Short-term effects of ultrafine particles on heart rate variability: A systematic review and meta-analysis

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Introduction

Cardiovascular diseases are the leading cause of death worldwide and accounted for 32.8% of all deaths globally in 2019[1]. Fine particulate matter ($PM_{2.5}$) has been causally linked to an increase in cardiovascular disease morbidity and mortality[2]. Notably, elevated ambient particles have been reported to trigger the onset of cardiovascular diseases, such as myocardial infarction (MI), within 1–6 hours after exposure[3-5]. One plausible pathophysiological pathway underlying this immediate response might be autonomic imbalance[6], which can be assessed by alterations in heart rate variability (HRV)[2]. Reduced HRV has been associated with mortality and incident cardiovascular events in populations without pre-existing cardiovascular diseases[7, 8]. It also provides prognostic implications in patients with MI or chronic heart failure (CHF)[9]. Particulate matter (PM) is a mixture of airborne particles varying in size. Compared to PM in the respirable size fraction of 10 to 1 μm in aerodynamic diameter, ultrafine particles (UFP, particles with a diameter ≤ 100 nm) are hypothesized to have independent adverse health effects due to higher pulmonary deposition efficiency, enhanced translocation into circulation, and larger surface area/mass ratio to carry toxic constituents[10-12]. However, relatively few epidemiological studies have assessed the health impacts of UFP. Besides, comparison of these study results is complicated by a variety of measuring approaches and the inconsistency in size distributions of UFP used across studies[13]. Therefore, a scientific review by the U.S. Environmental Protection Agency in 2019 concluded that current evidence was insufficient to infer a causal relationship between UFP and most health endpoints[13]. In the World Health Organization (WHO) global air quality guidelines published in 2021, despite the absence of short- and long-term guideline values for UFP, four good practice statements were proposed to guide the quantification, monitoring, and population exposure assessment of ambient UFP[14]. These statements are expected to facilitate further epidemiological studies on health effects of

UFP, and indicate a consensus that UFP has been recognized as a pollutant of public health concern.

Previous reviews on UFP and HRV have drawn inconsistent conclusions. The U.S. Health Effects Institute evaluated UFP health effects based on articles published until December 2011, finding that the evidence from 11 human studies on UFP and HRV was conflicting and inconclusive[15]. In 2018, an updated review including 16 studies published between January 2011 and May 2017 found suggestive evidence of UFP-related changes in HRV indices[11]. Nevertheless, both reviews presented only a qualitative assessment. Associations between UFP and HRV varied across different time courses (lags of minutes to days) and HRV indices, which might have increased the difficulty in discerning a consistent pattern.

Our study was conducted within the framework of a collaborative project that evaluates current knowledge of UFP exposure, toxicology, and epidemiology, with a view to provide evidence for policymakers[16]. We conducted this systematic review and meta-analysis to provide quantitative estimates of short-term UFP effects on HRV indices in different time courses. Due to the limited number of studies, we did not review the long-term effects of UFP.

Methods

This review was reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement[17].

Search strategy

We included articles on short-term associations between UFP and HRV in the two previous systematic reviews on UFP[11, 15], which covered the period through May 11, 2017. In addition, we searched *PubMed* (last search on April 5, 2021) for articles published between May 12, 2017 and March 31, 2021, and *Web of Science* (last search on April 5, 2021) for articles published between January 1, 2012 and March 31, 2021 (*Web of Science* was not searched in the more recent review[11]). We used the same search terms as those in Ohlwein et al. 2019[11]

complemented with HRV-related terms: (“Particulate matter" OR "Environmental exposure" OR "Air pollut*" OR "Air pollutants/adverse effects [Mesh]” OR "Air pollution/adverse effects [Mesh]" OR "Environmental exposure/adverse effects" [Mesh]) AND (“Surface area” OR “Ultrafine” OR “Ultrafine particle*” OR “Nano particle*” OR Nanoparticle* OR PM0.1 OR PM0.25 OR PNC OR “Particle Number” OR “Accumulation mode” OR “Aitken mode” OR Submicron*) AND (Health OR Epidemiolog*) AND (“heart rate variability” OR HRV OR autonomic OR electrocardiogram OR ECG). The Mesh terms were only used in *PubMed*. The reference lists of other reviews[18, 19] on particulate air pollution and HRV were also examined for relevant articles. Studies from conference proceedings or grey literature were not included.

Study selection

Two reviewers (SZ and EO) independently screened the records retrieved from *PubMed* and *Web of Science* and assessed the eligibility based on titles, abstracts, and full texts when necessary. Articles that met the following criteria were included in our review: (1) Epidemiological studies investigating at least one of the following HRV indices: standard deviation of the normal-to-normal intervals (SDNN), root mean square of successive R-R interval differences (RMSSD), low-frequency power (LF, normalized or non-normalized), high-frequency power (HF, normalized or non-normalized), and LF/HF ratio; (2) Studies assessing UFP measure/metric represented by particle number concentration (PNC) for a size range with a lower limit of ≤ 20 nm; (3) Studies investigating short-term UFP effects with a lag of ≤ 15 days; (4) Studies reporting quantitative measures of associations for an increase in UFP from single-pollutant models, with 95% confidence intervals (CIs) or standard errors; (5) Studies written in English.

Data extraction

Two reviewers (SZ and EO) independently extracted the following data from identified articles using a pre-defined Microsoft Excel form template: (1) first author and year of publication; (2)

study design, location, and population; (3) outcome and exposure indices, including descriptive statistics and exposure assessment approaches; (4) effect estimates of UFP with 95% CIs at all reported lags and the corresponding increment. For studies examining both UFP and $PM_{2.5}$, we also extracted the estimates of $PM_{2.5}$ with 95% CIs at all reported lags and the corresponding increment. We contacted the corresponding authors to acquire any missing data that were not provided in the main articles, supplemental materials, or associated publications (e.g. exposure assessment approach).

When multiple articles investigated identical study populations and time courses (i.e. lags, categorized as detailed below) and used the same exposure assessment approach (i.e. personal vs. central measurements), we extracted the effect estimates from the most recent articles or multi-center studies (over single-center studies). If different time courses or exposure assessment approaches were examined on the same study population, the effect estimates reported in all articles were extracted. For multi-center or multi-population studies, we extracted center- or population-specific estimates rather than the pooled estimates.

Risk of bias assessment

We assessed the risk of bias (RoB) of studies following rules that were adapted from a RoB assessment tool developed by WHO[20]. In brief, the RoB was assessed in six domains: confounding, selection bias, exposure assessment, outcome measurement, missing data, and selective reporting. Each domain comprised 1-3 subdomains. Two reviewers (SZ and EO) rated the RoB for each subdomain as "low", "moderate", or "high", and provided the rationale for all judgments in a Microsoft Excel Sheet. The RoB was rated as moderate when the information was not provided in the article or relevant references. If any subdomains had a rating of high RoB, the whole domain was rated as high RoB; if any subdomains had a rating of moderate RoB and no subdomain had a rating of high RoB, the whole domain was rated as moderate RoB; when all subdomains had a rating of low RoB, the whole domain was rated as low RoB.

Since the HRV indices were all measured together by an electrocardiogram (ECG), the RoB was evaluated at the study level rather than the outcome level.

Any disagreements in the study selection, data extraction, or RoB assessment were solved by discussion with a third person (AS or SB).

Statistical analysis

All effect estimates were standardized to percent changes in the geometric mean of HRV indices for an increment of 10,000 particles/cm^3 in PNC. For studies in which HRV indices were not log-transformed and the geometric mean was not given, we first generated 1,000 sequences of normally distributed random numbers using the arithmetic mean and SD of the HRV index and obtained the geometric mean of each sequence, and then used the median of the 1,000 simulated geometric means to calculate the percent changes. The detailed methods for the standardization are provided in Supplementary file 1. The use of personal measurements for exposure assessment is associated with a lower risk of exposure misclassification for UFP of outdoor origin but is influenced by potential indoor sources of UFP. Therefore, we separately synthesized the effects of exposures estimated using personal and central outdoor measurements. The following time courses, which are based on potential pathophysiological mechanisms, were applied in pooling the effect estimates:

(1) Immediate effects: We pooled effect estimates of UFP exposure at individual or cumulative lags of ≤ six hours.

(2) Acute effects: We pooled daily effect estimates of UFP exposure on the concurrent day of HRV measurements or moving averages of UFP within 24 hours preceding HRV measurements (lag 0). The moving average was set to be at least an 18-hour average to reflect the daily exposure level.

(3) Delayed effects: We pooled daily effect estimates of UFP exposure at individual lags of at least one day or cumulative lags of more than one day.

We further pooled hourly together with daily effect estimates of UFP assessed by central outdoor measurements as the overall effects. We did not synthesize the overall effects of personal-monitored UFP because personal measurements were only used in studies examining the immediate effects within six hours.

We conducted meta-analyses on HRV indices when at least four effect estimates were available for a specific time course and exposure assessment approach. In each analysis, we selected the lag time showing the most (statistically) significant effect per study population regardless of the effect direction, i.e. effects may indicate UFP-associated increases in HRV, which was opposite to the hypothesized direction. We applied both fixed- and random-effects models to pool the effect estimates and reported the pooled percent changes in HRV indices with 95% CIs. In the random-effects models, we used the restricted maximum likelihood (REML) approach for the between-studies variance estimation, with the Hartung-Knapp-Sidik-Jonkman correction for the overall variance. The heterogeneity across studies was assessed by the I^2 statistic and the *Q-test*. The study-specific and pooled effect estimates, I^2 and τ^2 statistics, *p*-values of the *Q*-test, and the 95% prediction intervals are presented in forest plots.

Sensitivity analysis

We conducted the following sensitivity analyses to explore the potential sources of heterogeneity and test the robustness of the pooled effect estimates:

(1) We excluded cross-sectional studies to assess the heterogeneity resulting from study designs;

(2) We restricted our meta-analyses to HRV indices measured in ECG segments ≤ one hour;

(3) We separately pooled effect estimates among populations with and without coronary artery disease (CAD);

(4) We excluded studies using normalized LF and HF in respective meta-analyses.

(5) In all analyses, we selected for each study population the effect estimate that was the most (statistically) significant and indicated a decrease in HRV indices in association with elevated PNC (which was the hypothesized direction). If the effect estimates were positive at all reported lags, we selected the smallest estimate.

To compare the short-term effects of UFP and $PM_{2.5}$ on HRV, we conducted additional meta-analyses pooling effect estimates of $PM_{2.5}$ on HRV indices following the same procedure as UFP. The $PM_{2.5}$ effect estimates were extracted only from the articles identified for the UFP meta-analysis.

We used the R software (version 3.6.2) and the "metafor" and "forestplot" packages for statistical analyses and the generation of related plots.

Results

Study characteristics

Our additional literature search retrieved 171 records. After removing 15 duplicates, we screened 156 records and identified eight new eligible articles (Figure 1). Along with the 21 articles in the two previous reviews, we included 29 articles in this systematic review. Of these, ten articles applied a crossover study design with participants exposed to semi-controlled exposure scenarios, which might not be comparable to daily UFP exposure levels and thus were excluded from the meta-analysis[21-30]. We further excluded three studies not reporting quantitative effect estimates that can be standardized as percent changes for an increment in UFP[31-33], two single-center studies analyzing the same participants with identical time courses and exposure assessment approaches as in a multi-center study[34, 35], one examining indoor UFP[36], and one only reporting effect estimates of UFP from multi-pollutant models[37], leaving 12 articles for the meta-analysis. The main characteristics of the 17 studies that could only be included in the qualitative summary are listed in Table S1.

Table 1 provides the characteristics of the studies included in the meta-analysis. Studies were conducted in Europe, North America, and Asia, and two of them were multi-center studies. Eleven out of twelve were panel studies using repeated measurements of HRV in each participant, with sample sizes (number of participants) ranging from 5 to 125. One was a cross-sectional study using data collected from 497 males in the Normative Aging Study[38]. Seven studies analyzed patients with pre-existing diseases, including CAD (n = 5), type 2 diabetes (T2D) or impaired glucose tolerance (IGT) (n = 3), and lung function impairment (n = 1). Three studies applied personal exposure assessment, and all of these examined the immediate effects within hours[39-41], and the remaining nine studies used exposure data from fixed monitoring sites. The most commonly investigated HRV indices were SDNN (n = 12) and RMSSD (n = 11), followed by HF (non-normalized n = 6, normalized n = 2), LF (non-normalized n = 5, normalized n = 2), and LF/HF (n = 4). Most studies measured HRV in ECG segments ≤ one hour except for Schneider et al. (2010)[42], who measured HRV in both 5-minute and 24-hour segments, and Huang et al. (2021)[43] who used 24-hour segments. The examined lag times between exposure and outcome assessments were heterogeneous across studies, ranging from minutes to days, including both individual and cumulative lags (moving averages).

Risk of bias assessment

Results of the RoB assessment based on the adapted WHO guidelines are presented in Supplementary Table S2 and Supplementary file 2. Overall, the selected studies were of good quality and the associations between UFP and HRV indices were adequately assessed. In the domains of selection bias, exposure assessment, outcome measurement, and selective reporting, all studies were rated as low RoB. The RoB due to missing data was rated as moderate for all studies because information on missing outcome and/or exposure data was not reported. Four studies were rated as moderate RoB in the domain of confounding either due to inadequate adjustment for critical potential confounders such as long-term trends, day of the week, and

socioeconomic status (only for cross-sectional studies) or due to not reporting the validity of measuring of confounding variables.

Meta-analysis

Figure 2 and Table S3 show the results of the random-effects meta-analyses for different HRV indices and time courses, including personal and central exposure assessment separately for the immediate effects. An increase of 10,000 particles/cm^3 in UFP assessed at central monitoring sites was associated with significant decreases in SDNN (-4.0%; 95% CI: -7.1, -0.9) and RMSSD (-4.7%; 95% CI: -9.1, 0.0) within six hours after exposure, which reflected the immediate UFP effects. Using the personal exposure assessment, the pooled immediate effect estimates on SDNN and RMSSD were smaller and borderline significant. When effect estimates (central exposure assessment) of all time courses were considered, the pooled overall effects on SDNN and RMSSD were similar to those of the immediate effects. For the frequency domain of HRV (LF, HF, and LF/HF), borderline significant decreases in LF (-8.4%; 95% CI: -17.3, 1.6) and LF/HF (-7.9%; 95% CI: -16.4, 1.6) were observed when estimates across various time courses were pooled. We did not observe acute (lag 0 day) or delayed (lag times $\geq$ one day) UFP effects on any HRV index.

The heterogeneity of effect estimates across studies was moderate to high (I^2: 66.2%–95.5%) for all time courses except for the delayed effects on SDNN (I^2 = 25.0%) and RMSSD (I^2 = 19.9%; Figure S1-S10). We did not perform meta-regression to investigate the sources of heterogeneity because of insufficient numbers of effect estimates. Instead, we conducted subgroup analyses to explore several potential sources and present a summary for the overall effect estimates in Figure 3 and Figure S11. The pooled estimates and heterogeneity remained stable when excluding the Park et al. study[38] that used a cross-sectional study design (Figure S12). Similar findings were observed after excluding HRV measured in 24-hour ECGs from Schneider et al.[42] and Huang et al.[43] (Figure S13). When we excluded groups of CAD patients,

the pooled overall effects on SDNN, RMSSD, and HF were slightly stronger, and the association was significant for SDNN [-4.6% (95% CI: -9.1, 0.0); Figure S14). On the other hand, among CAD patients, we did not find UFP effects on HRV, whereas the heterogeneity in the overall effects on SDNN, RMSSD, and HF was reduced (Figure S15). When selecting the most significant effect estimates that indicated a decrease (or the slightest increase) in HRV, the heterogeneity in the pooled delayed and overall effects on LF/HF was substantially reduced, and we additionally observed delayed decreases in SDNN and LF/HF (Figure S16). The UFP effects on LF and HF were not sensitive to the exclusion of normalized indices (Figure S17).

Similar to the findings of UFP, short-term exposure to $PM_{2.5}$ in the analyzed studies was associated with decreases in SDNN and RMSSD; for an increment of 10 $\mu g/m^3$ in $PM_{2.5}$, the pooled overall effect estimates for SDNN and RMSSD were -1.9% (95% CI: -3.5, -0.2) and -2.6% (95% CI: -4.5, -0.7), respectively . No delayed effects of $PM_{2.5}$ were observed on SDNN, RMSSD, HF, or LF/HF (Table S3, Figure S18).

Systematic review of crossover studies

To complement the meta-analysis, we summarized the exposure scenarios and results of the ten crossover studies that were included in the systematic review in Table 2. Most of the identified crossover studies assessed the immediate effects of UFP or traffic-related air pollutants (TRAP) within six hours after exposure. Three of them also examined the acute effects of exposure on the same day. One study investigated both acute and delayed effects. In terms of findings, six out of ten studies reported a significant decrease in at least one HRV index associated with UFP or TRAP exposure, three studies found only UFP-associated increases in HRV, and one study did not observe statistically significant associations between UFP and HRV.

Discussion

This systematic review and meta-analysis synthesized short-term effect estimates of UFP on HRV indices from 12 epidemiological studies. We found immediate decreases in SDNN and RMSSD within six hours after exposure to elevated UFP, as well as decreases in SDNN, LF, and LF/HF when pooling the estimates of all time courses from hours to days. Daily average exposures on the same day or preceding days were not associated with HRV. Our findings remained robust in multiple sensitivity analyses. The heterogeneity in effect estimates across studies could be partially explained by pre-existing CAD, with greater UFP-associated changes in HRV among populations without CAD. In contrast, the study design and the length of analyzed ECG segments were unlikely to be sources of heterogeneity based on our analyses.

HRV is an indicator of the autonomic nervous system balance. Our results of decreased HRV following UFP exposure suggest associations of UFP with reduced parasympathetic and/or increased sympathetic activity, which has been demonstrated in pathological conditions including MI, CHF, and diabetic autonomic neuropathy[9, 44], and plays an important role in sudden cardiac death and arrhythmia[45, 46]. Several potential mechanisms have been proposed that could link UFP exposure with an alteration in HRV. Inhaled particles can stimulate the autonomic reflexes in the respiratory tract that modify autonomic control of cardiovascular function[2] and potentially mediate an immediate response within hours. Moreover, cumulative evidence suggests both acute and delayed associations between UFP exposure and the release of pro-inflammatory mediators via oxidative stress and pulmonary/systemic inflammation[47, 48]. This may further affect the autonomic nervous system and lead to autonomic imbalance[49, 50]. In addition, air pollution-mediated oxidative stress could inactivate nitric oxide and contribute to impaired endothelial function[51], which has been associated with sympathetic activity[52].

Our study disentangled the UFP effects over different time courses and indicated the strongest association between UFP and HRV in the first six hours following exposure. It is of note that studies included in the meta-analysis of immediate effects mostly used an exposure window of

up to one hour[40, 41, 53, 54]. The immediate association suggested that particularly acute UFP exposures, such as those encountered while commuting in traffic, might affect HRV and further trigger cardiac events. This is supported by the finding that time spent in traffic was associated with the onset of MI within an hour[55]. In addition, we synthesized the immediate effects from studies using personal and central measurements of UFP separately and observed slightly greater UFP effects when using central monitoring. The differences could be due to the varying measurement errors in the exposure, e.g. classical error for personal measurements that mostly causes attenuation in effect estimates vs. combinations of classical and Berkson error for central measurements that are most likely to yield imprecise (with wider CIs) effect estimates[56]. Besides, personal measurements usually assess exposures in both indoor and outdoor environments, and many different sources of indoor and outdoor UFP might also result in variable outcomes due to the underlying differences in the chemical composition of the UFP[57]. In addition to observational studies, a limited number of controlled human exposure studies on short-term exposure to UFP and HRV have been conducted and yielded mixed results. Among the five studies that were systematically reviewed by Huang et al.[58], two observed a decrease in HF during or after 2-h UFP exposure while at rest[59, 60]. However, other studies showed no association[61, 62] or even increases in HF and LF[63]. For SDNN and RMSSD, most studies reported non-significant results except for a positive association by Zareba et al.[62]. The discrepancy might be attributable to the differences in the composition of particles (elemental carbon UFP vs. concentrated ambient UFP) as well as the age and health status of participants. Besides, it is noteworthy that the composition of UFP and the high exposure levels in controlled exposure studies may not reflect the UFP exposure in real life, and thus could lead to inconsistency with observational studies. In comparison, more consistent evidence is reported by animal studies. A meta-analysis based on 23 controlled animal studies reported decreased SDNN, LF, and LF/HF associated with short-term exposure to particulate matter via

instillation[64]. Specifically, most animal studies employing UFP exposure found UFP-induced decreases in HRV[65-67].

Traffic emissions are a major source of ambient UFP in urban areas. As a result, ambient concentrations of UFP are usually correlated with that of other traffic-related pollutants. Thus, it is important to disentangle the independent UFP effects from other particulate or gaseous co-pollutants when interpreting observed associations. Two-pollutant models are frequently applied to address this issue and were reported in seven studies included in our meta-analysis. Observed associations with UFP remained stable for RMSSD with adjustment for accumulation mode particles in Rich et al.[68] and for SDNN with adjustment for $PM_{2.5}$ in Peters et al.[40] and Breitner et al.[54]. Zhang et al.[69] applied two-pollutant models for all HRV indices investigated in our study by including carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), and sulfur dioxide (SO_2), and only found slightly attenuated associations of UFP with SDNN and RMSSD after adjusting for NO_2, and with LF/HF after adjusting for SO_2. Sun et al.[70] found that the association between UFP and SDNN was robust to the adjustment for NO_2 and O_3, and was reduced but remained significant with adjustment for CO. In the multi-center study by Timonen et al.[71], adjustment for CO and O_3 did not change the UFP effect on HRV much; unstable estimates were only observed in the two-pollutant model controlling for NO_2. In addition, Huang et al. [43] fitted multi-pollutant models by simultaneously including PNC with PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, and O_3, and reported stable associations for all HRV measures. To summarize, the impacts of co-pollutants varied across studies, but the results pointed to the potential confounding by NO_2 and CO, both of which share traffic as a common source. We could not perform meta-analyses to pool UFP effect estimates coming from two-pollutant models due to the limited number of studies. Further studies are needed to understand the role of UFP and gaseous components of combustion processes jointly as well as apportion their relative contributions.

Our sensitivity analysis of dividing study populations based on their CAD conditions suggested stronger UFP effects among participants without pre-existing CAD. Despite the hypothesis that clinical conditions may contribute to greater vulnerability[72], findings regarding the susceptibility of CAD patients to the adverse health effects of air pollution are inconsistent in previous studies, partly due to the impact of medication intake. Conventional cardiac medications, e.g. β-blockers and calcium channel blockers, have been demonstrated to affect the autonomic activity and enhance HRV in CAD patients[73], which could potentially block the air pollution-related decrease in HRV. For example, in the Normative Aging Study, Park et al.[38] observed lower associations of $PM_{2.5}$ and O_3 with LF among individuals on calcium-channel blockers and β-blockers. Consistent with this, de Hartog et al.[74] and Folino et al.[75] reported decreased SDNN in association with PM exposure only among CAD patients not using β-blockers.

We identified 17 additional articles that were related to UFP and HRV but did not meet the inclusion criteria in our meta-analysis. Among them, ten studies employed a crossover study design with semi-controlled exposures. Immediate or acute decreases in HRV associated with UFP or TRAP were reported in six of these studies[21-23, 25, 27, 28], whereas the other four studies observed either increased HRV[26, 29, 30] or no associations[24]. Specifically, Laumbach et al.[21, 24] assessed exposure to highway traffic and HRV indices, and observed an immediate increase in LF/HF and a next-day decrease in RMSSD and HF associated with in-vehicle UFP among patients with type 2 diabetes, but no association with HRV among healthy adults. Langrish et al.[23] observed that reducing TRAP exposure using a face mask had a protective effect on HRV, with lower RMSSD and HF on the study visits without masks during a walk in the city center. Moreover, Sarnat et al.[25] found lower SDNN and RMSSD post highway commute compared to the baseline values. Weichenthal et al.[22, 26] examined the relationship between HRV and UFP exposure on high- and low-traffic routes and indoors during cycling. They found that elevated

UFP concentrations were associated with decreased HF 2–4 hours after the start of cycling among healthy adults; however, an increase in SDNN over the 3-hour follow-up after cycling was observed among healthy women. In another four crossover studies on healthy adults, Cole-Hunter et al.[27] reported immediate decreases in HRV in response to UFP exposure, and the associations at the low-traffic measurement site were stronger compared to the high-traffic one; similar findings were observed in Shutt et al.[28] using exposure scenarios near a steel plant vs. at a college campus. However, Andersen et al.[29] and Moshammer et al.[30] showed UFP-associated acute and delayed increases in LF and an immediate increase in SDNN, respectively. The discrepancy of the results from crossover studies could be due to different exposure scenarios. It is of note that during the exposure period, participants were physically active in some studies[22, 23, 26, 30] whereas remained sedentary in others. Physical activity has been suggested to attenuate the adverse health effects of air pollution[27, 76]. Moreover, studies using traffic-related air pollution as the exposure did not disentangle the effects of UFP from that of other pollutants originating from road traffic, and therefore inhibited a direct assessment of the association between UFP and HRV. Furthermore, various participant characteristics, monitoring techniques, sources of UFP, and analytical approaches may also lead to inconsistent results among these studies.

Strengths and limitations

The key strength of our study is that it provides for the first time a quantitative evaluation of the UFP effects on HRV. Synthesizing effect estimates corresponding to various time courses enables us to distinguish the immediate, acute, and delayed UFP effects on HRV, which could act through different pathophysiological pathways. We also acknowledge the limitation that we were unable to conduct meta-regression to explore the sources of heterogeneity or synthesize the effect estimates from two-pollutant models due to a small number of studies. However, potential sources of heterogeneity were partly addressed in our subgroup analyses.

Further studies are still needed to disentangle the independent UFP effects from co-pollutants. Second, the standardization of effect estimates in studies using non-log-transformed HRV indices was based on simulated geometric mean. This procedure might have introduced additional uncertainty in the pooled effect estimates, but it was not expected to affect the direction of associations.

In conclusion, our study supports an association between short-term exposure to UFP and a decrease in HRV, in particular immediate decreases in SDNN and RMSSD. Our finding highlights the autonomic pathway through which UFP could contribute to the onset of cardiovascular events, and also implies the potential benefit of regulating ambient UFP concentrations in view of public health.

Conflict of interest

The authors declare that there is no conflict of interest.

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Table 1. Main characteristics of studies included in the meta-analysis.

Study	Study design	Location	Study period	Population / Sample size	Exposure assessment	Size range (nm)	Mean ± SD (range) ($\times 10^3$ particles/cm^3)	Exposure measure	Outcome	Length of analyzed ECG	Lags
Chan et al. 2004[39]	Panel study	Taiwan	NA	(1) Young healthy adults / 9 (2) Elderly patients with lung function impairments (male) / 10	Personal monitoring	20–1,000	Healthy adults: 23.4 ± 19.8 (6.1–351.0) Elderly patients: 25.5 ± 20.8 (1.7–211.0)	0-1 h, 0-2 h, 0-3 h, and 0-4 h moving averages	SDNN RMSSD LF HF	5 min	0-1 h 0-2 h 0-3 h 0-4 h
Park et al. 2005[38]	Cross-sectional study	U.S.	11.2000-10.2003	General (male) / 497	Monitoring site 1 km away from the exam site	NA	28.9 ± 13.5 (8.5–74.7)	0-48 h moving average	SDNN LF HF LF/HF	4 min	0-48 h
Timonen et al. 2006[71]	Panel study	The Netherlands	11.1998-06.1999	Elderly non-smoking patients with CAD / 37	Urban background monitoring station	10–100	17.3 (5.7–37.2)	Daily average	SDNN RMSSD HF Normalized HF LF/HF	5 min	2 days
		Germany	10.1998-04.1999	Elderly non-smoking patients with CAD / 47			21.1 (3.9–96.7)				
		Finland	11.1998-04.1999	Elderly non-smoking patients with CAD / 47			17.0 (2.3–50.3)				
Schneider et al. 2010[42]	Panel study	Germany	10.2000-04.2001	Non-smoking patients with CAD (male) / 56	Urban background monitoring station	10–100	11.6 ± 5.8 (2.5–28.4)	24-h moving average	RMSSD Normalized LF Normalized HF	5 min	0-23 h 24-47 h
									SDNN RMSSD	24 h	0 day-2 day
Rich et al. 2012[68]	Panel study	U.S.	06.2006-11.2009	Non-smoking patients with recent coronary event / 76	Monitoring site at the study center	10–100	4.0 ± 2.2 (0.3–16.8)	0-5 h moving average and 24-h moving average	SDNN RMSSD	5 min	0-5 h 0-23 h 24-27 h 48-71 h 72-95 h 96-119 h
Bartell et al. 2013[53]	Panel study	U.S.	2005-2007	Elderly non-smoking patients with CAD / 50	Monitoring sites at each retirement community	5–3,000+	12.8 ± 5.9 (2.0–30.2)	0-1 h, 0-4 h, 0-8 h, 0-24 h, 0-3 days, and 0-5 days moving averages	SDNN RMSSD	1 h	0-1 h 0-4 h 0-8 h 0-24 h 0-3 days 0-5 days

Table 1 (*continued*)

Study	Study design	Location	Study period	Population / Sample size	Exposure assessment	Size range (nm)	Mean ± SD (range) ($\times 10^3$ particles/cm^3)	Exposure measure	Outcome	Length of analyzed ECG	Lags
Zhang et al. 2013[69]	Panel study	China	06-10.2008	Non-smokers / 125	Monitoring site about 7 km from the study site	13–764.7	15.9 ± 4.7 (5.2–29.4)	24-h moving average	SDNN RMSSD LF HF LF/HF	10 min	0 day-6 day
Hampel et al. 2014[41]	Panel study	Germany	03.2008	Non-smokers / 5	Personal monitoring	20–1,000+	19.3 ± 32.7 (1.0–147.4)	5-min moving average	SDNN RMSSD Normalized LF Normalized HF	5 min	0 min 0-4 min 5-9 min 10-14 min 15-19 min 20-24 min 25-29 min
Peters et al. 2015[40]	Panel study	Germany	03.2007-12.2008	Non-smoking patients with T2D or IGT / 64	Personal monitoring	10–1,000	20.8 ± 39.2 (0.5–15.6)	5-min moving average	SDNN RMSSD	5 min and 1 h	0 min 0-4 min 5-9 min 10-14 min 0 h
Sun et al. 2015[70]	Panel study	China	04-09.2010	Elderly patients with T2D or IGT / 53	Monitoring site	5–560	20.2 ± 11.5	0-1 h, 0-4 h, 0-12 h, 0-18 h, and 0-24 h moving averages	SDNN RMSSD LF HF LF/HF	5 min	0-1 h 0-4 h 0-12 h 0-18 h 0-24 h
Breitner et al. 2019[54]	Panel study	Germany	03.2007-12.2008	(1) Non-smoking patients with T2D or IGT / 64 (2) Healthy adults / 46	Urban background monitoring station	10–100	9.5 ± 6.9 (0.9–80.9)	Hourly average	SDNN RMSSD	1 h	0 h-6 h
		U.S.	06.2006-11.2009	Non-smoking patients MI or unstable angina / 73	Monitoring site at the study center		4.0 ± 3.7 (0.01–155.0)				
Huang et al. 2021[43]	Panel study	China	01.2015-06.2019	Non-smokers / 78	Monitoring site about 8 km from the study site	10–100	3.9 ± 2.1 (0.6–11.8)	Daily average	SDNN RMSSD LF HF	24 h	0 day 1 day 2 day 3 day

CAD=coronary artery disease; ECG=electrocardiogram; HF=high-frequency power; IGT=impaired glucose tolerance; LF=low-frequency power; MI=myocardial infarction; RD=respiratory disease; RMSSD=root mean square of successive R-R interval differences; SDNN=standard deviation of the normal-to-normal intervals; T2D=type 2 diabetes.

Table 2. Short-term effects of ultrafine particles on heart rate variability in crossover (semi-controlled exposure) studies.

Study	Exposure scenario	Pollution	Immediate effects					Acute effects					Delayed effects				
			SDNN	RMSSD	LF	HF	LF/HF	SDNN	RMSSD	LF	HF	LF/HF	SDNN	RMSSD	LF	HF	LF/HF
Laumbach et al. 2010[21]	Car rides in rush hours	TRAP	→	→	→	→	↑	→	↓	→	↓	→					
Weichenthal et al. 2011[22]	Cycling on high- and low-traffic routes and indoors	UFP	→	→	→	↓	→										
Langrish et al. 2012[23]	Walk along city center routes with and without face mask	TRAP	→	↓	↑	↓	→	→	→	→	→	→					
Laumbach et al. 2014[24]	Car rides in rush hours with and without HEPA filter	TRAP	→	→	→	→	→	→	→	→	→	→					
Sarnat et al. 2014[25]	Car rides in rush hours	TRAP	↓	↓	→	→	→										
Weichenthal et al. 2014[26]	Cycling on high- and low-traffic routes and indoors	UFP	↑	→	→	→	→										
Cole-Hunter et al. 2016[27]	Rest or exercise in high- and low-traffic environments	UFP	↓	↓	↓	↓	→										
Shutt et al. 2017[28]	Outdoors near a steel plant and at a college campus	UFP	↓	→	↓	→	→										
Andersen et al. 2019[29]	Travel in diesel and electric trains	UFP						→	→	↑	→	→	→	→	↑	→	→
Moshammer et al. 2019[30]	Walk in traffic and park with and without traffic noise	UFP	↑	→	→	→											

Arrows ↓, ↑, and → indicate a significant decrease, a significant increase, and no significant change in HRV indices associated with elevated UFP, respectively.

HF=high-frequency power; LF=low-frequency power; RMSSD=root mean square of successive R-R interval differences; SDNN=standard deviation of the normal-to-normal intervals, TRAP=traffic-related air pollution; UFP=ultrafine particles.

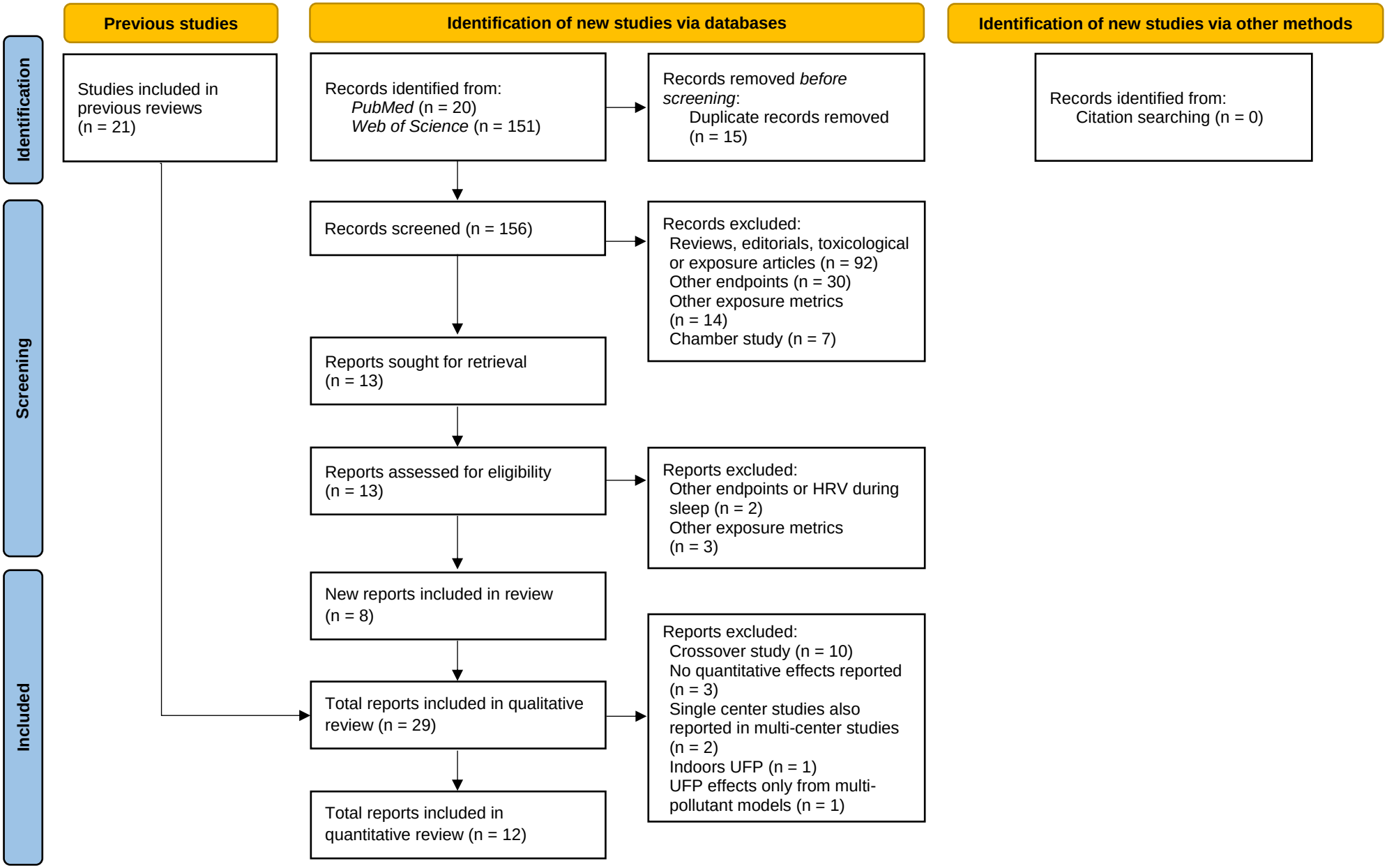

Figure 1. Flowchart of literature screening process.

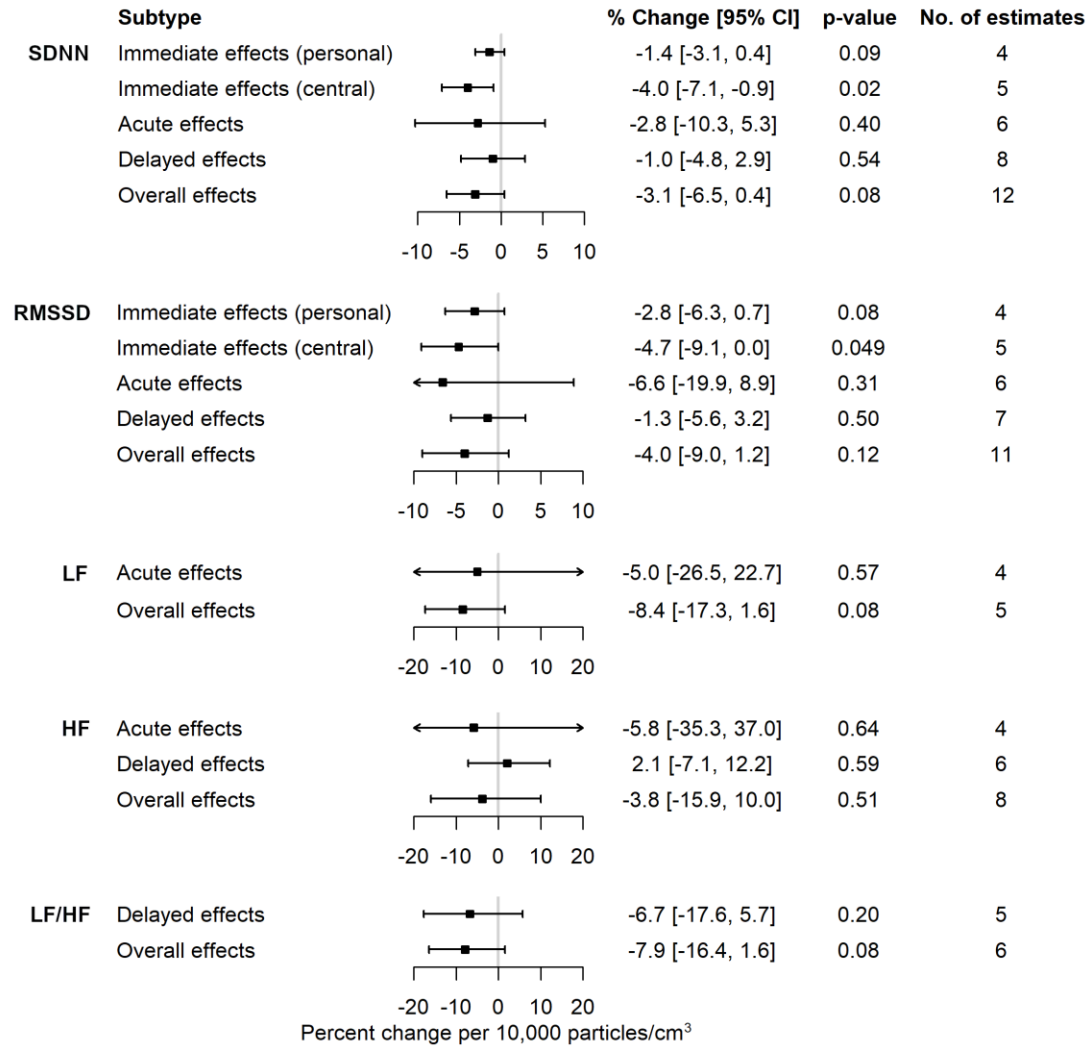

Figure 2. Pooled percent changes (95% CIs) in heart rate variability indices per 10,000 particles/cm^3 increase in particle number concentration from random-effects meta-analyses.

Note: The overall effects were estimated by pooling the most statistically significant effect estimates of ultrafine particles assessed by central outdoor measurements per study regardless of the time course. HF=high-frequency power; LF=low-frequency power; RMSSD=root mean square of successive R-R interval differences; SDNN=standard deviation of the normal-to-normal intervals.

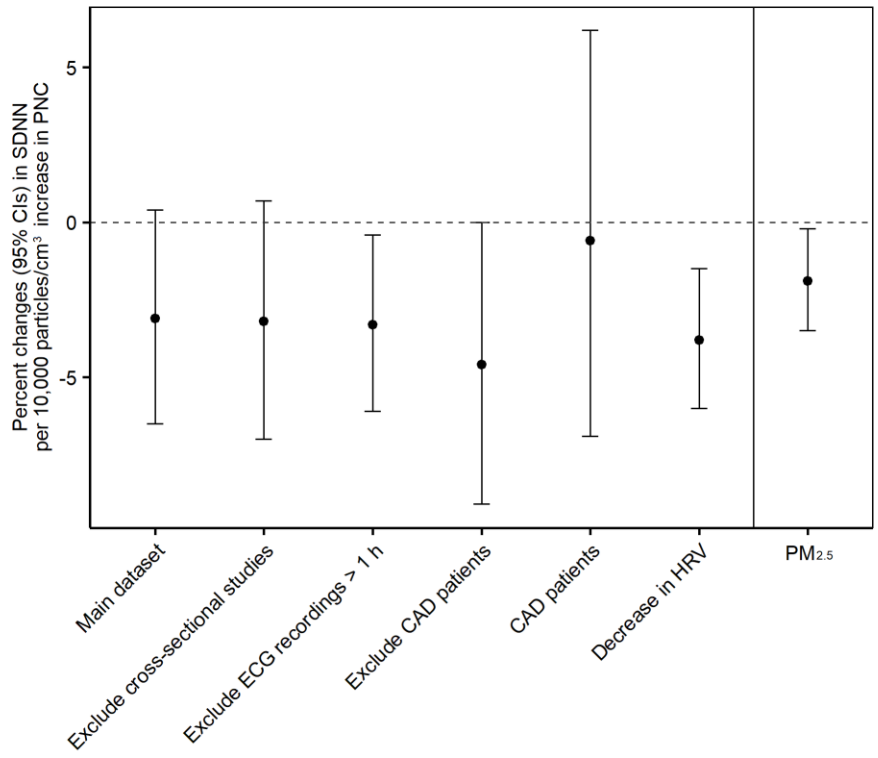

Figure 3. Pooled overall effects of ultrafine particles on SDNN from subgroup and sensitivity analyses and pooled overall effects of $PM_{2.5}$ on SDNN.

Note: The overall effects were estimated by pooling the most statistically significant effect estimates of UFP and $PM_{2.5}$ assessed by central outdoor measurements per study regardless of the time course.

CAD: coronary artery disease; HRV=heart rate variability; PM=particulate matter; PNC=particle number concentration; SDNN=standard deviation of the normal-to-normal intervals.