolute slope—$PM_{2.5}$	−0.089	0.001	0.370	−0.167	0.000	0.007
HOME ONLY						
Mean—$PM_{2.5}$	−0.410	0.914	0.095	−0.940	0.511	0.009
SD—$PM_{2.5}$	−0.625	0.120	0.000	−0.601	0.037	0.003
Absolute slope—$PM_{2.5}$	−0.060	0.002	0.606	−0.267	0.001	0.046
NIGHT ONLY						
Mean—$PM_{2.5}$	−0.795	1.858	0.032	0.347	0.228	0.344
SD—$PM_{2.5}$	−1.143	0.547	0.001	−1.095	0.081	0.002
Absolute slope—$PM_{2.5}$	−0.171	0.005	0.163	−0.699	0.001	0.000

Coefficients are standardized effect estimates per $log_2(PM_{2.5})$.

those city dwellers. Our findings raise serious questions about the long-term health of the populations of such cities, who are continuously exposed to such levels. However, note that our study was limited to a small sample of healthy male Swiss adults of good socioeconomic status. It would seem necessary to assess whether other population groups such as females, children, other ethnicities, unhealthy, and lower socioeconomic status may respond differently to the same level of exposure.

The decrease of both, average SDNN and PNN50 can be interpreted as a reduced autonomic activity (Ewing et al., 1984; Electrophysiology Taskforce Guidelines, 1996; Mietus et al., 2002). This type of acute response was reported by other groups before (Devlin et al., 2003; Pope et al., 2003; Wu et al., 2010; Huang et al., 2014; Nyhan et al., 2014; Wagner et al., 2014; Weichenthal et al., 2014; Cole-Hunter et al., 2015; Hemmingsen et al., 2015; Mordukhovich et al., 2015; Lee et al., 2016). Interestingly, SDNN at high exposure levels is just slightly below the average SDNN, while PNN50 drops to near zero, which is suggestive of mostly parasympathetic withdrawal. Our analysis also shows that the random modulation of HRV (SD and time trend of SDNN and PNN50) is strongly reduced following elevated $PM_{2.5}$-exposure, suggesting that this interference with regulatory autonomic mechanisms lasts for a while. $PM_{2.5}$ was previously reported to interfere with salt regulation (Tsai et al., 2012b), vascular function (Hemmingsen et al., 2015), and blood pressure (Tsai et al., 2015). It would be interesting to experimentally study if this could be a possible explanation for the observed reduced modulation of HRV over the 2-h window. Acutely altered HRV often represents a disturbance of normal homeostatic processes (Billman, 2011), which can pose a serious health concern especially for people having elevated cardiovascular risk factors such as those with previous infarction or existing arrhythmic disorders (Tsuji et al., 1996; Clyne et al., 2016; Patel et al., 2017).

The acute decrease of HRV following exposure identified in the regression analysis confirms our hypothesis that changing the time from exposure to HRV-response assessment explains the difference in direction observed in our previous analyses in the same road maintenance workers (Meier et al., 2014) and also other healthy individuals (Riediker et al., 2004a), where we observed an increase in mean HRV associated with exposure to $PM_{2.5}$ in the morning after exposure. Taken together, the previous analyses (Riediker et al., 2004a; Meier et al., 2014) and this one are in support of the idea that immediately after exposure, air pollutants disturb cardiac function, which will fade after a few hours and be followed later on by a recovery response.

TABLE 4 | Analysis of the sensitivity of the effect estimates to changing the averaging times of $PM_{2.5}$-exposure and HRV-values, with and without control for activity phases.

Control for activity	Time-interval:Exposure_HRV	Coefficient	variance	*p*-values	Coefficient	Variance	*p*-values
			Mean SDNN			**Mean pNN50**	
Crude	30_60	−0.277	0.106	0.001	−0.301	0.017	0.004
Crude	40_40	−0.245	0.137	0.000	−0.195	0.020	0.031
Crude	40_80	−0.652	0.285	0.000	−0.479	0.033	0.010
Crude	50_100	−0.907	0.582	0.001	−0.551	0.056	0.037
Crude	***60_120***	***−1.449***	***0.800***	***0.000***	***−0.997***	***0.106***	***0.008***
Crude	60_60	−0.555	0.362	0.000	−0.437	0.050	0.020
Crude	80_80	−1.115	0.887	0.000	−0.732	0.102	0.029
Crude	120_120	−2.664	1.505	0.000	−2.435	0.209	0.000
Controlled	30_60	−0.109	0.074	0.128	−0.155	0.008	0.042
Controlled	40_40	−0.149	0.114	0.020	−0.101	0.013	0.201
Controlled	40_80	−0.385	0.177	0.006	−0.245	0.015	0.066
Controlled	50_100	−0.575	0.364	0.013	−0.245	0.015	0.066
Controlled	***60_120***	***−1.026***	***0.471***	***0.000***	***−0.829***	***0.057***	***0.012***
Controlled	60_60	−0.209	0.296	0.150	−0.175	0.032	0.270
Controlled	80_80	−0.714	0.753	0.014	−0.386	0.064	0.171
Controlled	120_120	−2.025	1.140	0.000	−1.915	0.128	0.000
			SD SDNN			**SD pNN50**	
Crude	30_60	−0.259	0.035	0.000	−0.263	0.007	0.001
Crude	40_40	−0.210	0.032	0.000	−0.170	0.005	0.001
Crude	40_80	−0.492	0.107	0.000	−0.494	0.011	0.000
Crude	50_100	−0.758	0.140	0.000	−0.699	0.018	0.000
Crude	***60_120***	***−1.158***	***0.174***	***0.000***	***−0.977***	***0.028***	***0.000***
Crude	60_60	−0.378	0.159	0.002	−0.377	0.018	0.004
Crude	80_80	−0.739	0.208	0.000	−0.798	0.032	0.000
Crude	120_120	−2.111	0.365	0.000	−2.168	0.065	0.000
Controlled	30_60	−0.136	0.030	0.011	−0.142	0.004	0.018
Controlled	40_40	−0.099	0.030	0.007	−0.064	0.002	0.055
Controlled	40_80	−0.260	0.068	0.013	−0.307	0.005	0.000
Controlled	50_100	−0.434	0.072	0.001	−0.533	0.012	0.000
Controlled	***60_120***	***−0.685***	***0.095***	***0.000***	***−0.800***	***0.017***	***0.000***
Controlled	60_60	−0.183	0.129	0.097	−0.250	0.012	0.023
Controlled	80_80	−0.417	0.147	0.007	−0.611	0.023	0.001
Controlled	120_120	−1.365	0.264	0.000	−1.738	0.050	0.000
			abs(slope SDNN)			**abs(slope pNN50)**	
Crude	30_60	−0.103	0.002	0.000	−0.071	0.000	0.027
Crude	40_40	−0.090	0.003	0.000	−0.088	0.000	0.000
Crude	40_80	−0.159	0.002	0.001	−0.133	0.000	0.011
Crude	50_100	−0.240	0.002	0.000	−0.258	0.000	0.001
Crude	***60_120***	***−0.279***	***0.002***	***0.003***	***−0.347***	***0.000***	***0.001***
Crude	60_60	−0.129	0.003	0.000	−0.097	0.000	0.017
Crude	80_80	−0.205	0.002	0.000	−0.237	0.001	0.005
Crude	120_120	−0.329	0.003	0.003	−0.693	0.001	0.000
Controlled	30_60	−0.036	0.001	0.059	−0.011	0.000	0.635
Controlled	40_40	−0.018	0.002	0.259	−0.023	0.000	0.173
Controlled	40_80	−0.067	0.001	0.070	−0.059	0.000	0.149
Controlled	50_100	−0.147	0.001	0.004	−0.197	0.000	0.004
Controlled	***60_120***	***−0.149***	***0.001***	***0.047***	***−0.284***	***0.000***	***0.002***
Controlled	60_60	−0.036	0.001	0.140	−0.029	0.000	0.354
Controlled	80_80	−0.084	0.001	0.032	−0.122	0.000	0.054
Controlled	120_120	−0.192	0.001	0.025	−0.553	0.001	0.001

The main model is highlighted in bold-italic. Coefficients are standardized effect estimates per $log_2(PM_{2.5})$.

Another novel, and possibly troubling new insight of our analysis is the observed funnel plot-like reduced modulation of HRV following exposure. It supports the idea of an interference with homeostatic control mechanisms. It seems to pose a serious health risk if such a strong response was observed in people with already partly derailed control mechanisms, such as those having pre-existing cardiovascular disease, previous infarction, heart failure, or arrhythmic disorders. The acute impairment of homeostatic control would also explain the later occurring increase of HRV observed in the same workers (Meier et al., 2014) and also in an independent populations of healthy highway patrol men (Riediker et al., 2004a), which would represent the period of homeostatic recovery.

AVAILABILITY OF DATA AND MATERIAL

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of the article. MR: led the analysis and led the writing of the article; YF: conducted the statistical analysis and created figures and tables; VR: reviewed and contributed to the statistical planning and interpretation; RM: collected the health and exposure data, prepared the database, and helped with the statistical analysis; MB: contributed to the statistical assessment and provided homeostasis interpretation; WEC treated the ECG recordings, extracted 5-min HRV data, and contributed to the cardiac interpretation of the findings.

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