An epidemiological appraisal of the association between heart rate variability and particulate air pollution: a meta-analysis

Nicky Pieters,1 Michelle Plusquin,1 Bianca Cox,1 Michal Kicinski,1 Jaco Vangronsveld,1 Tim S Nawrot1,2

ABSTRACT

Objective Studies on the association between short-term exposure to ambient air pollution and heart rate variability (HRV) suggest that particulate matter (PM) exposure is associated with reductions in measures of HRV, but there is heterogeneity in the nature and magnitude of this association between studies. The authors performed a meta-analysis to determine how consistent this association is.

Data source The authors searched the Pubmed citation database and Web of Knowledge to identify studies on HRV and PM.

Study selection Of the epidemiologic studies reviewed, 29 provided sufficient details to be considered. The meta-analysis included 18667 subjects recruited from the population in surveys, studies from patient groups, and from occupationally exposed groups.

Data extraction Two investigators read all papers and computerised all relevant information.

Results The authors computed pooled estimates from a random-effects model. In the combined studies, an increase of 10 μg/m² in PM₁₀ was associated with significant reductions in the time-domain measurements, including low frequency (−1.66%, 95% CI −2.58% to −0.74%) and high frequency (−2.44%, 95% CI −3.76% to −1.12%) and in frequency-domain measurements, for SDNN (−0.12%, 95% CI −0.22% to −0.03%) and for rMSSD (−2.18%, 95% CI −3.33% to −1.03%). Funnel plots suggested that no publication bias was present and a sensitivity analysis confirmed the robustness of our combined estimates.

Conclusion The meta-analysis supports an inverse relationship between HRV, a marker for a worse cardiovascular prognosis, and particulate air pollution.

INTRODUCTION

A recent scientific report from the American Heart Association concluded that particulate matter (PM) is a modifiable risk factor contributing to cardiovascular morbidity and mortality.¹ We provided a novel insight that particulate air pollution is a relevant trigger for myocardial infarction at the community level.²⁻⁴ Altering cardiac autonomic function as measured by heart rate variability (HRV) is considered to be one of the pathophysiological pathways through which PM air pollution influences the cardiovascular system.⁵ ⁶ Reduced HRV has been associated with an increased risk of myocardial infarction among the population⁷ and has been considered as a predictor of increased risk of mortality in patients with heart failure.⁸ The importance of this pathway is still under debate.⁹ ¹⁰ Here we determine whether all the available observational data up to February 2012 support a positive association and how strong such a relationship between HRV and particulate air pollution may be.

METHODS

Data collection

We followed published guidelines for the reporting of this meta-analysis.¹¹ ¹² A systematic literature search of PubMed and Web of Knowledge, last accessed on 15 February 2012, was conducted to identify studies of HRV and air pollution published in English. In addition, we screened the reference list of all identified relevant publications and review articles found during our literature search. Two search terms were combined using the Boolean operator AND. The first term, air pollution, combined exploded versions of the Medical Subject Headings air pollution, particulate matter and air pollutants. The second term was heart rate variability.

Study selection

Two investigators (NP and MP) read all papers and extracted and computerised the relevant information independently (table 1). Reviews, case-reports, pilot studies, animal studies, manuscripts not written in English and studies that reported another association were excluded. Out of 509 initially selected articles, 98 studies reported an association between HRV and air pollution. If a group published two or more papers based on the same study population (n=31), only that publication providing the most detailed information was included. We selected only studies that used particulate matter with aerodynamic diameter of 10 μm or less (PM₁₀) or 2.5 μm or less (PM₂.₅) as indicators of air pollution. Studies were also excluded when a controlled exposure was used. Where applicable, preference was given to results adjusted for age and heart rate and additional factors of proven importance.⁴⁰ Quality assessment of the selected studies was performed with consideration of the following aspects: study design, response rate, information about responders versus non-responders, sample size, statistical methods, correction for meteorological conditions and personal or local PM assessment (supplementary data).

Statistical analysis

HRV was evaluated using different time-domain and frequency-domain measures, according to the
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Number of persons</th>
<th>Age</th>
<th>Men, %</th>
<th>Study design (measurements per person)</th>
<th>Exposure</th>
<th>Scale of HRV</th>
<th>Length of analysed ECG recordings</th>
<th>Average PM concentration, μg/m³</th>
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<tbody>
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<td>Liao</td>
<td>1999</td>
<td>All</td>
<td>4899</td>
<td>62.4±5.7*</td>
<td>43</td>
<td>Cross-sectional</td>
<td>24 h PM2.5</td>
<td>HF and LF Log</td>
<td>5 min</td>
<td>16.99±8.04*</td>
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<tr>
<td></td>
<td></td>
<td>Without hypertension</td>
<td>8</td>
<td>78 (65–84)*</td>
<td>37</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>With hypertension</td>
<td>18</td>
<td>82 (69–89)*</td>
<td>22</td>
<td></td>
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<td>Pope</td>
<td>1999</td>
<td>With COPD/respiratory disease</td>
<td>7</td>
<td>75 (23–82)*</td>
<td>85.7</td>
<td>Longitudinal (4.1)</td>
<td>24 h PM1.0</td>
<td>Log</td>
<td>24 h</td>
<td>83.92*</td>
</tr>
<tr>
<td>Gold</td>
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<td>Elderly</td>
<td>21</td>
<td>73.3 (53–87)*</td>
<td>48</td>
<td>Longitudinal (7.76)</td>
<td>4 h PM1.0</td>
<td>Log</td>
<td>5 min</td>
<td>15.3 (2.9–48.6)*</td>
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<td>With COPD</td>
<td>16</td>
<td>74 (54–86)*</td>
<td>43.8</td>
<td>Longitudinal (7)</td>
<td>24 h</td>
<td>Log</td>
<td>10 h</td>
<td>10.8 ± 1.4*</td>
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<td>Occupational</td>
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<td>4 h PM1.0</td>
<td>Log</td>
<td>24 h</td>
<td>223 ± 2203*</td>
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<td>Holguin</td>
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<td>Without hypertension</td>
<td>21</td>
<td>80 (65–96)*</td>
<td>52</td>
<td>Longitudinal (18)</td>
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<td>Log</td>
<td>5 min</td>
<td>30.4 ± 9.9*</td>
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<td>Liao</td>
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<td>43</td>
<td>Cross-sectional</td>
<td>24 h PM1.0</td>
<td>HF and LF Log</td>
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<td>48</td>
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<td>10 min</td>
<td>23 (7.1–38.7)*</td>
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<td>100</td>
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<td>Log</td>
<td>4 min</td>
<td>11.4 ± 8.0*</td>
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<td>Elderly</td>
<td>27</td>
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<td>Predominately female</td>
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<td>24 h PM1.0</td>
<td>Log</td>
<td>30 min</td>
<td>10 (7–17)*</td>
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<td>Ln</td>
<td>20 min</td>
<td>10.7 (8.0–15.6)*</td>
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<td>13</td>
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<td>Lipsett</td>
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<td>With CAD</td>
<td>19</td>
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<td>63.2</td>
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<td>Log</td>
<td>30 min</td>
<td>19.7 (11.6–25.0)*</td>
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<td>Ln</td>
<td>13 h</td>
<td>74 (49–111)*</td>
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<td>Log</td>
<td>5 min</td>
<td>23.2 ± 33.3*</td>
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<td>Longitudinal (2.7)</td>
<td>24 h PM1.0</td>
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<td>24 h</td>
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<td>Zanetti</td>
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<td>With CAD</td>
<td>46</td>
<td>57 (43–75)*</td>
<td>80.4</td>
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<td>24 h</td>
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<td>Park</td>
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<td>Cross-sectional</td>
<td>24 h PM1.5</td>
<td>Log</td>
<td>30 s</td>
<td>14.3 (102–20.4)*</td>
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<tr>
<td>Schneider</td>
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<td>With CAD</td>
<td>56</td>
<td>66±6B</td>
<td>100</td>
<td>Longitudinal (12)</td>
<td>24 h PM1.5</td>
<td>Log</td>
<td>24 h</td>
<td>20.3 ± 14.8*</td>
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<td>Suh</td>
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<td>30</td>
<td>65 (55–73)*</td>
<td>38.9</td>
<td>Longitudinal (7)</td>
<td>24 h PM1.5</td>
<td>Log</td>
<td>25 min</td>
<td>16.54 ± 9.33*</td>
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<tr>
<td></td>
<td></td>
<td>With COPD</td>
<td>18</td>
<td>38.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>With MI</td>
<td>12</td>
<td>83.3</td>
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<td>Wu</td>
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<td>Occupational</td>
<td>11</td>
<td>35.5 (27–41)*</td>
<td>45</td>
<td>Longitudinal (3)</td>
<td>2 h PM1.5</td>
<td>Log</td>
<td>12 h</td>
<td>56.6 (34.6–104.1)*</td>
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</tbody>
</table>

Continued...
## Table 1

<table>
<thead>
<tr>
<th>Study design, per person</th>
<th>Average PM concentration, g/m³</th>
<th>Length of analysed ECG recordings</th>
<th>Scale of HRV</th>
<th>Exposure Scale of HRV</th>
<th>Number of persons</th>
<th>Men, %</th>
<th>Age, year, mean</th>
<th>Study population</th>
<th>Population: description of persons included.</th>
<th>Descriptive statistics were only given for all participants. No calculations could be made for rMSSD.</th>
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</thead>
<tbody>
<tr>
<td>Longitudinal (48)</td>
<td>6 h PM₂.₅</td>
<td>HRF Log</td>
<td>Linear</td>
<td></td>
<td>1127</td>
<td>60.5</td>
<td>(40.5 – 90)</td>
<td>General</td>
<td>Jia et al. (2011) General 57.9%</td>
<td>Descriptive statistics were only given for all participants. No calculations could be made for rMSSD.</td>
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<tr>
<td>Longitudinal (116)</td>
<td>24 h PM₂.₅</td>
<td>HF, SDN, SDNN</td>
<td>Log</td>
<td></td>
<td>14.44</td>
<td>61.5</td>
<td>24 h PM₂.₅</td>
<td>General</td>
<td>Jia et al. (2011) General 57.9%</td>
<td>Descriptive statistics were only given for all participants. No calculations could be made for rMSSD.</td>
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</tbody>
</table>

Average PM₂.₅ concentration calculated with the assumption that PM₁₀ consists of 70% of PM₂.₅.

Average age/PM₂.₅ concentration during the first visit.

Mass, after shift.

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction; NAS, Normative Aging Study; PM₂.₅, particulate matter with aerodynamic diameter of 2.₅ µm or less; PM₁₀, particulate matter with aerodynamic diameter of 10 µm or less.

Sensitivity of the findings was examined by performing the analysis both with and without the occupational studies. The analysis was repeated separately for long-term (more than 18 h of analysable ECG recordings) and short-term (<1 h of analysable ECG recordings) ECG recordings. Three studies could not be classified according to this distinction and were excluded from the short- and long-term analyses. We determined whether there was a difference in the combined effect size when only studies with a high quality score were included. We also tested the difference between a 24-h exposure and 48-h exposure on the HRV. Since both 24 h and 48 h measurements were used in some of these studies, the effect size for the 48 h exposure, used in the sensitivity analysis, differed from the data given in table 1, figures 1 and 2. Further, we evaluated the influence of individual studies on pooled effect sizes by excluding one study at the time. If the point estimate of the combined effect size with one study omitted lies outside the CI of the overall estimate, the study in question has an excessive influence. We plotted the association size against the SE of the combined effect of PM2.5 on HRV.

RESULTS

Selection of studies

Of the studies reviewed 480 reports were excluded; 128 were duplicates, 174 were excluded based on screening the abstract, 24 studies were reviews, 57 studies reported on animal data, one study was a pilot-study, four publications were not written in
English, one study was a case report, 20 studies reported another association than PM and HRV, 19 studies with an estimated exposure from other measurements than the particulate air pollution (PM$_{10}$ or PM$_{2.5}$), two did not provide sufficient information to compute the association size, 17 were experimental studies, 31 used the same study population as reports included in the analysis and two studies used PM measurements longer than 24 h (supplementary data). As a result, we identified 29 studies, comprising 18,667 persons, which investigated the association between HRV and PM. This selection includes 25 longitudinal studies, and three occupational studies and four cross-sectional designs. These are listed in chronological order in table 1.

Characteristics of studies

All studies had a time window of PM measurements ranging from 2 h up to 1 day before HRV measurements. The length of ECG recordings varied from 10 s to 24 h. Whenever possible, preference was given to long-term ECG recordings (more than 18 h of analysable ECG recordings). The HRV measurements were expressed on a logarithmic scale in 23 studies and on a linear scale in five studies. One publication used both a linear and logarithmic scale. Only one study calculated the association between PM exposure and HRV without reporting possible confounders. One study included potential confounders but did not report them. In all but four reports the results were adjusted for age.

Eleven publications did not adjust for sex, however, in four, of these 11 reports, all subjects had the same sex. Most studies also considered additional confounding variables, such as heart rate, BMI, outdoor temperature, relative humidity, and (past) smoking. As a result, we identified 29 studies, comprising 18,667 persons, which investigated the association between HRV and PM. This selection includes 25 longitudinal studies, 6 occupational studies and three cross-sectional designs. These are listed in chronological order in table 1.

Figure 1 Forests plots of change in parameter (95% CI) of heart rate variability associated with a 10 µg/m$^3$ increase in PM$_{2.5}$ with inclusion of occupational studies. Squares represent individual groups. The area of each square is proportional to the inverse of the variance. HF, high frequency; LF, low frequency; PM$_{2.5}$, particulate matter with aerodynamic diameter of 2.5 µm or less; rMSSD, square root of the mean squared difference of successive normal to normal intervals; SDNN, SD of normal to normal intervals.

Summary statistics

We evaluated HRV using both frequency- and time-domain measurements. The combined estimates calculated for a 10 µg/m$^3$ increase in PM$_{2.5}$ showed a decrease of 1.66% (95% CI −2.58% to −0.74%) and 2.44% (95% CI −3.76% to −1.12%) for LF and HF, respectively. The corresponding estimates for the time-domain measurements were −0.12% (95% CI −0.22% to −0.03%) for SDNN and −2.18% (95% CI −3.33% to −1.03%) in rMSSD (figure 1).

Sensitivity analysis

When the analysis was repeated without three occupational studies, we found a minor difference in LF, −2.05% (95% CI −3.21% to −0.88%) and HF, −5.17% (95% CI −4.92% to −1.41%) for a 10 µg/m$^3$ increase in PM$_{2.5}$ (figure 2). However, the effect of exclusion of these three studies was much larger for SDNN, which results in a combined effect of −1.25% (95% CI −1.81% to −0.68%).

For LF and HF the majority of studies, 75% and 71% respectively, used short-term ECG recordings. When removing the...
studies with long-term ECG recordings, we found a decrease of 1.73% (95% CI 1.00% to 3.04%) and 1.75% (95% CI 3.20% to 0.29%) for LF and HF, respectively. When repeating the analysis separately for short-term and long-term recordings for SDNN, we observed a decrease in short-term and long-term recordings of 0.73% (95% CI 1.17% to 0.29%) and 1.39% (95% CI 2.37% to 0.41%), respectively. When including only short-term recordings for rMSSD, we still found a decrease of 3.21 (95% CI 4.66% to 1.76%) for a 10 μg/m³ increase PM2.5. However, when including only the long-term recordings PM2.5, we observed no statistically significant association with rMSSD (p=0.05), 0.93% (95% CI 1.10% to 0.76%) and 0.01% (95% CI 0.02% to 0.01%). When determining the effect of a 48-h exposure, we found a similar decrease in LF, HF and SDNN.

Also, when four studies with a cross-sectional design were excluded, the sensitivity analysis was also performed with only studies with a high quality score (more than the median score). The decrease was more pronounced for LF (−2.49%, 95% CI −4.52% to −0.36%) and HF (−5.74%, 95% CI −8.82% to −2.66%), similar for rMSSD (−1.89%, 95% CI −3.08 to −0.71%) but was no longer significant for SDNN (−0.05%, 95% CI −0.15% to 0.02%). When determining the effect of a 48-h exposure, we found a similar decrease in LF, HF and SDNN.

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dysfunction and a predictor of sudden cardiac death and arrhythmias. A reduction of HRV has been reported in several cardiological and non-cardiological diseases such as myocardial infarction, diabetic neuropathy, cardiac transplantation, myocardial dysfunction and tetraplegia. HRV measurements are also promising as risk markers for fatigue, ageing and stress situations. Despite the important prognostic power of HRV, it is still not a widely used tool in diagnostic settings, and agreed normative values for HRV remain missing. In terms of clinical significance the association between decreasing HRV with increasing air pollution is still under debate as the decrease in HRV can be a marker of cardiac disease or the cause of increased risk. The underlying mechanisms responsible for the association between fine PM exposure and impaired HRV are not yet fully understood. Substantial epidemiological literature links cardiovascular mortality and morbidity to exposures of ambient air pollution. Two main candidate mechanisms are release of pro-thrombotic and inflammatory cytokines from the lung, and effects on the electrical activity and autonomic function of the heart. HRV is indicative for the physiological responses of the autonomic nervous system, of the combined sympathetic and parasympathetic activity. Alterations in autonomic control of the heart, as represented by HRV, may represent a major pathophysiological mechanism by which air pollution leads to cardiovascular disease. Two possible pathways can lead to changes from cardiovascular disease: 

<table>
<thead>
<tr>
<th>HRV parameter</th>
<th>Number of studies included</th>
<th>Number of subjects included</th>
<th>Combined estimate (95% CI)</th>
<th>p Value for Cochran Q-statistics</th>
<th>I² degree of heterogeneity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>14</td>
<td>7172</td>
<td>−1.66 (−2.58 to −0.74)</td>
<td>0.02</td>
<td>45.0</td>
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<tr>
<td>Excluding occupational studies</td>
<td>12</td>
<td>7152</td>
<td>−2.05 (−3.21 to −0.88)</td>
<td>0.0175</td>
<td>48.8</td>
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<tr>
<td>Excluding studies with long-term ECG measurements</td>
<td>9</td>
<td>6949</td>
<td>−1.73 (−2.73 to −0.73)</td>
<td>0.4618</td>
<td>0.0</td>
</tr>
<tr>
<td>Excluding groups with patients suffering from cardiovascular disease</td>
<td>16 groups</td>
<td>7154</td>
<td>−1.71 (−2.74 to −0.68)</td>
<td>0.0178</td>
<td>47.7</td>
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<tr>
<td>Excluding studies with a cross-sectional design</td>
<td>11</td>
<td>427</td>
<td>−1.51 (−2.4 to −0.68)</td>
<td>0.0246</td>
<td>48.7</td>
</tr>
<tr>
<td>Excluding studies with PM10 measurements</td>
<td>11</td>
<td>924</td>
<td>−1.48 (−2.35 to −0.61)</td>
<td>0.0373</td>
<td>44.4</td>
</tr>
<tr>
<td>Excluding studies with a low quality score</td>
<td>8</td>
<td>6532</td>
<td>−2.49 (−4.36 to −0.62)</td>
<td>0.0121</td>
<td>57.4</td>
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<tr>
<td>HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>16</td>
<td>7356</td>
<td>−2.44 (−3.76 to −1.12)</td>
<td>&lt;0.0001</td>
<td>66.7</td>
</tr>
<tr>
<td>Excluding occupational studies</td>
<td>14</td>
<td>7336</td>
<td>−3.17 (−4.92 to −1.41)</td>
<td>&lt;0.0001</td>
<td>70.1</td>
</tr>
<tr>
<td>Excluding studies with long-term ECG measurements</td>
<td>10</td>
<td>7087</td>
<td>−1.75 (−3.20 to −0.29)</td>
<td>0.0005</td>
<td>62.3</td>
</tr>
<tr>
<td>Excluding groups with patients suffering from cardiovascular disease</td>
<td>16 groups</td>
<td>7140</td>
<td>−2.84 (−4.32 to −1.36)</td>
<td>0.0001</td>
<td>66.1</td>
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<tr>
<td>Excluding studies with a cross-sectional design</td>
<td>13</td>
<td>611</td>
<td>−1.93 (−3.12 to −0.73)</td>
<td>0.0003</td>
<td>63.4</td>
</tr>
<tr>
<td>Excluding studies with PM10 measurements</td>
<td>14</td>
<td>1108</td>
<td>−2.04 (−3.26 to −0.82)</td>
<td>0.0002</td>
<td>63.9</td>
</tr>
<tr>
<td>Excluding studies with a low quality score</td>
<td>9</td>
<td>6585</td>
<td>−5.74 (−8.82 to −2.66)</td>
<td>&lt;0.0001</td>
<td>71.8</td>
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<tr>
<td>SDNN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>21</td>
<td>13 521</td>
<td>−0.12 (−0.22 to −0.03)</td>
<td>&lt;0.0001</td>
<td>74.0</td>
</tr>
<tr>
<td>Excluding occupational studies</td>
<td>18</td>
<td>13 468</td>
<td>−1.25 (−1.81 to −0.68)</td>
<td>&lt;0.0001</td>
<td>76.1</td>
</tr>
<tr>
<td>Excluding studies with long-term ECG measurements</td>
<td>11</td>
<td>13 167</td>
<td>−0.73 (−1.17 to −0.29)</td>
<td>0.0006</td>
<td>60.7</td>
</tr>
<tr>
<td>Excluding studies with short-term ECG measurements</td>
<td>8</td>
<td>354</td>
<td>−1.39 (−2.37 to −0.41)</td>
<td>&lt;0.0001</td>
<td>84.5</td>
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<tr>
<td>Excluding groups with patients suffering from cardiovascular disease</td>
<td>19 groups</td>
<td>13 286</td>
<td>−0.08 (−0.17 to 0.004)</td>
<td>&lt;0.0001</td>
<td>74.5</td>
</tr>
<tr>
<td>Excluding studies with a cross-sectional design</td>
<td>18</td>
<td>6210</td>
<td>−0.11 (−0.21 to −0.02)</td>
<td>&lt;0.0001</td>
<td>75.6</td>
</tr>
<tr>
<td>Excluding studies with PM10 measurements</td>
<td>17</td>
<td>6595</td>
<td>−0.07 (−0.14 to 0.005)</td>
<td>&lt;0.0001</td>
<td>69.2</td>
</tr>
<tr>
<td>Excluding studies with a low quality score</td>
<td>12</td>
<td>12 666</td>
<td>−0.05 (−0.13 to 0.02)</td>
<td>&lt;0.0001</td>
<td>73.6</td>
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<tr>
<td>mSSD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>16</td>
<td>11 437</td>
<td>−2.18 (−3.33 to −1.03)</td>
<td>0.0007</td>
<td>57.8</td>
</tr>
<tr>
<td>Excluding occupational studies</td>
<td>8</td>
<td>11 033</td>
<td>−3.21 (−4.66 to −1.76)</td>
<td>0.1386</td>
<td>31.5</td>
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<tr>
<td>Excluding studies with long-term ECG measurements</td>
<td>8</td>
<td>404</td>
<td>−1.07 (−2.75 to 0.6)</td>
<td>0.0013</td>
<td>70.4</td>
</tr>
<tr>
<td>Excluding studies with short-term ECG measurements</td>
<td>8</td>
<td>404</td>
<td>−1.07 (−2.75 to 0.6)</td>
<td>0.0013</td>
<td>70.4</td>
</tr>
<tr>
<td>Excluding groups with patients suffering from cardiovascular disease</td>
<td>14 groups</td>
<td>11 256</td>
<td>−2.78 (−4.03 to −1.52)</td>
<td>0.022</td>
<td>48.3</td>
</tr>
<tr>
<td>Excluding studies with a cross-sectional design</td>
<td>15</td>
<td>5972</td>
<td>−2.29 (−3.56 to −1.02)</td>
<td>0.0004</td>
<td>60.0</td>
</tr>
<tr>
<td>Excluding studies with PM10 measurements</td>
<td>15</td>
<td>11 349</td>
<td>−1.86 (−2.96 to −0.76)</td>
<td>0.0051</td>
<td>51.5</td>
</tr>
<tr>
<td>Excluding studies with a low quality score</td>
<td>9</td>
<td>11 283</td>
<td>−1.89 (−3.08 to −0.71)</td>
<td>0.0643</td>
<td>40.4</td>
</tr>
</tbody>
</table>

HF, high frequency; HRV, heart rate variability; LF, low frequency; PM10, particulate matter with aerodynamic diameter of 10 μm or less; mSSD, square root of the mean squared difference of successive normal to normal intervals; SDNN, SD of normal to normal intervals.
These pollution sources and particulate constituents; indeed, a multi-
overall measure of changes in autonomic tone, also implies an
parasympathetic cardial vagal tone. A decrease in SDNN, an
Schwartz et al concluded that the effects of PM2.5 on HF
seemed to be mediated by reactive oxygen. The Normative
study has shown a strong effect modification of the PM
and HRV relationship by obesity and genes that modulate
endogenous oxidative stress or xenobiotic metabolism, such as
glutathione S-transferase M1, methylenetetrahydrofolate
reductase and the haemochromatosis gene.
Additional findings imply that pathways that
derive oxidative stress have a protective effect
that alleviates reductions in HRV due to exposure of particulate
air pollution. An alternative potential mechanism is provided
by Schulz et al who found that an altered ion-channel function
triggered by air pollution in myocardial cells can lead to cardiac
malfuction.

Observational studies as included in our meta-analysis do not
prove causation. However, repeated observation of an associa-
tion in different populations and different subgroups showing
the same or similar results suggest that the results of a single
study are not due to coincidence. Our forest plots showed that
the majority of studies showed a decrease in parameters of HRV
in association with particulate air pollution. We showed
consistent results between different study designs including
cross-sectional studies, panel and repeated measure studies,
which support a causal association. Furthermore, we observed
heterogeneity between studies but our estimates were robust.
Although in general the average concentration of occupational
PM2.5 exposure was much higher than environmental exposure,
exclusion of three occupational studies did not alter the
combined estimate.

Although most studies report negative associations between
time- or frequency-domain parameters of HRV and particulate
air pollution, the magnitudes of the effect differ among these
studies. We addressed the issue of heterogeneity between
studies by computing pooled estimates from a random-effects
model. Differences in magnitude between studies may be due to
variation in the composition of PM or length of ECG recordings
but also by including subgroups of populations on anti-
inflammatory drugs or lacking anti-inflammatory defence
(GSTM null). The effects of PM2.5 likely vary depending on
pollution sources and particulate constituents; indeed, a multi-
centre study by Timonen et al found that the effects of PM on
HRV were dependent on local sources of PM. Increases in PM2.5
concentration were associated with decreases in HF in Helsinki,
but a similar increase in PM10 was associated with an increase
in HF in Erfurt. Although a 5-min measurement is recom-
manded and highly reproducible, the 24-h measurement
includes the nocturnal period during which people in general
have a very different autonomic regulation and which is mainly
driven by the parasympathetic component. However, when we
performed a separate analysis for long-term and short-term
recordings, we found a decrease for SDNN and rMSSD in both
short-term and long-term recordings, although the decrease in
long-term recording for rMSSD was statistically not significant
(p=0.21). Differences between studies in the HRV particulate
air pollution association might also be explained by differences
in the disease status of the subjects. Various disease processes
(myocardial infarction, diabetes, chronic obstructive pulmonary
disease) as well as physiological conditions, including ageing,
and drugs (β-blockers) alter autonomic control, and therefore
change the HRV. However, when the study groups with subjects
suffering from cardiovascular diseases were excluded, the
combined estimate did not differ significantly from the
effect found when these groups were included. Hence, the
association between HRV and PM exposure is not only seen in
susceptible subgroups. Contrary to our meta-analysis, a recent
experimental study found no effects of dilute diesel exhaust
inhalation for 1 h on heart rhythm and HRV in healthy
volunteers or in an 'at-risk' population of patients with stable
coronary heart disease. Explanations for the discrepancy
between these epidemiological data and negative results in
controlled conditions may include too short exposure and
difference pollution mixture. Indeed, most of the observational
studies included an exposure window of 24 h. On the other
hand, in the observational studies confounding or residual
confounding by ambient temperature cannot be excluded. Of
the included studies in our meta-analysis, 20 (69%) adjusted for
meteorological conditions (see supplementary table I).

To determine whether the combined effect is influenced by
a particular publication, a sensitivity analysis was performed.
HRV parameters were not strongly determined by one study.
Our main analysis included only studies which used a lag of
±24 h of PM2.5 or PM10 exposure. However, we conducted
a separate meta-analysis with studies reporting the effect of
a 48-h exposure. The combined estimate for 48 h was similar to the effect found for 24 h when occupational
studies were excluded for LE, HF and SDNN. The effect of a 48-h exposure could not be calculated for rMSSD
due to the lack of studies reporting rMSSD.

The present results should be interpreted within the context of
their limitations. First, the analysis was not adjusted for
variation in length of ECG recordings. On the other hand,
a sensitivity analysis with the different lengths of the ECGs did
not reveal differences in combined effect sizes according to
length for LE, HF and SDNN. For rMSSD, the analysis stratified
for short- and long-term recordings showed only significant
results for short-term recordings. Third, if there was heteroge-
nity in the reporting strategy between studies, we had to
address this issue by calculating the β-coefficients to percentages
and calculated PM2.5 from PM10 by using the formulae as given
in the Methods section. Also, different study designs were used
in the combined estimate. Nevertheless, in the sensitivity
analysis, we confirmed the robustness of the overall estimate by
including only panel studies. In other words, the overall estimate
was not strongly influenced by the included studies with a cross-
sectional nature. And last, generally accountable for meta-anal-ysis is a publication bias in that studies with a positive result are more likely to be published than negative results. The funnel plots searching for publication bias did not reveal a deficit of small studies with negative results, suggesting that overall there was no publication bias.

The present meta-analysis shows an overall statistically significant inverse association between parameters of HRV and exposure to particulate air pollution, which might be rele-vant in biological terms. Indeed, the putative mechanisms of the acute effects of PM include sympathetic activation/para-sympathetic withdrawal leading to haemostatic and haemody-namic changes that are recognised to increase the risk of cardiovascular events.

Contributors TN and NP designed the study, NP and MP performed the systematic literature review, constructed the database and analysed the data with help of BC and MK. NP drafted the first version of the manuscript together with MP and TN. All authors took part in the interpretation of the results and prepared the final version.

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Competing interests None.

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REFERENCES