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Association between Particulate Air Pollution and QT Interval Duration in an Elderly Cohort

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Abstract

BACKGROUND—Short-term fine particulate matter (PM_{2.5}) exposure has been linked with increased QT interval duration, a marker of ventricular repolarization and a risk factor for cardiac arrhythmia and sudden death, in several studies. Only one previous study evaluated whether long-term PM exposure is related to the QT interval. We aim to evaluate whether sub-chronic and long-term exposure to PM_{2.5} at home is linked with QT duration in an elderly cohort.

METHODS—We measured heart-rate corrected QT interval duration among 404 participants from the Greater Boston area between 2003 and 2011. We modeled residential PM_{2.5} exposures using a hybrid satellite- and land use-based model. We evaluated associations between moving averages of short-term (1–2 day), sub-chronic (3–28 day) and long-term (1 year) pollutant exposures and corrected QT duration using linear mixed models. We also evaluated effect modification by oxidative stress genetic score using separated regression models and interaction terms.

RESULTS—We observed positive associations between sub-chronic and long-term PM_{2.5} exposure and corrected QT duration, with the strongest results for longer-term exposures. For example, a 1 standard deviation increase in 1-year PM_{2.5} was associated with a 6.3 ms increase in corrected QT (95% confidence interval: 1.8, 11). We observed somewhat greater effects among

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subjects with higher (8.5 ms) rather than lower (3.1 ms) oxidative stress allelic profiles (p-interaction=0.25).

CONCLUSIONS—PM_{2.5} was associated with increased corrected QT duration in an elderly cohort. While most previous studies focused on short-term air pollution exposures, our results suggest that longer-term exposures are associated with cardiac repolarization.

INTRODUCTION

Exposure to particulate air pollution is associated with cardiovascular morbidity and mortality in numerous epidemiologic studies, especially among the elderly and those with preexisting medical conditions.^{1,2} The mechanisms mediating this increase in risk are not fully understood, but may include particle-induced increases in oxidative stress,^{3,4} autonomic dysfunction,⁵ and systemic inflammation.⁶

On a functional level, associations between particulate pollution and cardiovascular events may be mediated in part by changes in cardiac repolarization.^{2,7} The QT interval represents the duration of ventricular depolarization and repolarization and prolongation of this interval is an established risk factor for arrhythmia and sudden cardiac death.^{8,9} Sudden deaths in particular have been associated with particulate air pollution.¹⁰ Short-term particulate pollutant exposure was associated with QT interval duration in several epidemiological and animal studies.^{7,11,12} However, although associations between particulate air pollution exposure and the risk of adverse cardiovascular outcomes are generally strongest for long-term rather than short-term pollutant exposures, only one cross-sectional study has previously examined the association between particles and QT interval duration.¹³ This study found a positive association between 1-year PM_{2.5} exposure and the risk of QT prolongation. Our aim was to further evaluate the association between intermediate-term and long-term air pollution exposures and QT interval duration among a longitudinal cohort of elderly men: the Normative Aging Study.

Specifically, we hypothesized that sub-chronic (3–28 day) and long-term (1 year) increases in exposure to particulate matter less than 2.5 micrometers in aerodynamic diameter (PM_{2.5}) would be related to increased duration of the heart-rate corrected QT interval in our study population. We also evaluated whether this association was modified by participants' oxidative stress allelic profile, obesity and diabetes status, and current use of beta blockers, and examined whether the association between PM and QTc varied across quantiles of the QTc interval distribution using quantile regression.

METHODS

Study Population

Our analysis included 400 men enrolled in the Veterans Administration Normative Aging Study (NAS) with information regarding residential PM_{2.5} concentrations, QT duration measures, and all covariates of interest. These participants underwent 610 study visits between January 14, 2003 and December 21, 2011. The NAS is a prospective cohort study, described in detail previously.¹⁴ Briefly, this closed cohort was established in 1963 and originally enrolled 2,280 adult male volunteers living in the Greater Boston area, who were

free of chronic medical conditions. Loss to follow-up has been mainly due to death or moving out of the study area.

There were 607 active NAS study participants during the time period of interest. Of these, 451 participants had complete information regarding sub-chronic or long-term residential PM_{2.5} exposures and QTc measurements for one or more study visits. Three participants were missing information on cholesterol levels and one was missing information on race. We also excluded 49 study participants with atrial fibrillation, pacemakers or QRS interval durations of 120 ms or greater from the analysis, which brought the final sample size to 400. Participants presented for 1–4 visits, with 27% (n=166) undergoing at least two study visits.

We administered detailed questionnaires and physical examinations at all center-based study visits, occurring every 3–5 years. Physical examinations included measurement of height and weight, which was used to calculate body mass index (BMI). We used fasting blood samples to assess cholesterol levels,¹⁵ and obtained smoking history from an American Thoracic Society (ATS) questionnaire. We defined participants' diabetes status based on a physician's diagnosis of type 2 diabetes, and/or use of diabetes medication assessed during the physician interview. We also assessed use of anti-hypertensive medications (ACE inhibitors, beta blockers, calcium channel blockers, angiotensin receptor blockers, and diuretics) during the physician interview. Finally, systolic and diastolic blood pressure (SBP and DBP) were measured by a physician, and mean arterial blood pressure was defined as $DBP + 1/3(SBP - DBP)$.

This study was approved by the Harvard School of Public Health and Veteran Administration institutional review boards, and all participants provided their written informed consent.

QT Interval Duration

We measured heart rate variability between 5:30AM and 2:00PM using a two-channel, five-lead ECG monitor (Trillium 30000; Forest Medical, East Syracuse, NY), as described in detail previously.¹⁶ QT duration was measured in one of two leads using a Holter recorder. Participants rested for 5 minutes, and then remained seated during the ECG, which was recorded at a sampling rate of 256 Hz per channel for 5–10 minutes. QT intervals were measured in ms from the onset of the QRS to the end of the T-wave on normal or supraventricular beats, and were not calculated when the T-wave did not have sufficient amplitude. We excluded participants with atrial fibrillation, pacemakers or QRS intervals 120 ms from our analysis (49 participants, 92 study visits). We calculated heart rate-corrected QT values, hereafter referred to as QT, using Fridericia's formula.¹⁷

PM_{2.5} Exposure and Temperature

We estimated spatially and temporally resolved daily residential PM_{2.5} exposures (in $\mu\text{g}/\text{m}^3$) at each participant's residence using a validated hybrid exposure model, described in detail previously.¹⁸ This model incorporated satellite based aerosol optical depth measurements as well as land-use and meteorologic variables, including temperature, wind speed, elevation, visibility, distance to major roads, percent of open space, population density, traffic density, proximity to point source emissions, and area emissions (NO₂, SO₂, PM₁₀, PM_{2.5}). We used a

mixed model approach by regressing daily PM_{2.5} against aerosol optical depth, spatial predictors, and temporal predictors. For days when aerosol optical depth data were not available for some grid cells, we fit a generalized additive model with a thin plate spline term of latitude and longitude to interpolate PM_{2.5}. Out of sample R² for this model was 0.89 for daily data and 0.87 for annual averages. We evaluated moving averages of PM_{2.5} exposure at 3, 7, 21, 14, and 28 days as well as 1 year before each visit. Although the focus of our study was sub-chronic and long-term PM exposures, we also evaluated averages of PM_{2.5} for 1 and 2 days before each study visit.

Apparent temperature, defined as a person's perceived air temperature in °C,¹⁹ was calculated using the following formula: $-2.653 + (0.994 \times \text{air temperature}) + (0.0153 \times \text{dew-point temperature})$. We calculated moving averages of apparent temperature corresponding to 3–28 days before each study visit, and averaged outdoor temperature for the year before each visit.

Oxidative Stress Genetic Scores

We hypothesized that the PM-QT association may be mediated by an oxidative stress-related mechanism. To evaluate this possibility, we calculated oxidative stress allelic profiles using a genetic score approach, in which variants of oxidative defense genes were selected using the least absolute shrinkage and selection operator (Lasso) based on their association with 8-hydroxydeoxyguanosine levels (8-OhdG is a marker of oxidative DNA damage).²⁰ The Lasso method performs variable selection and estimates regression coefficients by minimizing the residual sum of squares given a constraint for the sum of the absolute value of coefficients in a regression model.²¹ The genetic variants used to calculate the oxidative stress score were *CAT* (rs1001179, rs480575), *GC* (rs2282679), *GCLM* (rs3170633), *HMOX1* (rs2071746, rs5995098), and *NQO1* (rs1800566). We constructed scores representing participants' allelic profiles by summing these genetic variants, using the signs of the coefficients of the Lasso penalization.²⁰

Statistical Analyses

We evaluated the association between standard deviation (SD) increases in moving averages of PM_{2.5} exposure (1 day-1 year) and QT interval duration in ms, using linear mixed models.

All models controlled for potential confounders, which we identified through a literature search and chose on the basis of being related to both air pollution exposure and QT duration, as can be visualized using directed acyclic graphs.²² These potential confounders are age (years), BMI (in kg/m²), race (White, Black, Hispanic [White], and Hispanic [Black]), total cholesterol levels (mg/dL), smoking history (current, former, or never), current use of anti-hypertensive medications (ACE inhibitors, calcium channel blockers, angiotensin receptor agonists, alpha blockers, or diuretics: yes/no), diabetic status (based on physician's diagnosis and/or use of diabetes medications: yes/no), alcohol intake (vs. < two drinks/day), season (indicated using the sine and cosine of the date), mean arterial pressure (mmHg), and moving averages of temperature corresponding to the pollutant exposure duration of interest (using both a linear and quadratic term). We examined effect

modification of the association between 1-year PM_{2.5} exposure and QT duration by obesity (defined as BMI ≥ 30 kg/m²; yes/no), diabetes (yes/no), current use of beta blockers (yes/no) and oxidative stress allelic profile (high/low; dichotomized according to the median score) using separated regression models. We also used interaction terms in order to assess effect modification. When assessing interactions with beta blocker use, we adjusted for the individual anti-hypertensive medications listed above rather than an aggregated anti-hypertensive medication use variable.

We conducted a sensitivity analysis evaluating associations between 1-year PM_{2.5} exposure and QT, excluding participants with PM_{2.5} levels above 12 µg/m³ (representing 4 participants and 10 visits). We did this analysis in order to examine the PM_{2.5}-QT association only at pollutant exposure levels below EPA air quality standards. In addition, we conducted sensitivity analysis which accounted for possible survivor bias using inverse probability weighting. We modeled the probability of returning for a visit based on variables available at previous visits, including QT duration. The observations were given weights of one for the first visit, the inverse of the probability of returning for the second visit, the product of the inverse of the probabilities of returning for the second and third visits, etc. An additional sensitivity analysis restricted main effects and gene-environment interaction analyses to White participants.

Finally, we evaluated whether 1-year PM_{2.5} exposure was associated with QT duration at different percentiles of the QT distribution using quantile regression for longitudinal visits.²³ Instead of asking for the association between exposure and the average response, such analyses capture whether the shape of the distribution of QT in the population is changed, rather than just shifted, and if so, which part of the distribution is most affected. Specifically, we evaluated this association at the 10th, 20th, 30th, 40th, 50th, 60th, 70th, 80th, and 90th percentiles of QTc. We conducted analyses using SAS versions 9.3 and 9.4 (SAS Corporation, Cary, NC), and R version 3.1.1.

RESULTS

We report participants' characteristics at their baseline visit in Table 1. Briefly, participants presented with a mean age of 76 years, most were current or former smokers, 21% had diabetes, and 26% had a BMI over 30 kg/m².

We present residential PM_{2.5} concentrations for the averaging periods of 1 day to 1 year across all study visits in Table 2. For example, average 1-year PM_{2.5} exposure was 9.8 µg/m³ (interquartile range: 1.9 µg/m³, 5th-95th percentiles: 7.8–12 µg/m³).

We present associations between moving averages of PM_{2.5} exposure levels and QT interval duration in Table 3. We observed positive associations between increased sub-chronic and long-term PM_{2.5} exposure and QT duration. These associations were of greatest magnitude for longer-term exposures, although the trend wasn't linear. For example, 1-SD increases in PM_{2.5} exposure were associated with a 2.1 ms increase in QT (95% CI: -2.4, 6.7) for a 3 day moving average, a 3.7 ms increase in QT (95% CI: -1.0, 8.3) for a 14 day moving average, a 7.0 increase (95% CI: 2.3, 12) for a 28 day moving average, and a 6.3 ms increase

(95% CI: 1.8, 11) for a 1 year moving average. Standard deviation increases in 1 and 2 day PM_{2.5} exposures were associated with 1.7 and 2.3 ms increases in QT, respectively. The association between 1-year PM_{2.5} and QT was not changed materially by excluding participants with annual PM_{2.5} measurements above EPA air quality standards (6.6 vs. 6.3 ms; data not shown). Inverse probability weighting likewise did not appreciably alter main effects results, nor did limiting analyses to White participants only (data not shown).

We present quantile regression results in Supplemental Table 1. We observed a consistent change in QT interval duration of a bit under 6 ms at every decile of the QT distribution. For example, a SD increase in PM_{2.5} was associated with a 5.9 ms increase in QT at the 10th percentile of exposure (95% CI: 1.2, 11), and a 5.8 ms increase in QT duration at the 90th percentile (95% CI: 1.1, 11).

Finally, we report associations between 1-year PM_{2.5} exposure and QT interval duration stratified by obesity and diabetes status, current beta blocker use, and oxidative stress genetic score in Table 4. We found some limited evidence for interactions between oxidative stress allelic profile and PM_{2.5} exposure in relation to QT duration. Specifically, among those with low allelic risk profiles, a 1-SD increase in PM_{2.5} exposure was associated with a 3.1 ms increase in QT duration (95% CI: -3.7, 9.8), whereas among those with a high oxidative allelic risk profile, the same exposure increment was related to a larger increase in QT duration (8.5 ms, 95% CI: 1.9, 15; p for interaction = 0.25). Results were similar when restricting this analysis to White participants (data not shown). We also observed a somewhat stronger association between PM_{2.5} and QT among participants who were not taking beta blockers (6.5 ms, 95% CI: 0.14, 13), compared with current beta blocker users (2.1 ms, 95% CI: -4.7, 9.0; p-interaction = 0.34). The association between PM_{2.5} level and QT duration was very similar when stratified by diabetes or obesity status (Table 4).

DISCUSSION

We report positive associations between sub-chronic and long-term PM_{2.5} exposure and increased corrected QT duration, a risk factor for arrhythmia and cardiac death, in a cohort of elderly men. Effect estimates were strongest when evaluating longer-term moving averages of exposure, and among participants with a high oxidative stress allelic profile. The observed associations reflect PM_{2.5} levels that are consistently at or below EPA standards. Our results suggest that particulate pollution is associated with increased risk of adverse cardiovascular events in part through changes in ventricular repolarization, and that these associations are stronger among people with higher genetic susceptibility to oxidative stress.

A small number of studies previously explored the association between particulate air pollution and QT duration. These studies reported associations between short-term particulate levels and increased QT duration in both people and animals,^{7,11,12} though a previous NAS analysis which evaluated exposures up to 10 hours before the study visit reported associations only with black carbon (rather than PM_{2.5} as a whole).²⁴ A large cross-sectional study reported a positive association between long-term PM_{2.5} exposure and QT prolongation.¹³

Our analysis confirms an association between long term PM_{2.5} exposure and QT, and extends the literature by using a longitudinal study design with repeated visits and by examining sub-chronic exposure periods. We also examined the PM_{2.5}-QT association at different percentiles of QT duration, whereas epidemiologic studies generally evaluate changes in the mean outcome and may therefore miss associations in tails of the outcome distribution.²⁵ Our results indicate that the association between PM_{2.5} exposure and QT interval duration is stable across percentiles of the QT distribution, and the QT interval distribution is therefore shifted rather than changed in relation to pollutant exposure. Ours is also the first study to evaluate interactions between long-term PM_{2.5} exposure and oxidative stress genes, obesity, and beta blocker use in relation to QT, and the first to evaluate the association between long-term PM_{2.5} and QT among the elderly, a sub-population particularly vulnerable to pollutant-induced health effects.² The demonstration that long term exposure is associated with changes in QT is important because the studies showing QT associated with increased risk of subsequent arrhythmias interpret the longer QT as a relatively stable, long-term risk factor for the events. If long-term averages of PM_{2.5} are stronger predictors of QT than short term, this suggests that the long-term exposure is producing precisely the chronic effects on QT that are risk factors for cardiovascular events.

Potential mechanisms underlying the observed associations include a particulate-induced increase in pulmonary oxidative stress, which can in turn induce pro-inflammatory cytokines.²⁶ Particles can also induce oxidative stress and inflammation directly in the vasculature and myocardial substrate.²⁷ Furthermore, epidemiologic studies, including one in the NAS cohort, link PM exposure to methylation changes in the inducible nitric oxide synthase (*iNOS*) gene, which helps to regulate the inflammatory response.^{28,29} Increased pro-inflammatory signals and oxidative stress can alter cardiac autonomic control,²⁷ causing a prolonged period of ventricular polarization via changes in sodium and calcium channels.^{30,31} Oxidative stress also inhibits nitric oxide production,³² which could lead to changes in cardiac autonomic control, thereby triggering QT prolongation.³³

We observed some limited evidence for modification of the relation between PM_{2.5} and QT by oxidative stress genetic score, with somewhat stronger associations among participants with a high rather than low oxidative stress allelic profile. This result is consistent with a previous NAS study of short-term black carbon (BC) exposure and QT duration,²⁴ and with earlier reports of oxidative stress genes modifying pollutant effects on heart rate variability.^{34,35} As discussed above, probable mechanisms underlying the association between particulate air pollution and QT duration are heavily based on increases in oxidative stress.² Thus, genetic variants affecting reactive oxygen species formation and anti-oxidative defenses are expected to modify the PM_{2.5}-QT association. Nevertheless, our study's finding is modest and could be due to chance. Therefore, our result should be replicated in future studies, and then examined in light of the overall literature.

We also report some weak evidence of modification by beta blocker use, with somewhat larger effect estimates among those not currently using these medications. A possible causal mechanism underlying this finding involves effects of beta blockers on improved cardiac autonomic control.³⁶ However, we should note that the close association between

medication use and hypertension limits interpretability of our results, which could also be due to chance.

Our results are not suggestive of effect modification by obesity or diabetes on the association between $PM_{2.5}$ and QT. We expected to observe interactions because people with diabetes and obesity have elevated baseline oxidative stress levels and both conditions may be associated with increased QT duration.^{37–39} Our current findings are also inconsistent with a previous NAS study regarding short-term BC exposure and QT duration.²⁴ It should be noted that our study did not have sufficient power to examine effect modification in an optimal way, nor did we have the statistical power to examine three-way interactions, and larger studies will be needed in the future in order to examine the possibility of susceptible subgroups more thoroughly.

We acknowledge several other limitations of our study, including potential exposure misclassification of pollutant estimates. The limitation is reduced by the fact that we estimated individualized residential $PM_{2.5}$ exposures using a sophisticated, spatially and temporally resolved hybrid satellite based and land-use model, which is likely to reduce misclassification relative to fixed monitoring studies. Furthermore, pollutant measurement error from spatio-temporal models is likely to be of the Berkson type, which decreases precision without biasing effect size.⁴⁰

An additional limitation was our use of a lower than normal sampling rate of 256 Hz. This was the standard at the time these recordings were made and is still used by many clinical laboratories. Currently, a sampling rate of 1,000 Hz is considered preferable by most researchers and our lower sampling rate could lead to non-differential measurement error and contribute to a possible false negative finding. We also used a variable recording duration, though the sampling time-frame in our study was longer than the standard.

The changes in QT duration that we observed do not rise to a level requiring a clinical response.⁴¹ However, shifting the distribution of QT interval duration may be of public health, rather than individual, concern.⁴² Furthermore, $PM_{2.5}$ levels in the Boston area are generally below current EPA air quality standards. Other areas, especially in developing nations, may have consistently higher pollutant levels, which could affect ventricular repolarization more strongly. Finally, part of our goal was to identify mechanisms mediating the association between particulate pollutant exposure and adverse cardiovascular outcomes, and these results indicate that disturbance of cardiac repolarization may be part of that pathway.

A key factor in our ability to address the study question was development of a spatio-temporal model for daily exposure at the address of participants, due to the inclusion of satellite remote sensing data into the model, in contrast to exposures based solely on land use regression. While exposure was only estimated at the residence of participants, our subjects are elderly and for the most part no longer working.

Because the NAS comprises elderly, primarily Caucasian men, results may not be generalizable to other segments of the population. Our findings, however, are consistent

with those of a large study conducted among a younger population of both men and women.¹³

Strengths of our study include access to a large, general population longitudinal cohort with extensive and repeated information regarding PM_{2.5} exposures, potential confounders and effect modifiers, and QT data from multiple study visits. The QT interval was measured using a computer algorithm, which likely decreased measurement errors relative to manual measurement. Furthermore, longer-term rather than short-term exposures may be of most interest when assessing risk for chronic disease and dysfunction. Hence, an additional strength of our study was the reconstruction of participants' sub-chronic and long-term PM_{2.5} exposures.¹⁸ Finally, our use of oxidative stress genetic scores, designed in relation to their association with a valid marker of oxidative stress (8-OHdG), allowed us to reduce the number of statistical comparisons while examining the biological mechanisms potentially underlying the PM_{2.5}-QT interval association.

Conclusions

We report positive associations between sub-chronic and long-term PM_{2.5} exposures and QT interval duration, which may be strongest for longer-term exposures and among those with higher oxidative stress allelic profiles. Changes in ventricular repolarization may mediate associations between particle exposures and adverse cardiovascular outcomes, and assessing longer-term exposures is important to understanding effects of air pollution on chronic disease and dysfunction. Our main effects results are similar to previous studies evaluating short-term particulate exposure,^{7,11} and with one previous cross-sectional study of long-term exposure,¹³ but extend the literature by examining interactions between long-term PM exposure and oxidative stress genes and by using a longitudinal, repeated-measures design when assessing long-term exposures. Future high-powered studies should further evaluate associations between longer-term pollutant exposures and QT duration, including with respect to identifying susceptible subgroups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of participants at baseline (n=400), Normative Aging Study (2003–2011).

Study variable	Mean (SD)	N (%)
Age (years)	76 (6)	
Race		
White		387 (97)
Black		9 (2)
Hispanic (White)		3 (0.75)
Hispanic (Black)		1 (0.25)
Body mass index (kg/m ²)	28 (4)	
Obesity		
Yes		103 (26)
No		297 (74)
Total cholesterol (mg/dL)	181 (36)	
Smoking		
Never smoker		119 (30)
Former smoker		270 (68)
Current smoker		11 (3)
Mean arterial pressure (mmHg)	88 (11)	
Anti-hypertensive medicine use (n [%])		
Yes		272 (68)
No		128 (32)
Season		
Spring (March-May)		79 (20)
Summer (June-August)		106 (27)
Fall (September-November)		134 (34)
Winter (December-February)		81 (20)
Alcohol intake		
<2 drinks per day		320 (80)
2+ drinks per day		80 (20)
Diabetes		
Yes		83 (21)
No		317 (79)
Oxidative stress gene score		
Low		126 (39)
High		201 (61)

Table 2Study participants' PM_{2.5} exposure distributions, Normative Aging Study (2003–2011).

PM _{2.5} moving averages (µg/m ³)	N visits	Mean (SD)	5 th –95 th percentiles	Interquartile range
1 day	608	9.9 (5.6)	3.4–20	6.8
2 days	609	9.5 (4.7)	3.8–20	5.5
3 days	609	9.4 (4.0)	4.3–18	4.8
7 days	608	9.5 (3.1)	5.3–16	4.0
14 days	609	9.6 (2.7)	5.9–15	3.8
21 days	606	9.6 (2.5)	6.1–14	3.5
28 days	603	9.6 (2.4)	6.3–14	3.4
1 year	528	9.8 (1.3)	7.8–12	1.9

Table 3

Mixed linear effects models estimating the change in heart rate-corrected QT interval duration associated with 1 standard deviation increases in PM_{2.5}; Normative Aging Study, 2003–2011.^a

Exposure duration	N visits	Change in QTc (ms)	95% confidence interval
1 day	608	1.7	–2.9, 6.3
2 days	609	2.3	–2.3, 6.7
3 days	609	2.1	–2.4, 6.7
7 days	608	5.1	0.55, 9.7
14 days	609	3.7	–1.0, 8.3
21 days	606	5.8	1.2, 11
28 days	603	7.0	2.3, 12
1 year	528	6.3	1.8, 11

^a. Models are adjusted for age, race, BMI, cholesterol, smoking history, current use of anti-hypertensive medications, diabetic status, alcohol intake, season, mean arterial pressure, and moving averages of temperature corresponding to the PM_{2.5} exposure duration of interest (using linear and quadratic terms).

Table 4

Modification of the association between a standard deviation increase in the 1-year moving average of PM_{2.5} exposure and heart rate-corrected QT duration^a; Normative Aging Study, 2003–2011.

Characteristics	N visits	Change in QTc in ms (95% CI)
Oxidative stress genetic score < median	153	3.1 (−3.7, 9.8)
Oxidative stress genetic score > median	287	8.5 (1.9, 15)
P for interaction		0.25
Not obese ^b	392	6.1 (1.0, 11)
Obese	136	7.1 (−4.0, 18)
P for interaction		0.55
No diabetes	426	6.2 (1.4, 11)
Diabetes	102	6.0 (−7.5, 20)
P for interaction		0.83
No current beta blocker use ^c	294	6.5 (0.14, 13)
Current beta blocker use	234	2.1 (−4.7, 9.0)
P for interaction		0.34

^a. Models are adjusted for age, race, BMI, cholesterol, smoking history, current use of anti-hypertensive medications, diabetic status, alcohol intake, season, mean arterial pressure, and moving averages of temperature corresponding to the PM_{2.5} exposure duration of interest (using linear and quadratic terms).

^b. Models assessing interactions with obesity exclude BMI.

^c. Models assessing interactions with beta blocker use adjust for individual anti-hypertensive medications (ACE inhibitors, calcium channel blockers, angiotensin receptor agonists, alpha blockers, and diuretics), rather than a combined anti-hypertensive medication use variable.