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Original Contribution

Heart Rate Variability, Ambient Particulate Matter Air Pollution, and Glucose Homeostasis: The Environmental Epidemiology of Arrhythmogenesis in the Women's Health Initiative

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Metabolic neuropathophysiology underlying the prediabetic state may confer susceptibility to the adverse health effects of ambient particulate matter <10 μm in diameter (PM_{10}). The authors therefore examined whether impaired glucose homeostasis modifies the effect of PM_{10} on heart rate variability in a stratified, random sample of 4,295 Women's Health Initiative clinical trial participants, among whom electrocardiograms and fasting blood draws were repeated at 3-year intervals from 1993 to 2004. In multilevel, mixed models weighted for sampling design and adjusted for clinical and environmental covariables, PM_{10} exposure was inversely associated with heart rate variability. Inverse PM_{10}–heart rate variability associations were strongest for the root mean square of successive differences in normal-to-normal RR intervals (RMSSD). Among participants with impaired fasting glucose, there were −8.3% (95% confidence interval: −13.9, −2.4) versus −0.6% (95% confidence interval: −2.4, 1.3), −8.4% (95% confidence interval: −13.8, −2.7) versus −0.3% (95% confidence interval: −2.1, 1.6), and −4.3% (95% confidence interval: −9.4, 1.0) versus −0.8% (95% confidence interval: −2.7, 1.0) decreases in the RMSSD per 10-μg/m^3 increase in PM_{10} at high versus low levels of insulin ($P < 0.01$), insulin resistance ($P < 0.01$), and glucose ($P = 0.16$), respectively. These associations were stronger among participants with diabetes and weaker among those without diabetes or impaired fasting glucose. The findings suggest that insulin and insulin resistance exacerbate the adverse effect of PM_{10} on cardiac autonomic control and thus risk of coronary heart disease among nondiabetic, postmenopausal women with impaired fasting glucose.

diabetes mellitus; glucose; heart rate; insulin; particulate matter

Abbreviations: HOMA-IR, insulin resistance according to homeostatic model assessment; PM_{10}, particulate matter <10 μm in diameter; RMSSD, root mean square of successive differences in normal-to-normal RR intervals; SDNN, standard deviation of normal-to-normal RR intervals; WHI, Women's Health Initiative.

Measures of heart rate variability derived from short-term electrocardiographic recordings are inversely associated with risk of incident coronary heart disease (1–4). They are also inversely associated with concentrations of ambient particulate matter air pollution among persons with and without diabetes (5, 6), implicating altered heart rate variability as a mechanism linking particulate matter exposures to coronary heart disease events. It has been suggested that the associations observed among nondiabetics may be attributable to metabolic abnormalities related to insulin resistance (7, 8). The metabolic neuropathophysiology common to both the prediabetic and diabetic states may therefore confer susceptibility to the adverse autonomic and cardiovascular effects of particulate matter, including reduced heart rate variability.

Several studies have found evidence that indirectly supports this hypothesis (9–14), although most used administrative data to ascertain comorbid diabetes, an approach

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often characterized by insensitivity of disease detection, resulting misclassification, and potential for bias in corresponding measures of association, the direction and magnitude of which are difficult to evaluate adequately (15–17). Prospective epidemiologic studies relying on more sensitive methods of diabetes ascertainment have found comparatively little evidence supporting such particulate matter–diabetes interactions. In the Adventist Health Study of Smog (18) and the Harvard Six-Cities Study (19), for example, the particulate matter–mortality association was similar when stratifying by or excluding participants with diabetes. Moreover, in the Multiethnic Study of Atherosclerosis (20) and the Women's Health Initiative (WHI) observational study (21), the associations among particulate matter, coronary artery calcium, and coronary heart disease were stronger among nondiabetic than diabetic participants.

Collectively, these findings suggest that the susceptibility of persons with diabetes to the adverse effects of particulate matter is rather uncertain, despite being biologically plausible. Furthermore, modification of the particulate matter–heart rate variability association by fasting glucose, insulin, or insulin resistance in the nondiabetic state may be more important from the public health perspective than modification by diabetes per se, given the much larger population of nondiabetic individuals with subclinical impairments of glucose homeostasis who may be at risk of particulate matter-related cardiovascular health problems because of these metabolic abnormalities. However, the effects of subclinical impairments in glucose homeostasis (22) on the particulate matter–heart rate variability association among persons without diabetes have not been evaluated.

We therefore examined them in the Environmental Epidemiology of Arrhythmogenesis in the WHI, an ancillary study of proarrhythmic mechanisms linking air pollution and cardiovascular disease in the WHI clinical trials.

MATERIALS AND METHODS

Setting, design, and study population

The WHI clinical trials were designed to allow randomized, controlled evaluation of estrogen with or without progestin treatment, calcium/vitamin D supplementation, and dietary modification on the risk of breast and colorectal cancer, cardiovascular disease, and bone fractures (23). Between 1993 and 1998, the trials enrolled 68,132 postmenopausal women aged 50–79 years who were followed at 1 of 75 US examination sites (including satellites, remote sites, and their changes in location). Women were not eligible if they had medical conditions predictive of survival time less than 3 years, if they were known to have conditions inconsistent with study participation and adherence (e.g., alcohol dependence), or if they were active participants in another randomized, controlled trial. Women also were ineligible for reasons of competing risk and safety. Each intervention arm also incorporated specific eligibility criteria. Those who remained eligible and interested were invited to follow-up examinations at 1, 3, 6, and 9 years. Rigorous quality assurance programs were in place through closeout (September 2004–March 2005).

Electrocardiograms

Centrally trained and officially certified technicians recorded resting, supine standard 12-lead electrocardiograms at the baseline and year 3, 6, and 9 examinations (24). They placed disposable silver/silver chloride electrodes on the precordium relative to standard anatomic landmarks using the E-V6 Halfpoint Method (25), a HeartSquare device (NovaHeart, Inc., Weston, Florida), and strictly standardized protocols for positioning chest electrodes in women (26). They digitally recorded electrocardiograms with participants in the resting, supine position using MAC PC electrocardiographs (Marquette Electronics, Milwaukee, Wisconsin). Upon successful recording, they transmitted electrocardiograms by telephone modem to the Epidemiological Cardiology Research (EPICARE) Center (Division of Public Health Sciences, School of Medicine, Wake Forest University, Winston-Salem, North Carolina) for visual inspection, error/missing lead detection, quality grading, and electronic reading by the Marquette 12-SL program (GE Marquette, Milwaukee, Wisconsin).

Heart rate variability measures

Electronic reading of the 10-second electrocardiograms produced 3 measures that reflect influences of the autonomic nervous system on the heart: 1) the median duration of the RR interval across all 12 leads (RR, milliseconds); 2) the standard deviation of all normal-to-normal RR intervals (SDNN, milliseconds) $= \{[\Sigma(RR_{mean} - RR_j)^2]/(n-1)\}^{0.5}$; and 3) the root mean square of successive differences in normal-to-normal RR intervals (RMSSD, milliseconds) $= \{[\Sigma(RR_{j+1} - RR_j)^2]/n\}^{0.5}$ (27). The repeatability, accuracy, and predictive validity of these short-term, time domain measures of heart rate variability have been described (28–30).

Addresses and geocodes

Participants' addresses were collected at each visit and updated at least biannually. All of the participants' and examination site addresses in the contiguous United States from baseline through follow-up were geocoded following a standardized protocol by a single geocoding vendor selected from 4 candidates on the basis of its accuracy (31, 32). The vendor assigned coordinates (latitudes, longitudes) and unique census identifiers (2000 US Census Federal Information Processing Standards codes) to >99% of the addresses. Of these addresses, 91% were matched to specific streets.

Air pollutant concentrations

All ambient criteria air pollutant concentration data recorded at monitors operating in the contiguous United States during the study period were obtained from the US Environmental Protection Agency Air Quality System (33). Data recorded before and during 2004 were downloaded in January 2005 and October 2006, respectively. The data included the longitude and latitude of each monitor. A semiautomated program was used to produce time series of estimated daily mean (standard error) pollutant

concentrations at each geocoded address from baseline through closeout (34). The program relied on a spherical model to perform national-scale, lognormal ordinary kriging and the weighted least-squares method to estimate semivariograms (35–38). The program was run, and the default (visually unadjusted) semivariograms were cross-validated by using ArcView GIS, version 8.3, software (Environmental Systems Research Institute, Inc. (ESRI), Redlands, California) and its Geostatistical Analyst extension (39). The validity of the model was evaluated by using standard cross-validation statistics: the prediction error (predicted minus measured pollutant concentration at each monitor site), standardized prediction error (prediction error divided by its estimated standard error), root mean square standardized (standard deviation of standardized prediction error across sites), root mean square prediction error (empirical standard error based on the mean square of the predictions), and mathematically calculated standard error. Observed values of prediction error and standardized prediction error near 0, values of root mean square standardized near 1, and the similarity of root mean square prediction error and mathematically calculated standard error provided evidence of model validity (34, 40). Fifteen acute pollutant exposure measures were computed by averaging the daily mean concentrations within overlapping 1-, 2-, and 3-day lag combinations inside a 5-day exposure window ending on the examination date.

Weather variables

All meteorologic data recorded at stations operating in the contiguous United States during the study period were obtained from the National Climatic Data Center. The data included ambient temperature, dew point, and pressures, as well as station longitudes, latitudes, and altitudes. Missing sea level pressures were replaced with values computed from station and altimeter pressures by using the station altitude, ambient temperature, and US Standard Atmosphere temperature profile (41, 42). The station-specific daily mean temperature and sea level pressure were then computed at all stations with at least 75% of consecutive, hourly measures available for a given day. The daily mean temperature (°C), dew point (°C), and pressure (kPa) were estimated at each geocoded address from baseline to closeout by averaging these daily means across all stations within 50 km, a distance over which their station-to-station correlations exceed 0.90 (43). Thereafter, lagged weather variables were computed, as described above for particulate matter <10 μm in diameter (PM_{10}).

Measures of glucose homeostasis

An examination site- and race-stratified, 6% random sample of women with a 6:1 overrepresentation of ethnic minorities had fasting blood draws repeated at the year 3, 6, and 9 examinations. Samples were processed, frozen at −70°C, and then shipped to Medical Research Laboratories (Highland Heights, Kentucky) for assay of plasma glucose by the hexokinase method (44, 45) on a Hitachi 7474 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, Indiana) and serum insulin by a stepwise sandwich enzyme-linked immunosorbent assay (46) on an ES 300 analyzer (Boehringer Mannheim Diagnostics). Corresponding interassay coefficients of variation were <2% and 3.2%–9.5%. Insulin resistance according to homeostatic model assessment (HOMA-IR) was computed (47, 48). Standard diagnostic criteria were used to define impaired fasting glucose (glucose = 100–125 mg/dL (5.6–6.9 mmol/L)) and diabetes (antidiabetic medication use, glucose ≥126 mg/dL (7.0 mmol/L), or history) (49).

Other characteristics of participants

Self-reported education, medication use, health history (see below), and a variety of other attributes were determined at each visit by standardized participant interview and examination. Interim health events also were identified via standardized medical record review and physician adjudication, specifically: hypertension by antihypertensive medication use, systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or history; body mass index (weight (kg)/height $(m)^2$); total energy expenditure (kcal/kg × week) based on the type, frequency, and duration of recreational physical activity (50); hypercholesterolemia by antihyperlipidemic medication use or history; smoking as current, former, or never; chronic lung disease by history of asthma, emphysema, or lung cancer; coronary heart disease by antianginal medication use, history of angina or myocardial infarction, or medical record review/adjudication; revascularization by history of coronary artery angioplasty, stent or bypass, or medical record review/adjudication; and congestive heart failure by cardiac glycoside and diuretic use, history, or medical record review/adjudication.

Exclusions

Of the 68,132 participants examined between 1993 and 2004, 4,376 (6.4%) with sampled glucose or insulin concentrations and addresses in the contiguous 48 US states were included. Of these 4,376 participants, 81 (1.9%) were excluded because they had conditions that affect the availability or accuracy of heart rate variability measures: missing, duplicate baseline, nonroutine, fourth or later electrocardiograms; poor electrocardiogram quality grades; <5 or 50% normal-to-normal RR intervals; atrioventricular conduction defects; electronic pacers; frequent premature ventricular beats; arrhythmias; or antiarrhythmic medication use. All analyses were conducted among the remaining 4,295 participants, 50% of whom had 3, 32% had 2, and 18% had only 1 examination during the study period.

Statistical analysis

Analyses relied on a 3-level, random-effects model of the heart rate variability–PM_{10} association in which i, j, and k denote the ith examination (level 1) of the jth participant (level 2) in the kth examination site (level 3). The basic model is given by

$$Y_{ijk} = \beta_1 + \beta_2 P_{ijk} + \beta_3 t_{ijk} + \beta_4 C_{ijk} + b_{1k}^{(3)} + b_{2k}^{(3)}(P_{ijk}) + b_{1jk}^{(2)} + b_{3jk}^{(2)}(t_{ijk}) + e_{ijk}^{(1)},$$

where Y_{ijk} denotes a log-transformed heart rate variability measure, β_1–β_4 denote fixed effects parameter estimates, and both b_1–b_3 and e denote random effects. In this model, β_1 is the intercept, P_{ijk} is PM_{10} ($\mu g/m^3$), t_{ijk} is an interval-scale measure of time (year) since baseline, and $\boldsymbol{C}_{ijk}$ is a vector of covariates. The terms $(b_{1k}^{(3)}, b_{2k}^{(3)}) \sim N(\underline{0},G^{(3)})$ are a random intercept and a random slope for PM_{10} at level 3, $(b_{1jk}^{(2)}, b_{2jk}^{(2)}) \sim N(\underline{0},G^{(2)})$ are a random intercept and a random slope for time at level 2, and $e_{ijk}^{(1)} \sim N(0,\sigma^2)$ is the random error at level 1. The parenthetical superscripts indicate the levels within which random effects varied and were assumed independent.

To compensate for bias associated with unequal probabilities of sampling across examination sites and race, site- and race-specific sampling weights were empirically calculated from participant counts at each examination, participant weights as inverse probabilities of including participants within site-race strata, and examination weights as inverse response probabilities at each examination. The MULTILEV procedure in LISREL, version 8.8, software (Scientific Software International, Inc., Lincolnwood, Illinois) was used to incorporate these weights in the above models, thereby allowing inferences to the dynamic population of WHI clinical trial participants from which the site- and race-stratified, 6% random sample was drawn. The procedure proportionally scaled the participant weights to sum to participant sample sizes within site-race strata and examination weights to sum to number of examinations per participant, a process that decreases bias in random-effects parameters and improves efficiency (51, 52). To adjust for attrition, the models were rerun after multiplying examination weights by inverse participant response probabilities at follow-up examinations estimated in weighted logistic regression models, including their demographic and clinical characteristics at prior examinations.

Models were also run in subgroups of participants with diabetes, impaired fasting glucose, and normal fasting glucose. For simplicity, effect measure modification (significance of the $PM_{10} \times$ insulin, $PM_{10} \times$ HOMA-IR, and $PM_{10} \times$ glucose interactions) was tested within these subgroups by using subgroup-specific indicators for high versus low insulin, HOMA-IR, and glucose. Findings based on the dichotomization of these variables at the 50th–90th percentiles were compared to determine their sensitivity to use of arbitrarily chosen thresholds.

To control for potential confounding by season, day of week, time of day, health, and weather in analyses of the particulate matter–heart rate variability association, temporal, sociodemographic, clinical, and weather covariables were added to the models. Final models included the interval-scale weather variables mentioned above. Differences in findings based on final models and those containing single (or pairs of) weather variables were negligible. Final models also included 3 indicator variables for the 4 seasons: spring (i.e., March, April, or May), summer, fall, and winter. The indicator variable model was compared with models including 2 or 4 harmonic seasonal terms: $\sin(2\Pi jt/366)$ and $\cos(2\Pi jt/366)$, where $j = (1)$ or $j = (1, 2)$ and $t =$ (examination day, i.e., 1, 2, 3, …, or 366). Goodness of fit based on the Akaike Information Criterion was greatest for the indicator variable model, leading to its adoption.

Interval-scale covariables were centered, and a deviation from means coding scheme for categorical covariables was used to simplify interpretation. By convention, the resulting estimates of association are reported as percent changes in heart rate variability per 10-$\mu g/m^3$ increase in PM_{10} concentration.

Modeling was preceded by estimation of examination-specific summary statistics weighted for the sampling and response probabilities described above by using SUDAAN, version 9.0.1, software (SUDAAN Statistical Software Center, Research Triangle Park, North Carolina). The weighting method scaled participant contributions to the summary statistics in a manner inversely proportional to these probabilities, again allowing inference to the sampling frame from which the site- and race-stratified, 6:1 minority oversample was drawn. Combining participants examined in Iowa City and Davenport, Iowa, in Jacksonville and Gainesville, Florida, and at sites with an affiliated remote site and/or change in location allowed us to avoid analytical problems associated with sparse data within site-race strata at later examinations.

RESULTS

Participant, monitor, and examination site locations are illustrated in Web Figure 1. (These locations are shown in the first of 2 supplementary figures; each is referred to as "Web Figure" in the text and is posted on the *Journal*'s website (http://aje.oxfordjournals.org/).) Most participants were born in the 1930s, white, and not college educated (Table 1). They were examined less in winter, on weekends, and late in the day. Their coronary heart disease risk factor burden was substantial at examination 1, when 28% were randomized to estrogen with or without progestin treatment, 26% to calcium/vitamin D supplementation, and 25% to dietary modification. By examination 3, participants had aged an average of 5 years; they were being examined earlier in the year, week, and day; and they were more likely to have a major coronary heart disease risk factor or coronary heart disease itself. At examination 1, the mean values for RR, SDNN, and RMSSD were lower among participants with diabetes (868, 16, 19 milliseconds) than among those with impaired fasting glucose (915, 20, 21 milliseconds) or normal fasting glucose (947, 21, 22 milliseconds). Across examinations, RR increased, but SDNN and RMSSD decreased (Table 2). The PM_{10} concentration, temperature, and dew point averaged over lag 0 and 1 ($lag_{0\text{-}1}$) peaked in the summer to fall, while barometric pressure peaked in the winter (Web Figure 2). The mean values of these variables were comparatively stable across examinations (Table 2), a period during which $lag_{0\text{-}1}$ PM_{10} remained approximately 18% of the current, 24-hour standard (150 $\mu g/m^3$) (53).

Table 1. Characteristics of the Participants by Examination, the Environmental Epidemiology of Arrhythmogenesis in the Women's Health Initiative, 1993–2004

Characteristic	Mean (SE) or %[a]		
	Examination 1 (n = 4,097)	Examination 2 (n = 3,429)	Examination 3 (n = 2,459)
Age, years	64 (0.1)	67 (0.2)	69 (0.2)
Race/ethnicity			
White/non-Hispanic	83	84	85
Black/African American	10	9	8
Hispanic/Latino	4	4	4
Other	3	3	2
Education less than college graduate	64	63	62
Examination season			
Spring	27	27	28
Summer	25	27	28
Fall	24	24	23
Winter	23	23	21
Examination day			
Monday	18	21	22
Tuesday	25	23	23
Wednesday	23	20	23
Thursday	19	20	20
Friday	12	14	12
Saturday–Sunday	3	2	1
Examination time of day	12:10 (00:03)	10:14 (00:03)	9:54 (00:02)
Diabetes[b]	9	10	12
Impaired fasting glucose[b]	23	21	26
Normal fasting glucose[b]	68	69	62
Glucose, mg/dL[c]	100 (0.5)	99 (0.5)	101 (0.6)
Insulin, mIU/L[c]	12 (0.1)	12 (0.2)	10 (0.2)
HOMA-IR[c]	3.0 (0.1)	3.2 (0.1)	2.7 (0.1)
Hypertension	44	47	54
SBP/DBP, mm Hg	128/76 (0.4/0.2)	126/73 (0.4/0.2)	125/71 (0.4/0.2)
β-Blocker use	8	11	16
Body mass index, kg/m^2	29 (0.1)	29 (0.1)	29 (0.2)
Total energy expenditure, kcal/kg × week[d]	11 (0.3)	11 (0.3)	11 (0.3)
Hypercholesterolemia	12	17	26
Current smoker	9	6	5
Chronic lung disease	10	11	10
Coronary heart disease	6	7	9
Revascularization	1	2	3
Congestive heart failure	1	2	2

Abbreviations: HOMA-IR, insulin resistance according to homeostatic model assessment; SBP/DBP, systolic/diastolic blood pressure; SE, standard error.

[a] Mean (SE) and percent weighted for sampling design and attrition. Percentages may not sum to 100 because of rounding.

[b] "Diabetes" is defined as antidiabetic medication use, a fasting glucose level of ≥126 mg/dL (7.0 mmol/L), or history; "impaired fasting glucose" is a glucose level of 100–125 mg/dL (5.6–6.9 mmol/L); and "normal fasting glucose" is a fasting glucose level of ≤99 mg/dL (5.5 mmol/L).

[c] The 90th percentiles of glucose, insulin, and HOMA-IR were 116 mg/dL, 20 mIU/L , and 5.3 (examination 1), 117 mg/dL, 21 mIU/L, and 5.7 (examination 2), and 121mg/dL, 18 mIU/L , and 5.1 (examination 3), respectively.

[d] Missing 11% and 5% of values at examinations 1 and 2. For all other variables, ≤1% of values were missing.

Table 2. Heart Rate Variability and Environmental Measures by Examination, the Environmental Epidemiology of Arrhythmogenesis in the Women's Health Initiative, 1993–2004[a]

Measure	Examination 1 (n = 4,097)			Examination 2 (n = 3,429)			Examination 3 (n = 2,459)		
	Mean (SE)	10th Percentile	90th Percentile	Mean (SE)	10th Percentile	90th Percentile	Mean (SE)	10th Percentile	90th Percentile
RR, milliseconds	932 (2.8)	761	1,114	936 (3.0)	763	1,118	942 (3.4)	773	1,111
SDNN, milliseconds	20 (0.4)	7	37	20 (0.4)	6	36	19 (0.4)	6	34
RMSSD, milliseconds	22 (0.5)	7	40	21 (0.5)	6	39	21 (0.6)	7	38
PM_{10}, $\mu g/m^3$[b]	28 (0.2)	16	42	27 (0.2)	16	42	27 (0.3)	16	41
Temperature, °C[b]	14 (0.2)	1	25	14 (0.2)	1	24	14 (0.2)	1	25
Dew point, °C[b]	8 (0.2)	−5	19	8 (0.2)	−5	19	8 (0.2)	−5	19
Barometric pressure, kPa[b]	102 (0.01)	101	102	102 (0.01)	101	102	102 (0.01)	101	102

Abbreviations: PM_{10}, particulate matter of <10 μm in diameter; RMSSD, root mean square of successive differences in normal-to-normal RR intervals; RR, median RR interval across all 12 leads; SDNN, standard deviation of normal-to-normal RR intervals; SE, standard error.

[a] Summary statistics were weighted for sampling design and attrition.

[b] Daily means were averaged over a 2-day period ending on the examination date (lag_{0-1}).

Log-transformed heart rate variability measures were inversely associated with PM_{10} concentrations, more strongly so at shorter lags: The unadjusted percent change per 10-$\mu g/m^3$ increase in PM_{10} at lags 0–3 was: −0.9, −0.9, −0.4, and 0.0 for RMSSD; −0.7, −0.6, −0.2, and 0.1 for SDNN; and −0.2, 0.0, 0.1, and 0.1 for RR, respectively. $Lag_{0\text{-}1}$ PM_{10} concentrations also were weakly and inversely associated with heart rate variability in unadjusted models. P values associated with adding terms for the $lag_{0\text{-}1}$ PM_{10} × (normal, impaired fasting glucose, diabetes) interaction to the unadjusted models were 0.304 for RMSSD, 0.457 for SDNN, and 0.983 for RR. Overlapping 95% confidence intervals associated with the percent change in RMSSD, SDNN, and RR per 10-$\mu g/m^3$ increase in PM_{10} also were observed after stratification of the unadjusted models (Table 3). Adjustment of the stratified models strengthened the inverse particulate matter–RMSSD and particulate matter–SDNN associations among the diabetes and impaired fasting glucose subgroups.

Within these subgroups, the inverse associations tended to be significantly stronger at high (>90th percentile) versus low levels of insulin and HOMA-IR (Table 4). Differences persisted when insulin and HOMA-IR were dichotomized at the 70th or 50th percentile. Within the diabetes subgroup, the effects of further adjustment for use of antidiabetic medications were negligible. Findings based on models also adjusting for attrition, restricting to single cross-sectional examinations or the 50% of participants with all 3 examinations, excluding outlying $lag_{0\text{-}1}$ PM_{10} concentrations, and controlling for randomization status, were comparable.

DISCUSSION

Among US women aged ≥60 years, the prevalence of diabetes was approximately 19% between 1999 and 2002 (22). This value represented only one-third of the combined total burden of diabetes and impaired fasting glucose in this segment of the US population at the time. Indeed, of the remaining majority of women aged ≥60 years that did not have diagnosed or undiagnosed diabetes, fully 34% had impaired fasting glucose, a common condition previously identified as an important risk marker for cardiovascular disease (54).

With the cardiovascular implications of impaired fasting glucose and decreased heart rate variability (1–4) in mind, the present study examined the effects of common impairments in glucose homeostasis on the PM_{10}–heart rate variability association. It did so among a geographically heterogeneous, site- and race-stratified, randomly selected minority oversample of postmenopausal women enrolled in the WHI clinical trials. It focused on 3 subgroups of the women who were, on average, in their mid- to late sixties at the time of their examinations: those with diabetes, impaired fasting glucose, and normal fasting glucose.

The study found that, in women with diabetes, there was a much stronger inverse particulate matter–RMSSD association when either insulin or HOMA-IR was high. The direction of the association in this subgroup was fairly consistent across heart rate variability measures, but its magnitude tended to be greater for both RMSSD and SDNN than for RR. Perhaps more important, however, were the persistence of the PM_{10}–heart rate variability associations in women with impaired fasting glucose and, by comparison, its striking attenuation in those women with neither diabetes nor impaired fasting glucose.

The persistence and then attenuation of the PM_{10}–heart rate variability association across the spectrum of glucose homeostasis examined in this setting are consistent with findings in men with and without diabetes (9), but they also extend to the relatively mild forms of hyperinsulinemia and insulin resistance that characterize the much larger population of nondiabetic US women with impaired fasting glucose. The extensions imply that the metabolic neuropathophysiology underlying the prediabetic state may confer susceptibility to the adverse autonomic effects of particulate matter on the heart. Indeed, the findings presented here are consistent with a neuropathophysiologic model linking prediabetic metabolic abnormalities including hyperinsulinemia to altered autonomic

Table 3. Percent Change in Heart Rate Variability per 10-μg/m^3 Increase in lag_{0-1} PM_{10} Concentration, the Environmental Epidemiology of Arrhythmogenesis in the Women's Health Initiative, 1993–2004

Measure of Heart Rate Variability by Model[a]	Diabetes[b] (n = 770[c])		Impaired Fasting Glucose[b] (n = 1,559[c])		Normal Fasting Glucose[b] (n = 3,141[c])	
	Percent Change[d]	95% Confidence Interval	Percent Change[d]	95% Confidence Interval	Percent Change[d]	95% Confidence Interval
RMSSD						
Model 1	−0.1	−3.4, 3.3	−0.7	−2.3, 1.0	−1.9	−3.3, −0.5
Model 2	−0.7	−3.9, 2.7	−0.6	−2.2, 1.0	−1.9	−3.3, −0.5
Model 3	−3.7	−6.8, −0.5	−1.2	−3.0, 0.7	−2.1	−3.8, −0.5
SDNN						
Model 1	−0.3	−3.3, 2.9	−0.3	−1.7, 1.3	−1.4	−2.8, 0.0
Model 2	−0.6	−3.7, 2.6	−0.3	−1.8, 1.2	−1.3	−2.6, 0.1
Model 3	−2.5	−5.3, 0.5	−0.8	−2.4, 0.8	−1.1	−2.6, 0.5
RR						
Model 1	−0.4	−1.0, 0.3	−0.1	−0.5, 0.3	−0.2	−0.5, 0.0
Model 2	−0.4	−1.0, 0.2	−0.1	−0.5, 0.3	−0.2	−0.5, 0.0
Model 3	−1.0	−1.7, −0.3	0.1	−0.3, 0.6	−0.5	−0.7, −0.2

Abbreviations: PM_{10}, particulate matter of <10 μm in diameter; RMSSD, root mean square of successive differences in normal-to-normal RR intervals; RR, median RR interval across all 12 leads; SDNN, standard deviation of normal-to-normal RR intervals.

[a] Model 1, unadjusted; model 2, adjusted for age (year) and race/ethnicity; model 3, also adjusted for education, time of day (minutes), day of week, season, body mass index (kg/m^2), hypertension, systolic blood pressure (mm Hg), β-blocker use, total energy expenditure (kcal/kg × weeks), current smoker status, chronic lung disease, hypercholesterolemia, coronary heart disease, revascularization, congestive heart failure, lag_{0-1} temperature (°C), dew point (°C), and barometric pressure (kPa). Indicators were used to represent the categorical variables in Table 1.

[b] "Diabetes" is defined as antidiabetic medication use, a fasting glucose level of ≥126 mg/dL (7.0 mmol/L), or history; "impaired fasting glucose" is a glucose level of 100–125 mg/dL (5.6–6.9 mmol/L); and "normal fasting glucose" is a fasting glucose level of ≤99 mg/dL (5.5 mmol/L).

[c] Unweighted number of participants with diabetes, impaired fasting glucose, or normal fasting glucose at visit 1, 2, or 3.

[d] Percent change weighted for sampling design.

nervous system activity, the latter manifest as a reduction in heart rate variability (7, 8) and exacerbated by the previously documented effects of particulate matter (5, 6). Because reduced heart rate variability is, in turn, associated with risk of incident coronary heart disease (1–4), the clinical and public health implications of these findings are potentially important. However, autonomic processes are not solely accountable for the adverse effects of particulate matter on the heart. Recent findings suggest otherwise: Hemostatic, endothelial, inflammatory, and oxidative mechanisms of disease, as well as others not examined by this study, also have been implicated in the cardiovascular effects of particulate matter (55–59).

The extension nevertheless offers insight into the discrepant literature regarding the putative particulate matter–diabetes interaction, the existence of which is supported by some studies (10–14) but not by others (18–21). If the present findings can be confirmed, the confirmation would suggest that the observed inconsistency of the biologically plausible particulate matter–diabetes interaction may relate more to the residual effects of insulin and insulin resistance in nondiabetic persons with impaired fasting glucose than to the absence of effect measure modification by diabetes, per se. Such a conclusion would nonetheless have to be tempered by the possibility that, in the presence of strong effects of diabetes on, for example, heart rate variability, relatively weak environmental effects of particulate matter may be quite challenging to measure, particularly in administrative data sets (15–17).

This study has several limitations that may affect interpretation of its findings. First, it is an ancillary study of participants in the WHI clinical trials. As such, women in it were randomized to estrogen with or without progestin treatment, calcium/vitamin D supplementation, and/or dietary modification. Although women were randomized, these exposures may have affected the measures of both heart rate variability and glucose homeostasis. Second, heart rate variability was measured from resting, standard 12-lead electrocardiograms that were only 10 seconds in duration. Such measures reflect heart rate variation in the time domain and over the short term. Third, PM_{10} was not measured in the personal breathing space of participants. Instead, it was spatially interpolated at each participant's geocoded address, raising questions about its validity. Finally, there was considerable attrition of the examination site- and race-stratified minority oversample. In the face

Table 4. Percent Change in Heart Rate Variability per 10-μg/m^3 Increase in $lag_{0\text{-}1}$ PM_{10} Concentration, at High and Low Measures of Glucose Homeostasis, the Environmental Epidemiology of Arrhythmogenesis in the Women's Health Initiative, 1993–2004[a]

Measure of Heart Rate Variability and Glucose Homeostasis	Diabetes[b] (n = 770[c])			Impaired Fasting Glucose[b] (n = 1,559[c])			Normal Fasting Glucose[b] (n = 3,141[c])		
	Percent Change[d]	95% Confidence Interval	$P_{interaction}$[e]	Percent Change[d]	95% Confidence Interval	$P_{interaction}$[e]	Percent Change[d]	95% Confidence Interval	$P_{interaction}$[e]
RMSSD									
Insulin									
High	−16.9	−23.4, −9.9	<0.01	−8.3	−13.9, −2.4	<0.01	−0.1	−4.1, 4.0	1.00
Low	−1.9	−5.1, 1.5		−0.6	−2.4, 1.3		−2.3	−4.0, −0.6	
HOMA-IR									
High	−24.5	−33.3, −14.6	<0.001	−8.4	−13.8, −2.7	<0.01	−1.3	−5.3, 2.9	1.00
Low	0.3	−2.9, 3.7		−0.3	−2.1, 1.6		−2.2	−3.9, −0.4	
Glucose									
High	−15.7	−25.7, −4.4	<0.01	−4.3	−9.4, 1.0	0.16	−0.8	−4.3, 2.9	0.33
Low	−1.8	−5.0, 1.4		−0.8	−2.7, 1.0		−2.3	−4.0, −0.5	
SDNN									
Insulin									
High	−16.8	−23.5, −9.5	<0.01	−7.4	−12.9, −1.6	0.02	1.8	−2.1, 5.9	0.36
Low	−0.6	−3.5, 2.5		−0.1	−1.6, 1.4		−1.3	−2.9, 0.4	
HOMA-IR									
High	−21.5	−29.4, −12.7	<0.001	−5.4	−11.0, 0.5	0.08	1.8	−2.0, 5.7	0.37
Low	0.8	−2.1, 3.9		−0.1	−1.6, 1.3		−1.3	−2.9, 0.4	
Glucose									
High	−11.8	−20.8, −1.7	0.04	−0.4	−5.1, 4.5	0.89	−0.3	−4.1, 3.7	0.66
Low	−1.1	−4.0, 1.8		−0.9	−2.4, 0.7		−1.2	−2.7, 0.5	
RR									
Insulin									
High	−2.4	−4.2, −0.5	<0.01	−0.7	−1.9, 0.4	0.16	−0.4	−1.1, 0.3	0.88
Low	−0.8	−1.5, −0.1		0.3	−0.1, 0.7		−0.4	−0.8, −0.1	
HOMA-IR									
High	−3.2	−5.7, −0.6	<0.001	−1.1	−2.2, 0.0	0.02	−0.5	−1.2, 0.2	0.92
Low	−0.7	−1.4, 0.0		0.4	0.0, 0.8		−0.4	−0.8, −0.1	
Glucose									
High	−3.0	−5.4, −0.6	<0.001	−0.3	−1.2, 0.6	0.42	−1.6	−2.2, −0.9	<0.01
Low	−0.7	−1.4, 0.0		0.2	−0.2, 0.6		−0.3	−0.6, 0.0	

Abbreviations: HOMA-IR, insulin resistance according to homeostatic model assessment; PM_{10}, particulate matter of <10 μm in diameter; RMSSD, root mean square of successive differences in normal-to-normal RR intervals; RR, median RR interval across all 12 leads; SDNN, standard deviation of normal-to-normal RR intervals.

[a] High values of insulin, HOMA-IR, and glucose defined as >90th percentile.

[b] "Diabetes" is defined as antidiabetic medication use, a fasting glucose level of ≥126 mg/dL (7.0 mmol/L), or history; "impaired fasting glucose" is a glucose level of 100–125 mg/dL (5.6–6.9 mmol/L); and "normal fasting glucose" is a fasting glucose level of ≤99 mg/dL (5.5 mmol/L).

[c] Unweighted number of participants with diabetes, impaired fasting glucose, or normal fasting glucose at visit 1, 2, or 3.

[d] Weighted for sampling design and adjusted for age (year), race/ethnicity, education, time of day (minutes), day of week, season, body mass index (kg/m^2), hypertension, systolic blood pressure (mm Hg), β-blocker use, total energy expenditure (kcal/kg × weeks), current smoker status, chronic lung disease, hypercholesterolemia, coronary heart disease, revascularization, congestive heart failure, $lag_{0\text{-}1}$ temperature (°C), dew point (°C), and barometric pressure (kPa). Indicators were used to represent the categorical variables in Table 1.

[e] P value for the test of the PM_{10} × insulin, PM_{10} × HOMA-IR, or PM_{10} × glucose interaction.

of these limitations, the study took several precautions. It carefully established both the reliability and accuracy of its heart rate variability measures (28), geocodes (31), and spatial interpolations (34, 40) relative to criterion standards; it documented modest effects of exposure measurement error in the latter on particulate matter–coronary heart disease and particulate matter–RR associations (31, 60, 61); and it adjusted effect sizes for randomization

status and participant attrition, noting only small changes as a result of adjustment.

Despite such reassurance, participants with diabetes had both the *lowest* mean baseline heart rate variability measures and the *highest* particulate matter-related *decreases* in heart rate variability across examinations, while those with normal fasting glucose had both the *highest* mean baseline heart rate variability measures and the *lowest* particulate matter-related *decreases* in heart rate variability across examinations. Although these observations suggest that subgroup differences in baseline heart rate variability may have affected the strength of the particulate matter–heart rate variability association, they are inconsistent with regression to the mean, in which selection of participants from a population on the basis of a baseline measure is associated with increased proximity of subsequent measures to the population mean, not greater divergence from it. The interactions observed in this context are therefore unlikely to be simple reflections of subgroup differences in baseline heart rate variability that have been misattributed to the effects of PM_{10}.

We therefore conclude that insulin and insulin resistance increase susceptibility to the adverse effect of ambient particulate matter air pollution on cardiac autonomic control among nondiabetic, postmenopausal women with impaired fasting glucose. Such increases in susceptibility may, in turn, influence the risk of coronary heart disease among persons with this endocrinologic condition.

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