



# The relation between past exposure to fine particulate air pollution and prevalent anxiety: observational cohort study

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## ABSTRACT

### OBJECTIVE

To determine whether higher past exposure to particulate air pollution is associated with prevalent high symptoms of anxiety.

### DESIGN

Observational cohort study.

### SETTING

Nurses' Health Study.

### PARTICIPANTS

71271 women enrolled in the Nurses' Health Study residing throughout the contiguous United States who had valid estimates on exposure to particulate matter for at least one exposure period of interest and data on anxiety symptoms.

### MAIN OUTCOME MEASURES

Meaningfully high symptoms of anxiety, defined as a score of 6 points or greater on the phobic anxiety subscale of the Crown-Crisp index, administered in 2004.

### RESULTS

The 71271 eligible women were aged between 57 and 85 years (mean 70 years) at the time of assessment of anxiety symptoms, with a prevalence of high anxiety symptoms of 15%. Exposure to particulate matter was characterized using estimated average exposure to particulate matter <2.5 µm in diameter (PM<sub>2.5</sub>) and 2.5 to 10 µm in diameter (PM<sub>2.5-10</sub>) in the one month, three months, six months, one year, and 15 years prior to assessment of anxiety symptoms, and residential distance to the nearest major road two years prior to assessment. Significantly increased odds of high anxiety symptoms were observed with higher exposure to PM<sub>2.5</sub> for multiple averaging periods (for example, odds ratio per 10 µg/m<sup>3</sup> increase in prior one month average PM<sub>2.5</sub>: 1.12, 95% confidence interval 1.06 to 1.19; in prior 12 month average PM<sub>2.5</sub>: 1.15, 1.06 to 1.26). Models including multiple exposure windows suggested short term averaging periods were more

relevant than long term averaging periods. There was no association between anxiety and exposure to PM<sub>2.5-10</sub>. Residential proximity to major roads was not related to anxiety symptoms in a dose dependent manner.

### CONCLUSIONS

Exposure to fine particulate matter (PM<sub>2.5</sub>) was associated with high symptoms of anxiety, with more recent exposures potentially more relevant than more distant exposures. Research evaluating whether reductions in exposure to ambient PM<sub>2.5</sub> would reduce the population level burden of clinically relevant symptoms of anxiety is warranted.

### Introduction

Anxiety disorders, characterized by disruptive fear, worry, and related behavioral disturbances such as avoidance or physical sensations of hyperarousal,<sup>1</sup> are the most common type of psychiatric disorder in the general population.<sup>2</sup> Globally, approximately 16% of people will have an anxiety disorder in their lifetime and 11% will have experienced an anxiety disorder in the past year.<sup>2</sup> Anxiety disorders are associated with reduced productivity and increased psychiatric and non-psychiatric medical care, absenteeism, and risk of suicide.<sup>3</sup> In 2010, anxiety disorders accounted for approximately 26.8 million disability adjusted life years worldwide.<sup>4</sup> The monetary cost of anxiety disorders is also substantial; in the United States, the annual direct cost of anxiety disorders in the 1990s has been estimated to be \$42.3bn (£27.3bn; €37.3bn).<sup>5</sup> Women have a higher prevalence of anxiety disorders than men<sup>6</sup> and the onset for most anxiety disorders is commonly in adolescence or young adulthood. However, the incidence of anxiety disorders remains substantial in mid-life, and new cases continue to arise into later life, especially in the case of generalized anxiety disorder.<sup>7</sup> Although numerous pharmacologic and non-pharmacologic therapies are available, remission is not always possible. Many people have persistent symptoms despite use of first line treatments.<sup>8</sup>

Given the substantial personal and societal burden from anxiety and the problem of treatment resistance, it is imperative to identify modifiable risk factors for anxiety disorders and symptoms. One important environmental exposure that may be related to anxiety is air pollution. Specifically, exposure to particulate matter air pollution may induce or exacerbate anxiety through increased oxidative stress and systemic inflammation<sup>9-17</sup> or through promotion or aggravation of chronic disease.<sup>18-32</sup> Though there is a small set of studies considering the association between air pollution and mental health outcomes,<sup>33-44</sup> we are aware of only two small

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Toxicological work suggests exposure to particulate air pollution may induce or exacerbate anxiety through increased oxidative stress and systemic inflammation. While a small but growing body of literature suggests an association between air pollution and mental health outcomes, including anxiety, data on the relation between exposure to particulate air pollution and anxiety in humans is lacking.

## WHAT THIS STUDY ADDS

Our study suggests that higher exposure to PM<sub>2.5</sub> (particulate matter <2.5 µm in diameter) especially higher recent exposure, is associated with an increased risk of high symptoms of anxiety.

studies that considered anxiety, and neither looked at total particulate matter. The first (n=1002) reported that ozone levels in the prior week were associated with anxiety symptoms,<sup>33</sup> whereas the second (n=100) reported that cumulative exposure to airborne manganese was associated with anxiety symptoms.<sup>44</sup> Epidemiologic research on the relation between exposure to particulate matter and anxiety is clearly lacking; we evaluated this association in a large prospective cohort study. Specifically, we hypothesized that higher exposure to particulate matter would be associated with a greater risk of high symptoms of anxiety.

The most biologically relevant period of exposure is currently unknown. If particulate matter induces anxiety through chronic oxidative stress, inflammation, or induction of chronic disease, long term cumulative exposure is most likely relevant. If particulate matter aggravates an existing propensity for anxiety symptoms, through either aggravation of chronic disease or transient changes in oxidative stress or inflammation, exposures closer to the time of symptom assessment may be relevant. Therefore, we considered the association between high anxiety symptoms and exposure to particulate matter averaged over five periods prior to the assessment of anxiety symptoms, specified a priori, ranging from a measure of long term, cumulative exposure (prior 15 years) to a measure of recent exposure (prior month).

## Methods

### Study population

The Nurses' Health Study is a prospective cohort study of women that began in 1976. A total of 121 701 married registered nurses, ages 30–55, residing in 11 states, were originally enrolled; at least 10 participants now reside in each of the 48 continental states. All participants are mailed follow-up questionnaires every two years, with a response rate of greater than 90% for each questionnaire.<sup>45</sup> As such, we receive updated information on residential address biennially, and we have geocoded all home addresses 1986 to 2007 within the contiguous United States to obtain latitude and longitude, allowing estimation of exposure to particulate air pollution. The Crown-Crisp index phobic anxiety scale, one of six scales from the Crown-Crisp experiential index, is a measure of anxiety symptom levels and was included in the 1988 and 2004 questionnaires. As our exposure data were available from 1988 onward (inclusive), we used data from the 2004 Crown-Crisp index phobic anxiety scale as our outcome measure of anxiety. The nurses' provided implied informed consent by completion and return of each questionnaire.

### Residential proximity to roadways

Using geographic information software (ArcGIS, Version 10.2; Esri, CA), we computed distance from the residential address of each participant in 2002, up to 500 m, with a street level geocoding match to the nearest US census feature class code A1 (limited access to primary roads with defined exits and divided directions of travel, that is, interstate highways), A2 (primary major,

non-interstate highways and major roads without access restrictions), or A3 (smaller, secondary roads, typically with more than two lanes) road segment. Distance to a major road is a commonly used proxy for traffic related exposures, including traffic related air pollution (which typically contains a high proportion of ultrafine particles, those <0.1 µm in diameter).<sup>46–48</sup> We classified distance to the nearest major road a priori as <50 m, 50 to <200 m, or ≥200 m, based on the observed pattern of particulate concentrations with increasing distance<sup>47–49</sup> and the distribution of roadway proximity in our sample.

### Particulate matter air pollution

We used spatiotemporal prediction models yielding monthly estimates of exposure to particulate matter <10 µm (PM<sub>10</sub>) and <2.5 µm (PM<sub>2.5</sub> or fine particulate matter) in aerodynamic diameter from January 1988 onward at the residential address with at least a zip code level geocoding match for each participant to derive multiple exposure metrics for each participant. These models cover the contiguous United States and are extensions of previously described models covering a more limited area.<sup>50–52</sup> Data used in these models included nationwide monitor data, geographic data (for example, distance to major roadway, population density, elevation, proportion of urban land use, point or area source emissions), and meteorological data (for example, temperature, wind speed, precipitation, barometric pressure). As nationwide PM<sub>2.5</sub> monitor data were unavailable prior to 1999, our pre-1999 estimates of PM<sub>2.5</sub> exposure were derived from a model that estimates the predicted ratio of PM<sub>2.5</sub> to PM<sub>10</sub> between 1988 and 1999; to get PM<sub>2.5</sub> predictions we combined the results of this model with estimates from the PM<sub>10</sub> model. We derived estimates of exposure to coarse (PM<sub>2.5–10</sub>) particulate matter by taking the difference between PM<sub>10</sub> and PM<sub>2.5</sub> estimates. For the current analyses we used these models to derive measures of average exposure to PM<sub>2.5</sub> and PM<sub>2.5–10</sub>, at the residential address of each participant for several exposure periods, including the average exposure between 1 January 1988 and 31 December 2003, and over the 1, 3, 6, and 12 calendar months prior to the participant's 2004 questionnaire cycle return date (that is, for a questionnaire returned in July 2004, we use the average exposure in June 2004 for the one month averaging period).

### Anxiety symptoms

The Crown-Crisp index phobic anxiety scale consists of eight self rated questions about fearfulness and desire for avoidance of common situations or environments (that is, having “unreasonable fear of enclosed spaces”, being “scared of heights”, disliking “going out alone”, feeling “panicky in crowds”, feeling “more relaxed indoors”, feeling “uneasy traveling on buses or trains”) and tendency to worry (that is, “about getting some incurable illness”, worrying “unduly when relatives are late coming home”); total possible index scores range from 0–16 points, with higher scores indicating more anxiety.<sup>53</sup> We required complete data on all eight items

to compute a total score. The Crown-Crisp index phobic anxiety scale has been shown to differentiate between people with general anxiety or phobias from those with other psychiatric conditions and healthy comparison participants<sup>53 54</sup> and has been used in population based research.<sup>55–61</sup> For primary analyses, we dichotomized Crown-Crisp index phobic anxiety scale scores from 2004 and considered those with a score of 6 points or more to have high symptoms of anxiety, as prior work suggests that this cut-off represents a clinically important threshold.<sup>58 61</sup>

### Covariates

Covariates included in all models were selected a priori because they were thought to be potential confounders or proxies for potential confounders (for example, socioeconomic status) and include calendar month of questionnaire return (categorical month), educational attainment (RN, BA, MA, or PhD), husband's educational attainment ( $\leq 12$  years, 12–16 years,  $>16$  years, not applicable, missing), age, age squared, married or has a partner (yes/no), employment status (yes/no), physical activity ( $<12$ , 12 to 30,  $>30$  metabolic equivalent task hours per week), three residential census tract level characteristics (percent white race/ethnicity, percent of adults without a high school diploma, and median home value; in fourths), region of residence (north east, south, midwest, west), residence within a metropolitan statistical area (yes/no), and social support<sup>62</sup> (low, low-medium, medium, high social networks). Many covariates were assessed at multiple cycles; we used the value at the 1988 or closest available questionnaire when considering the 1988–2003 averaging period and the 2002 or closest available questionnaire in models considering roadway proximity or particulate matter exposures within the year prior to the 2004 questionnaire return. With the exception of month of questionnaire return, we used missing indicators when covariate data were missing for more than 2% of our sample and replaced missing data with median or mode values when covariate data were missing in less than 2% of our sample.

### Primary analysis

For each model we restricted our analytical sample to people with 2004 Crown-Crisp index phobic anxiety scale scores and relevant exposure data. We used separate logistic regression models to estimate the association between each exposure and high anxiety symptoms (Crown-Crisp index phobic anxiety scale score  $\geq 6$ ). For models considering exposure to particulate matter, we evaluated the shape of the dose-response curve using penalized splines and report analyses using both fifths of exposure and linear terms. As exposures to particulate matter are correlated across averaging periods (see supplementary table e1), it is challenging to determine which exposure periods are most relevant when multiple periods appear associated with anxiety. Therefore, we also considered mutually adjusted models including either 1988–2003 and past one month or past 12 month and past one month exposures to particulate matter parameterized using penalized splines to tackle

whether long term or short term exposures were more relevant when we observed an association between anxiety and multiple averaging periods. To avoid the potential for differences in the variability of metrics for exposure to particulate matter across the two averaging periods to influence the findings, we used z score transformations of each of the particulate matter exposures (that is, one month, 12 months, and 1988–2003) in the mutually adjusted models.

### Sensitivity analyses

We conducted several sensitivity analyses to examine the robustness of our primary findings, including use of alternate categorizations for roadway proximity ( $<50$  m, 50–200 m, and  $>200$  m from A1 or A2 roadways;  $<100$  m, 100–300 m, and  $>300$  m from either A1, A2, or A3 roadways or A1 or A2 only roadways; and as a continuous variable for distance from A1, A2, or A3 roadways using a linear or spline parameterization within the range of 0 to 500 m); additional adjustment for individual level covariates often correlated with anxiety symptoms but which were not expected to be confounders, including physical functioning<sup>63</sup> (high, low), self rated health (excellent or very good, poor to average), number of major medical comorbidities ( $\geq 3$ ,  $<3$ ), alcohol consumption (non-drinker,  $<3$ , 3–6,  $>7$  alcoholic drinks per week), body mass index (normal, overweight, obese), and smoking status (never, former, current); restriction to non-movers (to reduce misclassification of exposure measures given some participants changed addresses but exact move dates are unknown); restriction to those who returned the questionnaire within three months of the initial mailing (to reduce misclassification of short term exposure measures, which are based on the return date for the questionnaire); restriction to those living in a metropolitan area, defined using rural-urban commuting codes<sup>64</sup> (to reduce potential confounding by urban versus rural environments); restriction to non-Hispanic white participants (96.7% of the sample, to allay concerns about confounding by race); use of negative binomial regression, which considers Crown-Crisp index phobic anxiety scale scores as count data and is similar to, but more appropriate and generally more conservative than Poisson regression when dealing with over-dispersed count data; and use of an alternate case definition with improved sensitivity but less specificity where we considered all people with a Crown-Crisp index phobic anxiety scale score of 6 or more and/or self report of use of anti-anxiety or antidepressant medications on the 2004 questionnaire to have high anxiety symptoms.

### Effect modification

We used multiplicative interaction terms and likelihood ratio tests to evaluate evidence for effect modification by several factors. These were residence within a metropolitan statistical area (yes/no) and United States census region (north east, south, midwest, west), as particulate matter composition may vary spatially; prevalent reactive airway disease (chronic obstructive pulmonary disease or asthma), atrial fibrillation, heart

failure, or multiple major medical conditions at the time of anxiety assessment (yes/no), as particulate matter may lead to anxiety through aggravation of symptoms of common medical conditions; age (over or under 65 at the time of anxiety assessment), as anxiety incidence and prevalence change with age; and 1988 Crown-Crisp index phobic anxiety scale score (0–1, 2–5, ≥6), given that high anxiety symptoms may have been present prior to the 2004 assessment. To limit the number of tests, we evaluated effect modification only when primary analyses indicated a main effect, and then only for the averaging period we judged to have the strongest association. We made no other adjustments to account for multiple comparisons. We report 95% confidence intervals and consider a P value <0.05 to be statistically significant. All analyses were conducted using SAS, Version 9.3 or R, Version 3.0.1.

**Results**

Sample sizes differed across analyses, based on availability of valid estimates on exposure (n=63 677 for roadway proximity analyses, n=69 966 for 1988–2003 average analyses of exposure to particulate matter, and n=71 271 for all other analyses). Among the largest group (n=71 271), at the time of completion of the Crown-Crisp index phobic anxiety scale the women in our sample were on average aged 70 (SD 7, range 57–85) years, 16% (n=11 320) of them reported current use of antidepressants and/or anti-anxiety medications, and the prevalence of high anxiety symptoms (Crown-Crisp index phobic anxiety scale ≥6) was 15% (n=10 818) (fig 1). Table 1 shows the socioeconomic characteristics of this sample. Of the 63 677 with valid estimates of 2002 residential roadway proximity, distance to the nearest major road was >200 m for 59.0% (n=37 545), 50–200 m for 26.4% (n=16 802), and <50 m for 14.7% (n=1120). In line with temporal trends, mean estimates for exposure to PM<sub>2.5</sub> and PM<sub>2.5–10</sub> were highest for the 1988–2003 exposure period (Table 2 and supplementary table e1). For example, the mean (SD) of exposures to PM<sub>2.5–10</sub> particulate matter was 9.0 µg/m<sup>3</sup> (SD 4.1) in 1988–2003 compared with 7.3 (4.8 µg/m<sup>3</sup>) for the one month averaging period. Similarly, the mean (SD) of exposures to PM<sub>2.5</sub> particulate matter was 13.8 (2.8 µg/m<sup>3</sup>) in 1988–2003

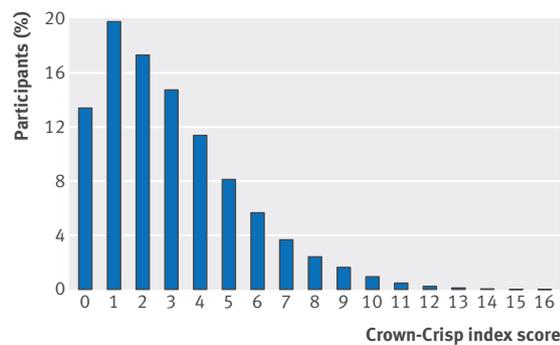


Fig 1 | Distribution of Crown-Crisp index phobic anxiety scale scores among eligible participants of Nurses' Health Study

**Table 1 | Socioeconomic characteristics from 2002 or nearest available Nurses' Health Study questionnaire**

Characteristics	No (%) of women (n=71 271)
<b>Educational attainment:</b>	
Registered nurse	44 907 (63.0)
Bachelors degree	13 368 (18.8)
Masters degree or PhD	6607 (9.3)
Missing	6389 (9.0)
<b>Husband's education:</b>	
High school degree or less	24 664 (34.6)
College degree	16 321 (22.9)
Professional or graduate school degree	13 978 (19.6)
Not applicable	4977 (7.0)
Missing	11 331 (15.9)
<b>Marital/partner status:</b>	
No current life partner	20 521 (28.8)
Current life partner	49 855 (70.0)
Missing	895 (1.3)
<b>Employment status:</b>	
Currently not employed outside the home	46 617 (65.4)
Currently employed outside the home	23 891 (33.5)
Missing	763 (1.1)
<b>Physical activity:</b>	
<12 METS/week	32 161 (45.1)
12 to <30 METS/week	27 582 (38.7)
≥30 METS/week	11 290 (15.8)
Missing	238 (0.3)
<b>Percent of census tract, white race/ethnicity:</b>	
<85%	15 627 (21.9)
85% to <94%	18 858 (26.5)
94% to <97%	15 992 (22.4)
≥97%	20 789 (29.2)
Missing	5 (0.0)
<b>Percent of census tract, adult residents without a high school diploma:</b>	
<5%	8911 (12.5)
5% to <10%	19 211 (27.0)
10% to <15%	18 037 (25.3)
≥15%	25 107 (35.2)
Missing	5 (0.0)
<b>Median home value (\$):</b>	
<95 000	16 934 (23.8)
95 000 to <135 000	18 143 (25.5)
135 000 to <210 000	19 959 (28.0)
≥210 000	16 139 (22.7)
Missing	96 (0.0)
<b>Region of residence:</b>	
North east	35 040 (49.2)
Midwest	12 355 (17.3)
West	10 199 (14.3)
South	13 677 (19.2)
<b>Residence within a metropolitan statistical district:</b>	
Yes	64 648 (90.7)
No	6623 (9.3)
<b>Social support (Berkman-Syme index):</b>	
Low	4264 (6.0)
Low-medium	20 148 (28.3)
Medium	10 283 (14.4)
High	28 310 (39.7)
Missing	8266 (11.6)
\$1.00 (€0.65; €0.88).	

**Table 2 | Odds ratio (95% confidence interval) for 10 µg/m<sup>3</sup> increase in exposure to PM<sub>2.5</sub> over multiple averaging periods and high symptoms of anxiety in participants of Nurses' Health Study**

Period	Mean (SD) PM <sub>2.5</sub> (µg/m <sup>3</sup> )	Odds ratio* (95% CI)	P value
1 month	12.74 (4.18)	1.12 (1.06 to 1.19)	0.0001
3 months	12.13 (3.40)	1.13 (1.06 to 1.21)	0.0004
6 months	11.59 (2.77)	1.14 (1.05 to 1.23)	0.002
12 months	11.38 (2.60)	1.15 (1.06 to 1.25)	0.001
1988–2003	13.75 (2.82)	1.09 (1.01 to 1.18)	0.03

PM<sub>2.5</sub>=particulate matter <2.5 µm in diameter.

\*Adjusted for month of questionnaire return, nurse's education, husband's education, age, age squared, whether the nurse has a partner, employment status, physical activity, percent of residential census tract that is white, percent of residential census tract adults who lack a high school education, median home value of residential census tract, geographic region, residence within a metropolitan statistical area, and social support.

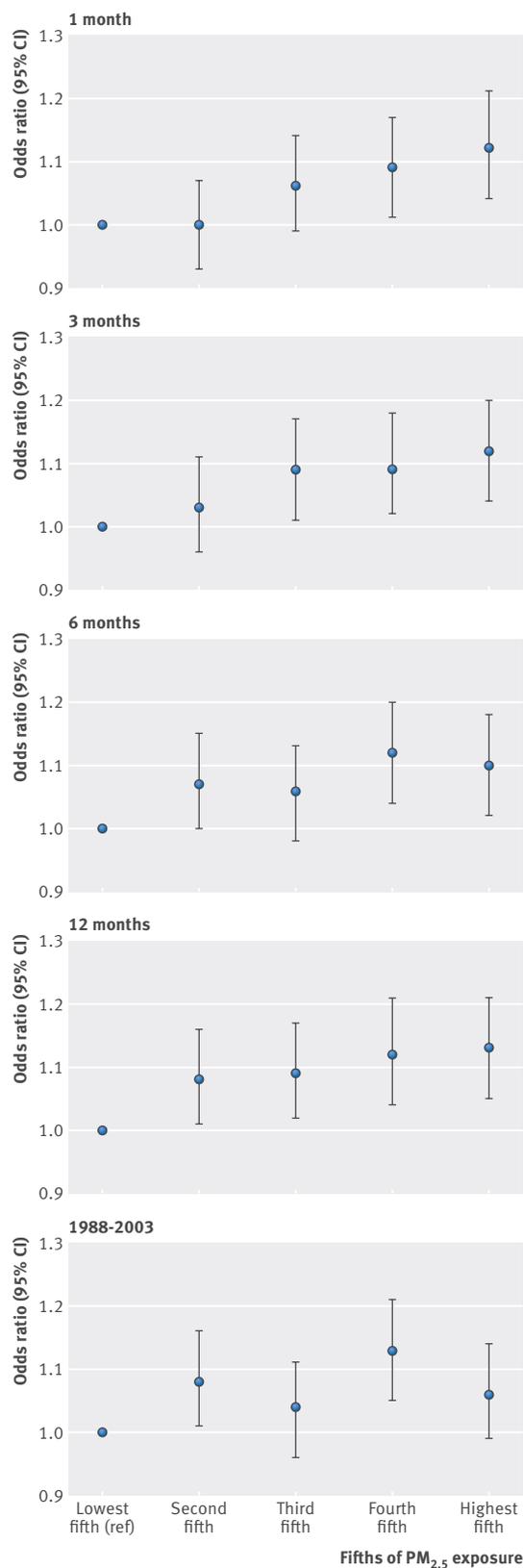
compared with 12.7 (4.2 µg/m<sup>3</sup>) for the one month averaging period.

### Residential proximity to roadways

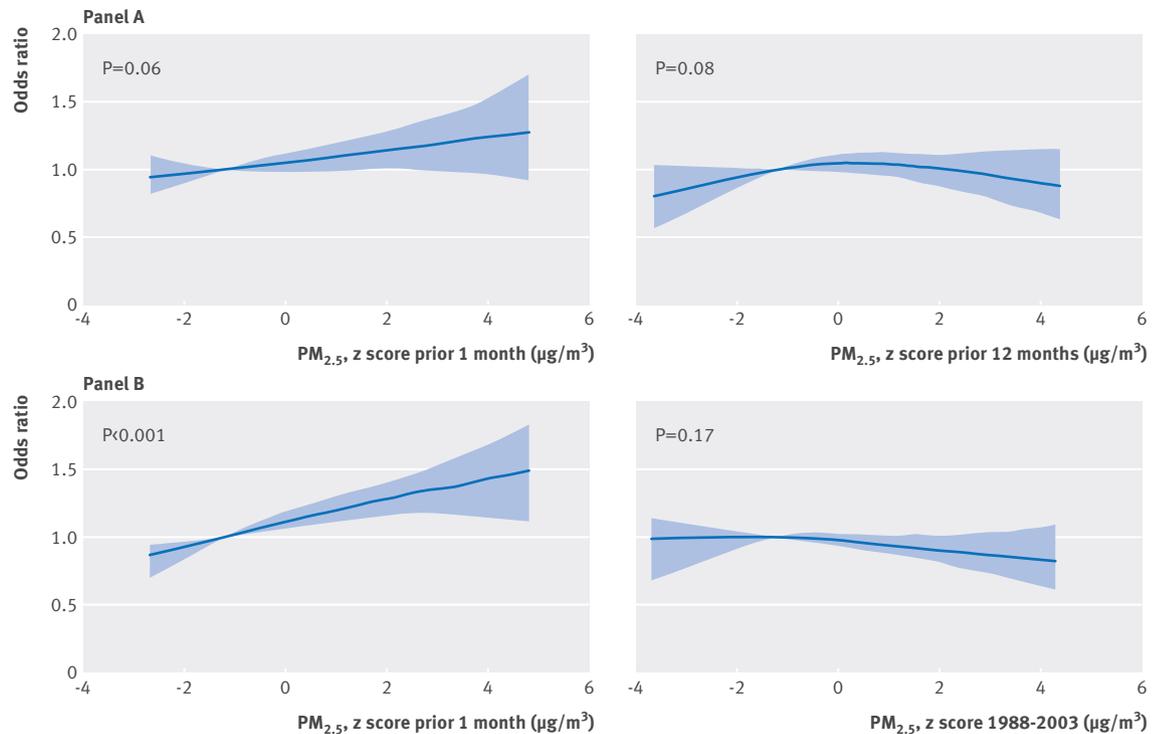
Nurses who lived 50 to 200 m from the nearest major road were more likely to have increased Crown-Crisp index phobic anxiety scale scores than those living >200 m away (adjusted odds ratio 1.06, 95% confidence interval 1.01 to 1.12; P=0.03). However, there was no evidence of a dose-response pattern, as those living within 50 m of the nearest major road did not have increased odds (adjusted odds ratio 1.01, 0.95 to 1.08; P=0.74). Findings of all sensitivity analyses were similar or more uniformly null (see supplementary table e2 and figure e1).

### Particulate matter

We observed associations between higher PM<sub>2.5</sub> and high anxiety across several averaging periods. Given evidence for slightly non-linear dose-response patterns in some averaging periods (see supplementary figure e2), we report associations with both fifths of exposure (fig 2) and per 10 µg/m<sup>3</sup> increase in exposure (table 2). Notably, while associations were similar across 1, 3, 6, and 12 month averaging periods, associations for the 1988–2003 averaging period were weaker than for the shorter averaging periods. All sensitivity analyses were reasonably consistent with our primary models (see supplementary tables e4 to e10). Mutually adjusted models suggest that these associations were primarily driven by an association between anxiety and shorter averaging periods (fig 3). There was little evidence to support an association between high anxiety and exposure to PM<sub>2.5-10</sub> in either our primary (see supplementary table e3 and figure e3) or our sensitivity analyses (see supplementary tables e4 to e10). We did not observe significant effect modification of the association with one month PM<sub>2.5</sub> by any of the proposed variables (all likelihood ratio test P>0.16).



**Fig 2 | Adjusted\* odds ratios (95% confidence intervals) between particulate matter <2.5 µm in diameter (PM<sub>2.5</sub>) considered using fifths of exposure, over multiple averaging periods and high symptoms of anxiety in Nurses' Health Study. \*Adjusted for month of questionnaire return, nurse's education, husband's education, age, age squared, whether the nurse has a partner, employment status, physical activity, percent of residential census tract that is white, percent of residential census tract adults who lack a high school education, median home value of residential census tract, geographic region, residence within a metropolitan statistical area, and social support**



**Fig 3 | Odds ratio (95% confidence interval) exposure to particulate matter <2.5 µm in diameter (PM<sub>2.5</sub>) on high symptoms of anxiety in Nurses' Health Study when multiple averaging periods are included in same model, parameterized using splines. Results of a model including both z transformed prior 12 month and z transformed prior one month PM<sub>2.5</sub> exposure (panel A), and including both the z transformed prior 15 years (1988–2003) and z transformed prior one month PM<sub>2.5</sub> exposure (panel B). The 10th centile was chosen as the reference level for the corresponding exposure of interest. P values indicate strength of evidence for an association (versus no association) for exposure to particulate matter, over its entire range, on high anxiety**

### Discussion

Our data support an association between exposure to particulate matter of <2.5 µm in diameter (PM<sub>2.5</sub>) but not 2.5 to 10 µm in diameter (PM<sub>2.5–10</sub>) or proximity to roadways, and high symptoms of anxiety. The association between PM<sub>2.5</sub> and high anxiety seems primarily driven by a relation with shorter term average exposures to PM<sub>2.5</sub>. There is little evidence to suggest differences in this association by demographic, geographic, or health related characteristics.

### Limitations and strengths of this study

Our study has some limitations. We were unable to consider the clinical diagnosis of specific anxiety disorders. However, prior epidemiologic work suggests that Crown-Crisp index scores are a valid<sup>16 17</sup> and clinically relevant measure, as they are associated with accelerated aging,<sup>58</sup> ischemic heart disease,<sup>56</sup> and sudden cardiac death.<sup>55 59 65</sup> We were unable to consider the association between anxiety and fluctuations in PM<sub>2.5</sub> over periods of less than one month, or short term fluctuations in ultrafine particulate matter (residential distance to a major road as a proxy measure is necessarily a longer term indicator). It is possible that the association we observed with PM<sub>2.5</sub> is attributable, in whole or in part, to a correlation between PM<sub>2.5</sub> and another exposure. Ambient ozone and noise are unlikely, although still possible, candidates given relatively weak correlations

with PM<sub>2.5</sub>.<sup>66 68</sup> Similarly, we cannot preclude a contribution of other pollutants that share sources with PM<sub>2.5</sub> (for example, nitrogen dioxide, sulphur dioxide).<sup>67</sup> Our models provide predictions of exposure at each participant's residential address. Given lack of information on the activity pattern of each participant, this could lead to bias due to misclassification. Nevertheless, any such bias is expected to be towards the null<sup>69</sup> and so would not account for the observed associations with PM<sub>2.5</sub>. Furthermore, as environmental regulations set acceptable exposure limits based on outdoor measures, we believe that this exposure is most relevant from the public health perspective. Our study considered only women; it is possible that our results may not be generalizable to men. Similarly, the women in our study were relatively old. Given that advancing age is related to lower physiologic reserve,<sup>70</sup> it is possible that our results would not generalize to younger age groups.

Our study also has several strengths. While discussed previously as a limitation, our focus on anxiety symptoms is also a strength. Our data suggest a short term, potentially reversible relation between exposures to particulate matter and severity of anxiety symptoms, which may not have been identified if we had focused exclusively on anxiety disorders. Although the relevant exposure period was unknown, we considered multiple averaging periods of exposure; this ultimately suggested that short term exposure to PM<sub>2.5</sub> may be the

most relevant exposure. We had access to a large prospective cohort, allowing adequate power to detect modest but meaningful associations. Attrition was small and any potential selection bias due to informative drop-out would be expected to be a downward bias, and so our estimate of an adverse association with PM<sub>2.5</sub> may be an underestimate. We were able to adjust for many socioeconomic and sociodemographic factors, which we thought to be the strongest potential confounders. Our results were robust to multiple sensitivity analyses.

### Comparison to other studies and discussion of potential mechanism

To our knowledge this is the first study to consider the association between exposure to particulate matter and anxiety. However, our findings are consistent with two prior studies of other air pollutants and anxiety,<sup>33 44</sup> as well as work suggesting associations between air pollution and other related, but distinct, mental health outcomes, including depressive symptoms,<sup>34 35</sup> psychiatric emergency,<sup>36–38</sup> emergency room visits for depression or suicide,<sup>39–42</sup> and reported suicide.<sup>43</sup>

Exposure to particulate matter could induce or exacerbate anxiety through increased oxidative stress and inflammation or through inducing or aggravating major medical conditions. Inflammation and oxidative stress have been hypothesized to contribute to the incidence and severity of anxiety.<sup>9 10</sup> Several toxicological studies have shown that oxidative stress<sup>71–75</sup> or systemic inflammation<sup>75 76</sup> induces anxiety-like behaviors in mice and rats. These results are consistent with cross sectional associations between anxiety symptoms and inflammatory markers in people,<sup>77–79</sup> as well as epidemiologic findings linking C reactive protein, an inflammatory marker, to generalized anxiety disorder in patients with stable coronary heart disease.<sup>80</sup> Inhaled particulate matter may therefore contribute to anxiety through induction of systemic<sup>11–17</sup> or brain based<sup>81–83</sup> oxidative stress and inflammation. Alternatively, anxiety may occur as a result of a respiratory or cardiac medical condition. Reduced lung function, reactive airway diseases such as asthma and chronic obstructive pulmonary disease, atrial fibrillation, and congestive heart failure are associated with an increased prevalence of anxiety symptoms or disorders.<sup>18–23</sup> These associations are likely mediated by fear and misinterpretation of symptoms, although an impact of the stress of dealing with major medical conditions or a purely physiological reaction to oxygenation changes associated with dysfunctional breathing and/or heart function may also contribute.<sup>84–89</sup> As particulate matter has been linked to multiple medical conditions and aggravation of symptoms,<sup>24–32</sup> particulate air pollution may also contribute to anxiety through this alternative mechanism. While our findings are consistent with the oxidative stress/inflammatory mechanistic hypothesis, our data do not support the hypothesis that particles promote anxiety through induction or aggravation of medical conditions, as there was no

difference in the association by whether or not people had major medical comorbidities. The reported association with PM<sub>2.5</sub>, but not PM<sub>2.5–10</sub> may be related to size related differences in toxicity, which are likely a function of differences in lung penetrability, surface area, and composition by particle size.<sup>90–94</sup>

### Conclusions

Anxiety is a common and costly disorder. Our data support an association between exposure to PM<sub>2.5</sub>, a common environmental exposure, and high symptoms of anxiety. If confirmed, our findings may have policy and clinical implications, as it is possible that reductions in exposure to PM<sub>2.5</sub>, through changes to regulations or individual behavior, may help reduce anxiety symptoms. Future work directly evaluating this possibility is warranted.

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