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Long-Term Exposure to Ambient Air Pollution and Incidence of Postmenopausal Breast Cancer in 15 European Cohorts within the ESCAPE Project

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Background: Epidemiological evidence on the association between ambient air pollution and breast cancer risk is inconsistent.

Objective: We examined the association between long-term exposure to ambient air pollution and incidence of postmenopausal breast cancer in European women.

Methods: In 15 cohorts from nine European countries, individual estimates of air pollution levels at the residence were estimated by standardized land-use regression models developed within the European Study of Cohorts for Air Pollution Effects (ESCAPE) and Transport related Air Pollution and Health impacts - Integrated Methodologies for Assessing Particulate Matter (TRANSPHORM) projects: particulate matter (PM)

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≤2.5 μm, ≤10 μm, and 2.5–10 μm in diameter ($PM_{2.5}$, PM_{10}, and PM_{coarse}, respectively); $PM_{2.5}$ absorbance; nitrogen oxides (NO_2 and NO_x); traffic intensity; and elemental composition of PM. We estimated cohort-specific associations between breast cancer and air pollutants using Cox regression models, adjusting for major lifestyle risk factors, and pooled cohort-specific estimates using random-effects meta-analyses.

Results: Of 74,750 postmenopausal women included in the study, 3,612 developed breast cancer during 991,353 person-years of follow-up. We found positive and statistically insignificant associations between breast cancer and $PM_{2.5}$ {hazard ratio (HR) = 1.08 [95% confidence interval (CI): 0.77, 1.51] per 5 μg/m^3}, PM_{10} [1.07 (95% CI: 0.89, 1.30) per 10 μg/m^3], PM_{coarse} [1.20 (95% CI: 0.96, 1.49 per 5 μg/m^3], and NO_2 [1.02 (95% CI: 0.98, 1.07 per 10 μg/m^3], and a statistically significant association with NO_x [1.04 (95% CI: 1.00, 1.08) per 20 μg/m^3, $p = 0.04$].

Conclusions: We found suggestive evidence of an association between ambient air pollution and incidence of postmenopausal breast cancer in European women. https://doi.org/10.1289/EHP1742

Introduction

Established risk factors for breast cancer, including genetic mutations, age, family history, alcohol consumption, smoking, reproductive history, and postmenopausal hormone therapy (HT) use, explain only approximately one-third of new cases (Brody et al. 2007b). Observations of higher incidence of breast cancer in urban than in rural areas (Binachon et al. 2014; Reynolds et al. 2004), as well as an increase in breast cancer incidence along with increasing traffic emissions over the last 30 y (Chen and Bina 2012; Wei et al. 2012) suggested the relevance of air pollution for breast cancer etiology. Air pollution is a risk factor for lung cancer (Hamra et al. 2015; Raaschou-Nielsen et al. 2013), and it was recently classified as carcinogenic to humans (Loomis et al. 2014). Experimental data provide some evidence supporting a link between a number of carcinogens present in ambient air pollution and breast cancer (Brody et al. 2007a), most consistently for polycyclic aromatic hydrocarbons (PAHs), which can cause oxidative stress and mammary tumors in laboratory animals (Mordukhovich et al. 2010). Furthermore, benzene, present in traffic exhaust, has been linked to mammary tumors in mice (Huff et al. 1989), and particulate matter (PM) showed DNA-damaging activity and estrogenicity in human breast cancer cells (Chen et al. 2013).

Epidemiological evidence is inconsistent and sparse, consisting of five case–control (Bonner et al. 2005; Crouse et al. 2010; Hystad et al. 2015; Lewis-Michl et al. 1996; Nie et al. 2007) and four cohort (Andersen et al. 2016; Hart et al. 2016; Reding et al. 2015; Raaschou-Nielsen et al. 2011a) studies. An early case–control study found no association between either pre- or postmenopausal breast cancer risk and living close to busy roads in Long Island, New York (Lewis-Michl et al. 1996). The Western New York Exposures and Breast Cancer (WEB) Study reported relevance of early (at birth) but not of later life (at menarche, first birth, 10- and 20-y before breast cancer) exposure to total suspended particles (TSP), assumed to be a proxy for PAHs, to postmenopausal breast cancer (Bonner et al. 2005). A study adding traffic emissions data to the WEB study found a statistically significantly increased risk of postmenopausal breast cancer risk with exposures at first birth, but none with other exposure windows (Nie et al. 2007). A Canadian case–control study found a statistically significant increased risk of postmenopausal breast cancer with increasing levels of nitrogen dioxide (NO_2) at the residence 10 y before diagnosis (Crouse et al. 2010). Another Canadian case–control study study found an increased risk of premenopausal and none with postmenopausal breast cancer related to NO_2 levels over the 20-y period before diagnosis (Hystad et al. 2015). In contrast, cohort studies found no association between breast cancer (primarily postmenopausal) and nitrogen oxides (NO_x) levels over 35 y (Raaschou-Nielsen et al. 2011a) or NO_2 levels over a few years before diagnosis (Andersen et al. 2016; Reding et al. 2015) except for a statistically significant positive association of NO_2 with the risk of estrogen receptor (ER)+/progesterone receptor (PR)+ breast cancer subtype (Reding et al. 2015). Finally, three recent cohort studies, all in primarily postmenopausal women, found no association between exposure to PM with diameter <2.5 μm ($PM_{2.5}$) or <10 μm (PM_{10}) at the time window close to diagnosis and breast cancer (Andersen et al. 2016; Hart et al. 2016; Reding et al. 2015). With air pollution established as carcinogenic to humans, suggestive experimental evidence on the biological plausibility, and inconclusive epidemiological evidence, it is important to further examine associations between air pollution and breast cancer.

We aimed to examine the association between long-term exposure to ambient air pollution and incidence of postmenopausal breast cancer in 15 European cohorts within the framework of the European Study of Cohorts for Air Pollution Effects (ESCAPE; http://www.escapeproject.eu/) (Beelen et al. 2014; Raaschou-Nielsen et al. 2013).

Methods

Study Population

We approached 22 cohorts that have contributed to earlier ESCAPE analyses on the association of ambient air pollution with lung cancer (Raaschou-Nielsen et al. 2013) and mortality (Beelen et al. 2014). We included 15 cohorts from nine European countries (Table 1, Figure 1) that had information on postmenopausal breast cancer incidence and that had the resources (statistical analyst available) for participation. We included five Swedish cohorts: European Prospective Investigation into Cancer and Nutrition (EPIC)-Umeå, Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), Stockholm Screening Across the Lifespan Twin study and TwinGene (SALT/TwinGene), Stockholm 60 y old/IMPROVE study (60YO/IMPROVE), and Stockholm Diabetes Prevention Program (SDPP); one Norwegian cohort: Oslo Health Study (HUBRO); one Danish cohort: Diet, Cancer and Health (DCH) study; two Dutch cohorts: EPIC-Monitoring Project on Risk Factors and Chronic Diseases in Netherlands (EPIC-MORGEN) and EPIC-Prospect; one United Kingdom cohort: EPIC-Oxford; one Austrian cohort: Vorarlberg Health Monitoring and Prevention Programme (VHM&PP); one French cohort: EPIC-E3N; two Italian cohorts: EPIC-Varese and EPIC-Turin; and one Spanish cohort: EPIC-San Sebastian (Figure 1). The majority of cohorts recruited participants from large cities and the surrounding suburban or rural communities, and a few covered large regions of the country, such as EPIC-MORGEN in Netherlands, EPIC-Oxford in the United Kingdom, and the VHM&PP cohort in Austria. For DCH, EPIC-Oxford, EPIC-E3N and VHM&PP, exposure to air pollution was assessed for part of the original cohort only. Data from the four Swedish cohorts from Stockholm (SNAC-K, SALT/TwinGene, 60YO/IMPROVE, and SDPP) as well as from the two Dutch cohorts (EPIC-MORGEN and EPIC-Prospect) were pooled and analyzed as single cohorts, which were named Cardiovascular Effects of Air pollution and Noise in Stockholm (CEANS) and EPIC Netherlands (EPIC-NL), respectively. All of the cohorts that contributed data to the present

Table 1. Description of the 74,750 postmenopausal women ($n = 3{,}612$) from 15 European cohorts included in the study.

Cohort, country	Enrollment	Original n^a	Final n	% Original n	Mean ± SD age, y	n Cases	Person-years at risk	Mean follow-up time, years	IR
EPIC-Umeå, Sweden	1992–96	4,238	3,762	88.8	54.4 ± 6.0	175	50,720	13.5	3.45
HUBRO, Norway	2000–01	4,077	1,931	47.4	57.2 ± 5.7	68	16,606	8.6	4.10
CEANS, Sweden[b]	1992–2002	6,930	5,997	86.5	59.8 ± 12.9	226	57,215	9.5	3.95
DCH, Denmark	1993–97	15,910	15,835	99.5	57.7 ± 4.2	1,054	237,655	15.0	4.44
EPIC-NL, Netherlands[c]	1993–97	14,219	12,837	90.3	58.6 ± 5.9	542	147,788	11.5	3.67
EPIC-Oxford, UK	1993–2001	10,742	7,299	67.3	59.7 ± 8.3	319	95,430	13.2	3.34
VHM&PP, Austria	1985–2005	14,552	13,387	92.0	65.1 ± 7.5	628	218,960	16.4	2.87
EPIC-E3N, France	1993–96	11,207	5,319	47.5	57.2 ± 5.6	267	68,248	12.8	3.91
EPIC-Varese, Italy	1993–97	4,932	4,727	95.8	56.6 ± 6.5	201	51,851	11.0	3.88
EPIC-Turin, Italy	1993–98	2,376	1,950	82.1	55.2 ± 5.1	76	25,028	12.8	3.04
EPIC-San Sebastian, Spain	1992–95	1,806	1,776	98.3	55.3 ± 5.7	57	21,852	12.3	2.61

Note: CEANS, Cardiovascular Effects of Air Pollution and Noise in Stockholm; DCH, Danish Diet, Health and Cancer cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; EPIC-E3N, French cohort of the Etude Epidemiologique de Femmes de la Mutuelle Générale de l'Education Nationale; HUBRO, Oslo Health Study; IR, incidence rate per 1,000 person-years; SD, standard deviation; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme.
[a]Number of postmenopausal women in the original cohort.
[b]Pooled data from the 4 cohorts from Stockholm Sweden: SNAC-K, SALT/TwinGene, 60YO/IMPROVE, and SDPP.
[c]Pooled data from 2 Dutch cohorts: EPIC MORGEN and EPIC Prospect.

analysis received ethical approval, and all participants provided informed consent.

Breast Cancer Definition

Cohorts have followed participants for cancer incidence via linkage to national or regional cancer registries or via self-administered questionnaires (in EPIC-E3N). Analyses were restricted to women who were postmenopausal or who were older than 55 y at the cohort baseline (in cohorts without information on menopausal status) and who did not have cancer before the study baseline (excluding nonmelanoma skin cancers) to study incidence of breast cancer. We chose not to exclude women with nonmelanoma skin cancers before baseline because these cancers are very commonly diagnosed and, unlike other malignant cancers, are easily treated if detected early, have very low case fatality (<5%), and very low risk of metastasis. The reason for excluding cancer before baseline (i.e., including only first cancer) is that receiving a cancer diagnosis likely changes the risk of a subsequent cancer for (at least) two reasons: carcinogenic cancer treatment and change in lifestyle habits because of the cancer diagnosis; neither of these applies to nonmelanoma skin cancer. Moreover, many cancer registries do not even register nonmelanoma skin cancer. We chose to focus on postmenopausal women only based on the existing evidence available at the time the present study was planned in 2014, suggesting the relevance of air pollution for postmenopausal breast cancer only, with no associations reported for premenopausal breast cancer (Bonner et al. 2005; Crouse et al. 2010; Lewis-Michl et al. 1996; Nie et al. 2007). Our outcome was incident, malignant, primary breast cancer, defined according to *International Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10; WHO 1990) code C50, *International Classification of Diseases and Related Health Problems, 9th Revision* (ICD-9; WHO 1977) code 174, and *International Classification of Diseases and Related Health Problems, 7th Revision* (ICD-7; WHO 1955) code 170.

Exposure Assessment

We estimated individual levels of air pollution at the baseline residence for each cohort participant using standardized area-specific land-use regression (LUR) models developed within the ESCAPE study (Beelen et al. 2013; Eeftens et al. 2012b). In brief, the LUR models were based on measurements of NO_2 and NO_x in all 15 study areas and on measurements of $PM_{2.5}$, PM_{10}, and $PM_{2.5}$ absorbance in 11 study areas (owing to budgetary reasons) for 1-y period and were conducted between October 2008 and May 2011 (Cyrys et al. 2012; Eeftens et al. 2012a). The concentration of PM_{coarse} was calculated as the difference between PM_{10} and $PM_{2.5}$. Subsequently, LUR models were developed for each pollutant in each study area to predict air pollution levels at the residences of the cohort participants using traffic and land-use predictors obtained from Geographic Information Systems (GIS). Data from the nearest routine monitoring stations were used to back-extrapolate the LUR estimates to the baseline year in 14 of the 15 study areas. Air pollution measurements were performed in 2008–2011, but the exposure window relevant for development of breast cancer extends further back in time. We therefore extrapolated air-pollution concentrations predicted by the LUR models around 2010 back to the time of enrollment in the 1990s for the majority of cohorts, using the absolute difference and the ratio between the two periods, based on data from routine background monitoring network site(s) in each study area. Details on this procedure can be found here: http://www.escapeproject.eu/manuals/. We also used traffic intensity on the nearest road (vehicles per day) as an indicator of exposure to traffic-related air pollution. Furthermore, we used estimated concentrations of eight elements in $PM_{2.5}$ and PM_{10} (copper, iron, zinc, sulfur, nickel, vanadium, silicon, and potassium) as indicators of exposure (de Hoogh et al. 2013). PM filters were then sent to Cooper Environmental Services (Portland, OR) to analyze elemental compositions using X-ray fluorescence (XRF) (de Hoogh et al. 2013). We selected eight of the 48 measured elements for epidemiological evaluation based on evidence of their health effects (toxicity), their representivity of major anthropogenic sources, a high percentage of detected samples (>75%), and precise measurements. We selected copper, iron, and zinc as indicators mainly of nontailpipe traffic emissions such as brake and tire wear, sulfur mainly of long-range transport, nickel and vanadium of mixed oil-burning and industry, silicon of crustal material, and potassium of biomass burning (de Hoogh et al. 2013; Eeftens et al. 2014; Viana et al. 2008; Wang et al. 2014). Each element can have multiple sources. We collected information about potential predictor variables relating to nearby traffic intensity, population/household density, and land use from GIS and used regression modeling to evaluate this information to explain spatial variation of annual average concentrations. We have previously reported the LUR model results for all study areas (Raaschou-Nielsen et al. 2016). LUR models for copper, iron, and zinc in both fractions (PM_{10} and $PM_{2.5}$) had average cross-validation–explained variance (r^2) between 52% and

Figure 1. Map of the study sites in the breast cancer analyses.

84% with a large variability between areas (Eeftens et al. 2012a). Traffic variables contributed to most of these models, reflecting nontailpipe emissions. Models for the other elements performed moderately with average cross-validation r^2 generally between $\sim 50\%$ and $\sim 60\%$. For $PM_{2.5}$, the average cross-validation r^2 was 32% and ranged from 2% to 67%, consistent with the relatively low spatial variation of sulfur concentrations within the cohort areas.

Statistical Analyses

We used Cox proportional hazards models for the cohort-specific analyses with age as the underlying timescale and censoring at the time of any other cancer diagnosis (except nonmelanoma skin cancer), death, emigration, or end of follow-up, whichever came first. We analyzed air pollution exposure as a continuous variable. Potential confounders were available from questionnaires at baseline. We specified three confounder models *a priori*: Model 1, adjusted for age (time scale) and calendar time (years of enrollment); Model 2, additionally adjusted for smoking status (never, former, or current), smoking intensity (grams/day), smoking duration (years), alcohol consumption (grams/day; linear term), physical activity in leisure time (yes/no), body mass index (BMI; kilograms per meter squared; linear term), educational level (low, medium, or high), employment (yes/no), parity (yes/no), number of children (linear term), breastfeeding (yes/no), age at first childbirth (years; linear term), postmenopausal hormone therapy (HT) use (never/previous/current, never/ever), HT use duration (years; linear term), oral contraceptive use (never/ever); and Model 3, adjusted for Model 2 and additionally adjusted for area-level socioeconomic status variables (mean income of the neighborhood or municipality, in the majority of cohorts), using random effects of the spatial area units in each cohort to check for spatial clustering of residuals of the models. Model 3 was the main confounder model. Model 2 included all established risk factors for breast cancer at the individual level, and Model 3 also included area-level socioeconomic status, which is a possible risk factor for breast cancer but is possibly one of the strongest determinants of predicted air pollution concentrations at the cohort participants' addresses. Available confounders differed between cohorts (see Table S1 for an overview of available variables in each cohort). Complete case analyses were defined within each cohort so that the numbers of women included in Models 1, 2, and 3 were identical. The complete case analyses method gives unbiased estimates when data can be assumed to be missing completely at random (van der Heijden et al. 2006). We performed a number of sensitivity analyses within each cohort: We restricted analyses to participants who were long-term residents (i.e., who had lived at the cohort baseline address at least 10 y before enrollment); we restricted analyses to participants who did not move during follow-up; we added the rural/urban indicator to adjust for different degrees of urbanization

within the study area; we used diagnostic tools to check the proportional hazards (PH) assumption for the categorical predictors in Model 3 and stratified the Cox model for predictors that did not meet the PH assumption; and we tested whether back-extrapolation (difference and ratio method) of the concentrations to the baseline year had any effect on the estimates. Next, we evaluated smoking status and educational level as effect modifiers in stratified analyses. Finally, we examined the shape of the association and evaluated if there was a deviation from linearity between each pollutant and breast cancer risk by *a*) inputting the exposure term as a natural cubic spline with two equally spaced inner knots and comparing the model fit of the linear and the spline models using a likelihood-ratio test; *b*) implementing "threshold models" in which the following threshold concentrations were defined *a priori* for each pollutant: $PM_{2.5}$: 10 $\mu g/m^3$, 15 $\mu g/m^3$, 20 $\mu g/m^3$, 25 $\mu g/m^3$; $PM_{2.5}$ absorbance: 1, 2, 3, 4; PM_{10}: 10 $\mu g/m^3$, 20 $\mu g/m^3$, 30 $\mu g/m^3$, 40 $\mu g/m^3$; PM_{coarse}: 5 $\mu g/m^3$, 10 $\mu g/m^3$, 15 $\mu g/m^3$; NO_2: 10 $\mu g/m^3$, 20 $\mu g/m^3$, 30 $\mu g/m^3$, 40 $\mu g/m^3$; and NO_x: 20 $\mu g/m^3$, 30 $\mu g/m^3$, 40 $\mu g/m^3$, 60 $\mu g/m^3$, 80 $\mu g/m^3$. Then, threshold analyses were performed by consecutively running models including only participants who had exposure estimates below the prespecified thresholds in the analyses [e.g., starting at 25 $\mu g/m^3$ for $PM_{2.5}$, which is the European Union (EU) annual mean limit value (European Commission 2013), 20 $\mu g/m^3$, 15 $\mu g/m^3$, and lastly, <10 $\mu g/m^3$, which is the World Health Organization (WHO) limit value (WHO 2006)]. Similarly, for other pollutants, starting threshold values were set based on EU limit values (European Commission 2013) (40 $\mu g/m^3$ for PM_{10} and NO_2). Threshold values were based on the concentration distributions obtained from the ESCAPE measurement period between 2008 and 2011. We used the same analytical strategy for analyses of elemental components of $PM_{2.5}$ and PM_{10} as we used for the main pollutants (described above). Analyses with elemental components of PM were identified *a priori* as secondary analyses to limit the issue of multiple comparisons. All cohort-specific analyses were performed in STATA versions 10–12 (StataCorp LLC) using a common script.

Meta-Analyses

We performed meta-analyses of cohort-specific effect estimates using the DerSimonian-Laird method with random effects (DerSimonian and Laird 1986). We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for fixed increments that were chosen to cover the range in concentrations within the different cohorts and to keep increments broadly comparable between pollutants. We considered summary estimates statistically significant when the *p*-value was <0.05. We evaluated the heterogeneity between cohort-specific results by applying the Chi-squared test from Cochran's Q statistic, which was quantified by the I^2 statistic (Higgins and Thompson 2002). We considered cohort-specific estimates to be heterogeneous when $I^2 > 50\%$ or when the *p*-value of the Chi-squared test was <0.05. We evaluated the effect modification across the strata of each modifier by meta-analyzing the pooled estimates from the different strata and by performing the Chi-squared test of heterogeneity. We investigated the robustness of the results by examining the effect of NO_x in a subset of cohorts with PM data, by excluding the cohort with the smallest number of confounders available in Model 3 (VHM&PP) from the meta-analyses, by performing meta-analyses including the five cohorts (DCH, EPIC-Oxford, EPIC-E3N, EPIC-Varese, and EPIC-Turin) with the most available confounders in Model 3, and by excluding cohorts with the largest number of postmenopausal women (>30%) in the original cohort (HUBRO, EPIC-E3N, and EPIC-Oxford). We used STATA version 12.1 (StataCorp LLC) for all meta-analyses.

Results

Study Population

A total of 74,750 postmenopausal women from 15 European cohorts participated in the study (Figure 1), of whom 3,612 developed breast cancer during a mean follow-up of 12.4 y and a total of 991,353 person-years (Table 1). The crude overall incidence rate of postmenopausal breast cancer was 3.64 per 1,000 person-years, ranging from 2.61 per 1,000 person-years in EPIC-San Sebastian (Spain) to 4.44 per 1,000 person-years in DCH (Denmark). The mean age at the time of enrollment ranged from 54.4 y in EPIC-Umeå (Sweden) to 65.1 y in EPIC-E3N (France). The proportion of women included in the study ranged from 47.4% to 99.5% (overall 82.1%) of the total number of postmenopausal women in the original cohorts after excluding women with missing values for any of the covariates included in Model 3. Women were recruited into the cohorts between 1985 and 2005, with the majority recruited between 1992 and 2002 (Table 1).

The majority of cohorts had low numbers of women with missing data (<5%) on lifestyle (smoking, alcohol use, BMI, physical activity) and education. However, a number of cohorts either lacked altogether or had large amounts of missing data for variables on reproductive factors (age at first birth, parity, breastfeeding) and HT use. HUBRO had excluded a large number of postmenopausal women because of missing information on HT use, and EPIC-Oxford had excluded a large number because of missing information on reproductive factors and HT use, which explains the low percentage of the original cohort participating in the study, 47.4% and 67.3%, respectively (Table 1). In EPIC-E3N, the majority of postmenopausal women were excluded owing to lack of follow-up data on breast cancer or failure to complete the baseline questionnaire, leaving 47.5% of women for the analyses.

The majority of cohorts had information on smoking (status, duration, and intensity), alcohol use, physical activity, BMI, and education, except for EPIC-Umeå, which lacked information on physical activity, and VHM&PP, which lacked information on physical activity, alcohol use, and education (see Table S1). Current baseline smoking rates were highest in Denmark (34.7%) and Norway (28.6%) and lowest in the Austrian (4.7%) and Spanish (7.2%) cohorts. Alcohol consumption at baseline was highest in Denmark (14.4 g/d) and France (12.2 g/d) and lowest in Sweden (1.8–2.5 g/d) (see Table S1). Women who were excluded from analyses because of missing data on potential risk factors did not differ from those included in the analyses with regard to age, smoking status, alcohol consumption, and BMI in the majority of the cohorts, but in a few cohorts (HUBRO, E3N), the excluded women were older, less likely to be smokers, or both, than the included women (data not shown).

Air Pollution Exposure

The air pollution levels at the participants' residences varied substantially within and between study areas, with increasing levels from northern to southern study areas (Table 2). The mean concentration of NO_2 ranged from 5.4 $\mu g/m^3$ in Umeå, Sweden, to 53.0 $\mu g/m^3$ in Turin, Italy (Table 2); the mean concentration of $PM_{2.5}$ ranged from 7.3 $\mu g/m^3$ in Stockholm, Sweden, to 30.2 $\mu g/m^3$ in Turin, Italy. Correlations between pollutants were generally >0.5 (see Tables S3–S13). Mean levels of $PM_{2.5}$ and PM_{10} elements also varied substantially between study areas (see Table S2). However, air pollutant levels were identical in excluded and included women (results not shown).

Table 2. Description of the air pollution and traffic intensity levels at the participants addresses in 15 cohorts.

Cohort, country	$PM_{2.5}$, $\mu g/m^3$	$PM_{2.5}$ absorbance, $10^{-5}/m$	PM_{10}, $\mu g/m^3$	$PM_{2.5-10}$, $\mu g/m^3$	NO_2, $\mu g/m^3$	NO_x, $\mu g/m^3$	Traffic intensity on the nearest road (vehicles/d)
EPIC-Umeå, Sweden							
Mean ± SD	—	—	—	—	5.4 ± 2.5	9.1 ± 5.8	863 ± 1,511
Min–max	—	—	—	—	3.5–18.2	4.8–49.2	1–17,433
HUBRO, Norway							
Mean ± SD	8.9 ± 1.4	1.2 ± 0.3	13.4 ± 3.1	3.9 ± 1.9	19.6 ± 7.2	35.9 ± 13.9	2,266 ± 4,310
Min–max	3.7–14.6	0.5–2.4	8.4–32.9	3.2–18.0	6.9–48.7	15.8–120.4	500–1,600
CEANS, Sweden[a]							
Mean ± SD	7.3 ± 1.3	1.6 ± 0.2	15.1 ± 4.3	7.5 ± 3.4	11.8 ± 5.0	21.1 ± 11.3	1,856 ± 5,396
Min–max	4.2–11.7	0.4–1.4	6.0–31.1	0.7–20.3	6.0–35.8	11.1–86.5	30–140,000
DCH, Denmark							
Mean ± SD	11.3 ± 0.8	1.2 ± 0.2	17.2 ± 1.9	5.7 ± 1.0	16.5 ± 7.0	27.2 ± 18.5	3,109 ± 7,412
Min–max	7.4–12.8	0.7–1.9	12.6–22.4	4.0–8.5	5.6–43.3	1.6–92.4	0–93,240
EPIC-NL, Netherlands[b]							
Mean ± SD	16.8 ± 0.5	1.4 ± 0.2	25.3 ± 1.2	8.5 ± 0.7	26.3 ± 5.0	39.0 ± 10.4	1,072 ± 3,477
Min–max	15.6–20.7	1.0–2.6	23.7–33.2	7.6–13.1	13.6–54.6	21.6–89.5	0–92,524
EPIC-Oxford, UK							
Mean ± SD	9.6 ± 1.0	1.1 ± 0.2	15.9 ± 2.0	6.3 ± 0.9	22.9 ± 7.0	38.1 ± 13.9	1,425 ± 4,513
Min–max	8.2–17.8	0.8–3.2	11.8–31.1	5.6–10.6	12.9–89.0	19.7–231.5	500–114,356
VHM&PP, Austria							
Mean ± SD	13.6 ± 1.2	1.7 ± 0.2	20.8 ± 2.4	6.7 ± 0.9	20.4 ± 5.5	40.5 ± 9.8	1,844 ± 3,903
Min–max	9.6–16.5	1.0–2.6	11.5–28.9	4.2–11.0	2.9–41.9	17.6–91.7	500–25,949
EPIC-E3N, France							
Mean ± SD	—	—	—	—	30.9 ± 12.7	56.0 ± 28.3	6,538 ± 8,257
Min–max	—	—	—	—	8.7–93.7	4.0–228.7	0–124,848
EPIC-Varese, Italy							
Mean ± SD	—	—	—	—	44.2 ± 17.4	87.8 ± 42.1	—
Min–max	—	—	—	—	1.5–85.7	0.0–202.4	—
EPIC-Turin, Italy							
Mean ± SD	30.2 ± 1.6	3.1 ± 0.4	46.6 ± 4.1	16.6 ± 2.7	53.0 ± 10.3	96.1 ± 20.3	4,044 ± 9,596
Min–max	21.8–35.3	0.3–4.1	30.8–55.1	6.6–20.2	14.9–83.0	32.9–179.3	0–85,696
EPIC-San Sebastian, Spain							
Mean ± SD	—	—	—	—	24.1 ± 6.7	47.7 ± 12.5	—
Min–max	—	—	—	—	9.8–45.1	20.6–87.9	—

Note: —, missing data on these pollutants; CEANS, Cardiovascular Effects of Air Pollution and Noise in Stockholm; DCH, Danish Diet, Health and Cancer cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; EPIC-E3N, French cohort of the Etude Epidemiologique de Femmes de la Mutuelle Générale de l'Education Nationale; HUBRO, Oslo Health Study; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, particulate matter <2.5 μm; $PM_{2.5-10}$, particulate matter 2.5–10 μm; PM_{10}, particulate matter <10 μm; SD, standard deviation; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme.
[a]Pooled data from the 4 cohorts from Stockholm Sweden: SNAC-K, SALT/TwinGene, 60YO/IMPROVE, and SDPP.
[b]Pooled data from 2 Dutch cohorts: EPIC MORGEN and EPIC Prospect.

Associations between Air Pollutants and Breast Cancer

We found positive and statistically nonsignificant associations between most of the main pollutants in the fully adjusted model (Model 3) and postmenopausal breast cancer except for $PM_{2.5}$ absorbance and traffic intensity on the nearest road, for which no association (HRs 1.00 and 1.01, respectively) was found (Table 3, Figure 2, Figure 3; see also Figure S1). Only the association with NO_x was statistically significant [HR = 1.04 (95% CI: 1.00, 1.08) per 20 $\mu g/m^3$; $p = 0.04$], with no heterogeneity between individual cohort estimates ($I^2 = 0.0$) (Table 3, Figure 2). The main NO_x results (Model 3) were robust to confounding and to model specification as observed in extensive sensitivity analyses (Table 4). However, we found large and statistically significant heterogeneity between individual cohort estimates for NO_x when the analyses were restricted to nonmovers from 10 cohorts with available information on moving (Table 4). Three cohorts mostly

Table 3. Results from random-effects meta-analyses for the association between exposure to air pollution and breast cancer incidence in 15 European cohorts.

Exposure	Fixed increase	*n* cohorts	*n*	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	*p*-Value model 3	I^2 (*p*-value)[d]
$PM_{2.5}$	5 $\mu g/m^3$	11[e]	68,806	0.99 (0.73, 1.33)	1.03 (0.76, 1.40)	1.08 (0.77, 1.51)	0.67	56.7 (0.03)
$PM_{2.5}$ absorbance	$10^{-5}/m$	11[e]	68,806	0.95 (0.80, 1.15)	0.97 (0.80, 1.17)	1.00 (0.80, 1.25)	0.98	23.6 (0.25)
PM_{10}	10 $\mu g/m^3$	11[e]	68,806	1.08 (0.90, 1.28)	1.05 (0.88, 1.25)	1.07 (0.89, 1.30)	0.46	16.0 (0.30)
PM_{coarse}	5 $\mu g/m^3$	11[e]	68,806	1.20 (0.97, 1.49)	1.16 (0.95, 1.43)	1.20 (0.96, 1.49)	0.10	40.2 (0.12)
NO_2	10 $\mu g/m^3$	15	74,750	1.02 (0.98, 1.06)	1.02 (0.97, 1.06)	1.02 (0.98, 1.07)	0.33	0.0 (0.72)
NO_x	20 $\mu g/m^3$	15	74,750	1.04 (1.00, 1.08)	1.04 (1.00, 1.08)	1.04 (1.00, 1.08)	0.04	0.0 (0.78)
Traffic intensity[f]	5,000 mv/d	15	74,750	1.02 (0.98, 1.05)	1.02 (0.99, 1.05)	1.01 (0.97, 1.05)	0.54	24.5 (0.22)

Note: CI, confidence interval; HR, hazard ratio; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, particulate matter <2.5 μm; PM_{10}, particulate matter <10 μm; PM_{coarse}, coarse particulate matter.
[a]Adjusted for age and year of enrollment.
[b]Model 1 adjusted for smoking status, smoking duration among ever smokers (y), smoking intensity among ever smokers (g/d), alcohol use (g/d), physical activity, BMI, educational level, employment, age at 1st birth, parity, hormone therapy use, hormone therapy duration (maximum of available variables).
[c]Model 2 plus area-level socioeconomic status.
[d]Cochran's test for heterogeneity for Model 3 of effect estimates between the cohorts.
[e]PM not available for EPIC-Umeå, EPIC-E3N, EPIC-Varese, and EPIC-San Sebastian.
[f]Traffic intensity on the nearest road.

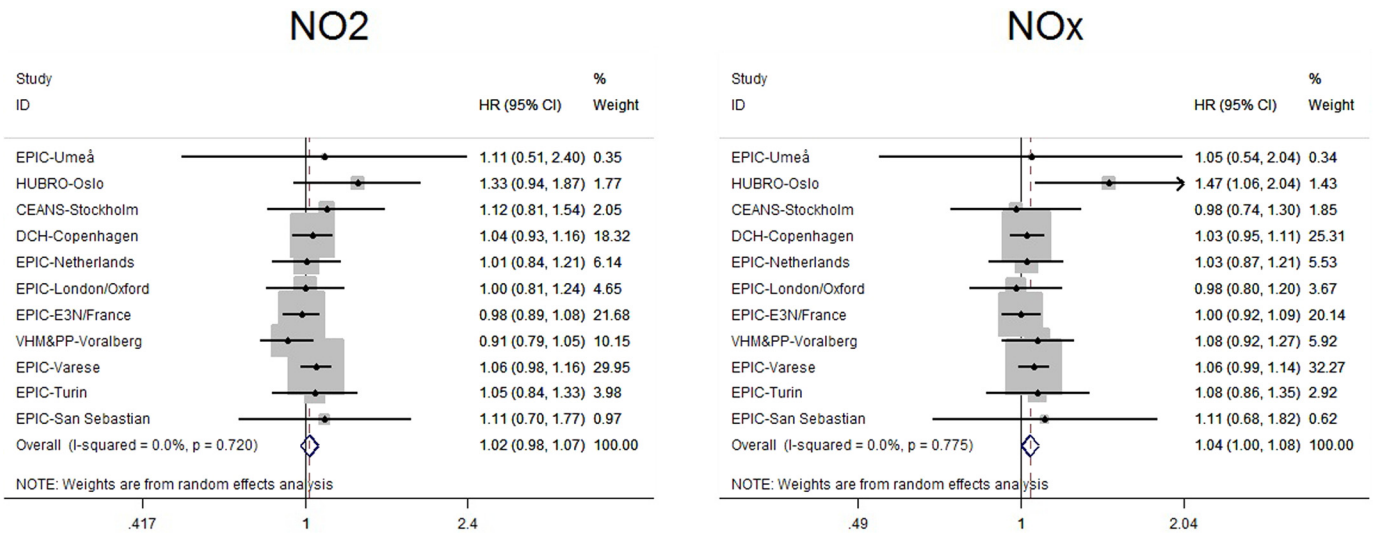

Figure 2. Adjusted associations (Model 3) between breast cancer and nitrogen dioxide (NO_2) (per $10\,\mu g/m^3$) and nitrogen oxides (NO_x) (per $20\,\mu g/m^3$) in 15 European cohorts [Cardiovascular Effects of Air pollution and Noise in Stockholm (CEANS)-Stockholm consists of four Stockholm, Sweden, cohorts: Study on Aging and Care in Kungsholmen (SNAC-K), Screening Across the Lifespan Twin study (SALT)/TwinGene, 60 Years Old (60YO)/IMPROVE, and Stockholm Diabetes Prevention Program (SDPP); European Prospective Investigation into Cancer and Nutrition (EPIC)-Netherlands consists of two Dutch cohorts: EPIC-MORGEN and EPIC-Prospect]: Results from cohort-specific analyses and random-effects analyses.

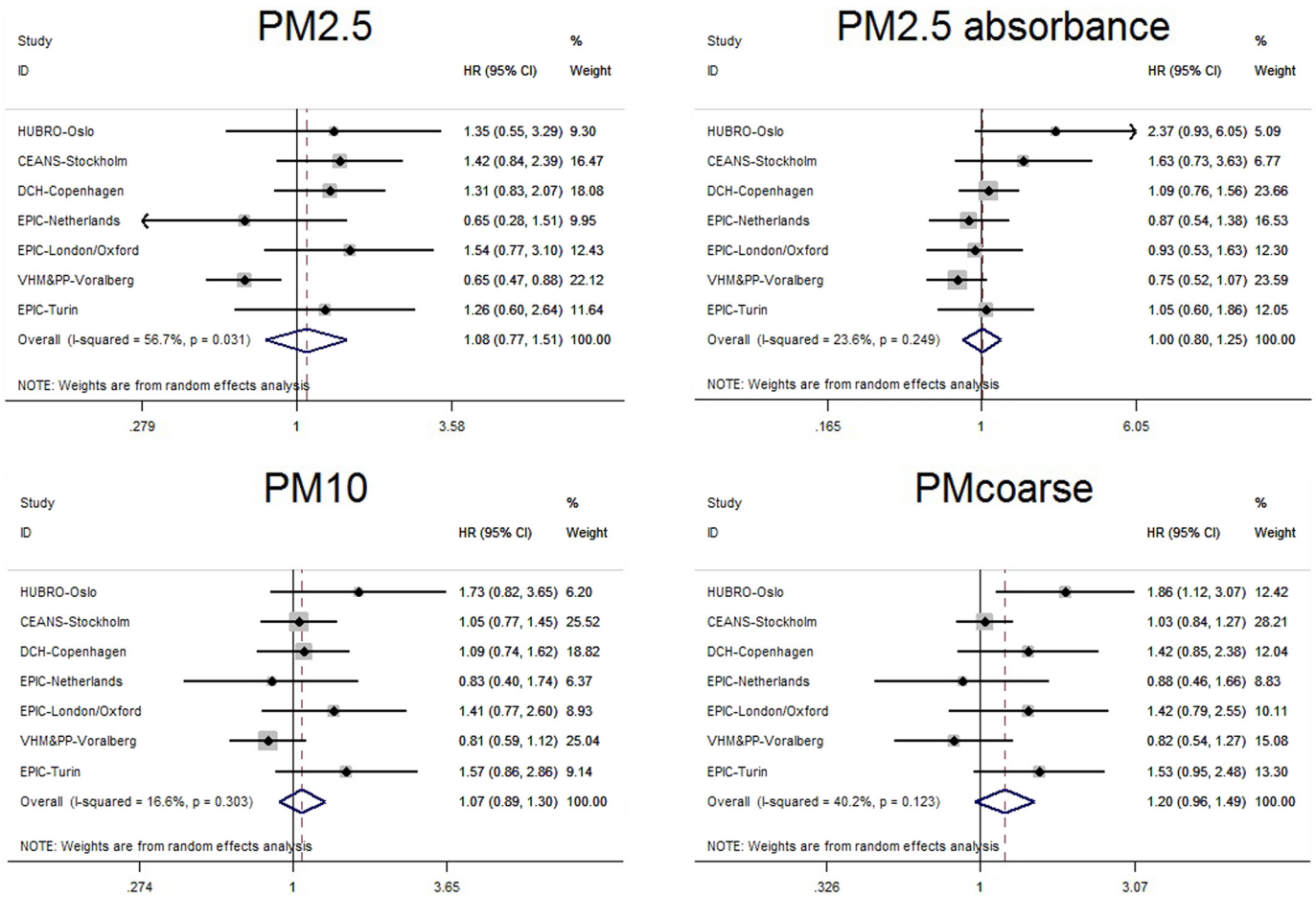

Figure 3. Adjusted associations (Model 3) between breast cancer and particulate matter <2.5 μm ($PM_{2.5}$), (per $5\,\mu g/m^3$), $PM_{2.5}$ absorbance (per $10^{-5}/m$), particulate matter <10 μm (PM_{10}) (per $10\,\mu g/m^3$), and particulate matter 2.5–10 μm (PM_{coarse}) (per $5\,\mu g/m^3$) in 11 European cohorts [Cardiovascular Effects of Air pollution and Noise in Stockholm (CEANS)-Stockholm consists of four Stockholm, Sweden, cohorts: Study on Aging and Care in Kungsholmen (SNAC-K), Screening Across the Lifespan Twin study (SALT)/TwinGene), 60 Years Old (60YO)/IMPROVE, and Stockholm Diabetes Prevention Program (SDPP); European Prospective Investigation into Cancer and Nutrition (EPIC)-Netherlands consists of two Dutch cohorts: EPIC-MORGEN and EPIC-Prospect]: Results from cohort-specific analyses and random-effects analyses.

Table 4. Results from random-effects meta-analyses for the association between exposure to NO_x and breast cancer incidence in 15 European cohorts: The sensitivity analyses.

NO_x	*n* Cohorts	*n*	HR (95% CI)	I^2 (*p*-value)[a]
Main model	15	74,750	1.04 (1.00, 1.08)	0.0 (0.77)
Limited to cohorts with PM data	11[b]	68,806	1.04 (0.99, 1.10)	1.8 (0.40)
Excluding VHM&PP (poor covariate adjustment)	14	61,363	1.04 (1.00, 1.08)	0.0 (0.71)
Including cohorts with all breast cancer risk factors (Model 3)	5[c]	35,130	1.03 (0.99, 1.08)	0.0 (0.82)
Restricted to long-term residents	7[d]	37,150	1.05 (0.98, 1.12)	0.0 (0.92)
Restricted to nonmovers	10[e]	54,425	1.04 (0.95, 1.13)	67.5 (<0.01)
Further adjustment for urbanization	12[f]	67,107	1.03 (0.99, 1.08)	0.0 (0.99)
Variables that do not meet PH assumption as strata	15	74,750	1.04 (1.00, 1.08)	0.0 (0.79)
Cohorts with back-extrapolation (difference, method)	12[g]	71,467	1.05 (1.00, 1.11)	0.0 (0.99)
Cohorts with back-extrapolation (ratio, method)	12[g]	71,467	1.04 (0.98, 1.09)	0.0 (0.98)
Excluding cohorts with >30% of original cohort excluded	12[h]	60,271	1.05 (1.00, 1.10)	0.0 (0.99)
Excluding HUBRO and EPIC-Oxford (lack of information on HT)	13[i]	65,500	1.04 (1.00-1.08)	0.0 (0.99)

Note: CEANS, Cardiovascular Effects of Air Pollution and Noise in Stockholm; CI, confidence interval; DCH, Danish Diet, Health and Cancer cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; EPIC-E3N, French cohort of the Etude Epidemiologique de Femmes de la Mutuelle Générale de l'Education Nationale; HR, hazard ratio; HT, hormone therapy; HUBRO, Oslo Health Study; NO_x, nitrogen oxides; PH, proportional hazard; PM, particulate matter; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme.
[a]Cochran's test for heterogeneity for Model 3 of effect estimates between the cohorts.
[b]PM not available for EPIC-Umeå, EPIC-E3N, EPIC-Varese, and EPIC-San Sebastian.
[c]Five cohorts with information on all breast cancer risk factors: DCH, EPIC-Oxford, EPIC-E3N, EPIC-Varese, EPIC-Turin.
[d]Seven cohorts: HUBRO, CEANS (4 Swedish cohorts pooled), DCH, and VHM&PP.
[e]Ten cohorts: HUBRO, CEANS (4 Swedish cohorts pooled), DCH, EPIC-Oxford, EPIC-E3N, VHM&PP, and EPIC-Varese.
[f]Twelve cohorts: CEANS (4 Swedish cohorts pooled), DCH, EPIC-Netherlands (2 Dutch cohorts pooled), EPIC-Oxford, EPIC-E3N, VHM&PP, EPIC-Varese, and EPIC-San Sebastian.
[g]Twelve cohorts: CEANS (4 Swedish cohorts pooled), DCH, EPIC-Netherlands (2 Dutch cohorts pooled), EPIC-Oxford, VHM&PP, EPIC-Varese, EPIC-Turin, and EPIC-San Sebastian.
[h]Twelve cohorts: EPIC-Umeå, CEANS (4 Swedish cohorts pooled), DCH, EPIC-Netherlands (2 Dutch cohorts pooled), VHM&PP, EPIC-Varese, EPIC-Turin, and EPIC-San Sebastian.
[i]Thirteen cohorts: EPIC-Umeå, CEANS (4 Swedish cohorts pooled), DCH, EPIC-Netherlands (2 Dutch cohorts pooled), VHM&PP, E3N, EPIC-Varese, EPIC-Turin, and EPIC-San Sebastian.

explain the increase in heterogeneity in nonmovers from 10 cohorts compared with analyses in 15 cohorts with all cohort participants: The HR for HUBRO increased from 1.47 (Figure 3) to 1.75 (not shown) and the HR for VHM&PP increased from 1.08 to 1.14, whereas the HR for EPIC-Oxford decreased from 0.98 to 0.80. The summary HR for NO_2 was similar to that for NO_x [HR = 1.02 (95% CI: 0.98, 1.07) per $10\,\mu g/m^3$], also with no heterogeneity between individual cohort HRs, although it did not reach statistical significance (Table 3, Figure 2). Estimates for all pollutants remained unchanged after adjustment for individual-level confounders except for $PM_{2.5}$, which increased from <0.99 in the crude model (Model 1) to 1.08 in the fully adjusted model (Model 3) (Table 3, Figure 3). The summary estimates for all PM proxies showed moderate to low heterogeneity between the individual cohorts, although they were statistically significantly heterogeneous for $PM_{2.5}$ in Model 3 [HR = 1.08 (95% CI: 0.76, 1.53); $I^2 = 58.2$, per $5\,\mu g/m^3$] (Table 3, Figure 3). HRs for $PM_{2.5}$ were both enhanced and attenuated in sensitivity analyses, with substantial heterogeneity between individual cohort estimates (Tables 4 and 5). The summary estimates for PM_{10} [HR = 1.07 (95% CI: 0.89, 1.30); $I^2 = 16.0$, per $5\,\mu g/m^3$] and PM_{coarse} [HR = 1.20 (95% CI: 0.96, 1.49); $I^2 = 40.2$, per $5\,\mu g/m^3$] showed a similar pattern to that of $PM_{2.5}$ but with less heterogeneity between individual cohort HRs (Figure 3). There was no evidence of deviation from linearity in associations between air pollutants and breast cancer risk (results not shown). We found no statistically significant modifications of associations between any of the main pollutants and breast cancer by smoking status or education. For example, for NO_x, we found similar HRs among never [HR = 1.05 (95% CI: 0.99, 1.11)], former [HR = 0.98 (95% CI: 0.90, 1.07)], and current [HR = 1.09 (95% CI: 1.01, 1.18)] smokers (*p* for interaction = 0.69).

Secondary analyses of the elemental components of PM_{10} and $PM_{2.5}$ showed mostly positive associations except for weak

Table 5. Results from random-effects meta-analyses for the association between exposure to $PM_{2.5}$ and breast cancer incidence in 15 European cohorts: The sensitivity analyses.

$PM_{2.5}$	*n* Cohorts	*n*	HR (95% CI)	I^2 (*p*-value)[a]
Main model	11	68,806	1.08 (0.77, 1.51)	56.7 (0.03)
Excluding VHM&PP (poor covariate adjustment)	10	55,419	1.28 (0.99, 1.65)	0.0 (0.71)
Including cohorts with all breast cancer risk factors (Model 3)	3[b]	25,014	1.35 (0.96, 1.90)	0.0 (0.91)
Restricted to long-term residents	7[c]	37,150	2.19 (0.29, 16.58)	75.9 (<0.01)
Restricted to nonmovers	8[d]	44,449	1.01 (0.22, 4.74)	62.8 (0.03)
Further adjustment for urbanization	9[e]	57,286	1.20 (0.18, 7.86)	75.4 (<0.01)
Variables that do not meet PH assumption as strata	11	68,806	1.21 (0.23, 6.40)	72.3 (<0.01)
Excluding cohorts with >30% of original cohort excluded	10[f]	54,559	0.99 (0.67, 1.48)	64.5 (0.02)

Note: CEANS, Cardiovascular Effects of Air Pollution and Noise in Stockholm; CI, confidence interval; DCH, Danish Diet, Health and Cancer cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; EPIC-E3N, French cohort of the Etude Epidemiologique de Femmes de la Mutuelle Générale de l'Education Nationale; HR, hazard ratio; HUBRO, Oslo Health Study; PH, proportional hazard; $PM_{2.5}$, particulate matter $\leq 2.5\,\mu m$; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme..
[a]Cochran's test for heterogeneity for Model 3 of effect estimates between the cohorts.
[b]Three cohorts with information on PM and all breast cancer risk factors: DCH, EPIC-Varese, and EPIC-Turin.
[c]Seven cohorts: HUBRO, CEANS (4 Swedish cohorts pooled), DCH, and VHM&PP.
[d]Eight cohorts: HUBRO, CEANS (4 Swedish cohorts pooled), DCH, EPIC-Oxford, and VHM&PP.
[e]Nine cohorts: CEANS (4 Swedish cohorts pooled), DCH, EPIC-Oxford, EPIC-Netherlands (2 Dutch cohorts pooled), and VHM&PP.
[f]Ten cohorts: CEANS (4 Swedish cohorts pooled), DCH, EPIC-Oxford, EPIC-Netherlands (2 Dutch cohorts pooled), VHM&PP, EPIC-Turin.

Table 6. Association between exposure to elemental components of $PM_{2.5}$ and breast cancer incidence in 11 European cohorts with available data.

Exposure	Fixed increase	*n* Cohorts	*n*	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	I^2 (*p*-value)[a]
$PM_{2.5}$ Cu	$5\,ng/m^3$	10[b]	51,937	1.02 (0.74, 1.39)	0.99 (0.74, 1.33)	1.02 (0.75, 1.39)	64.8 (0.01)
$PM_{2.5}$ Fe	$100\,ng/m^3$	10[b]	51,937	1.05 (0.94, 1.16)	1.04 (0.92, 1.18)	1.11 (0.89, 1.39)	44.1 (0.11)
$PM_{2.5}$ K	$50\,ng/m^3$	10[b]	51,937	0.88 (0.78, 0.98)	0.87 (0.78, 0.97)	0.98 (0.79, 1.23)	36.2 (0.16)
$PM_{2.5}$ Ni	$1\,ng/m^3$	6[c]	44,009	1.15 (0.89, 1.49)	1.08 (0.86, 1.37)	1.13 (0.89, 1.44)	3.7 (0.38)
$PM_{2.5}$ S	$200\,ng/m^3$	10[b]	51,937	1.02 (0.75, 1.38)	1.10 (0.81, 1.51)	1.09 (0.78, 1.52)	0.0 (0.55)
$PM_{2.5}$ Si	$100\,ng/m^3$	9[d]	50,006	1.20 (0.88, 1.64)	1.06 (0.89, 1.27)	1.06 (0.88, 1.27)	0.0 (0.58)
$PM_{2.5}$V	$2\,ng/m^3$	8[e]	36,619	1.42 (1.04, 1.94)	1.27 (0.92, 1.76)	1.29 (0.93, 1.78)	0.0 (0.96)
$PM_{2.5}$ Zn	$10\,ng/m^3$	10[b]	51,937	0.92 (0.79, 1.08)	0.93 (0.78, 1.11)	0.97 (0.76, 1.23)	36.4 (0.16)

Note: CEANS, Cardiovascular Effects of Air Pollution and Noise in Stockholm; CI, confidence interval; Cu, copper; DCH, Danish Diet, Health and Cancer cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; EPIC-E3N, French cohort of the Etude Epidemiologique de Femmes de la Mutuelle Générale de l'Education Nationale; Fe, iron; HR, hazard ratio; HUBRO, Oslo Health Study; K, potassium; Ni, nickel; PH, proportional hazard; $PM_{2.5}$, particulate matter <2.5 μm; S, sulfur; Si, silicon; V, vanadium; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme; Zn, zinc. CEANS consists of 4 Stockholm, Sweden, cohorts: SNAC-K, SALT/TwinGene, 60YO/IMPROVE, and SDPP; EPIC-Netherlands consists of 2 Dutch cohorts: EPIC MORGEN and EPIC Prospect. *Relating to Model 3.
[a]Cochran's test for heterogeneity for Model 3 of effect estimates between the cohorts.
[b]Ten cohorts: HUBRO, CEANS (4 Swedish cohorts pooled), DCH, EPIC-Netherlands (2 Dutch cohorts), VHM&PP, and EPIC-Turin.
[c]Six cohorts: HUBRO, DCH, EPIC-Netherlands (2 Dutch cohorts), VHM&PP, and EPIC-Turin.
[d]Nine cohorts: CEANS (4 Swedish cohorts pooled), DCH, EPIC-Netherlands (2 Dutch cohorts), VHM&PP, and EPIC-Turin.
[e]Eight cohorts: CEANS (4 Swedish cohorts pooled), DCH, EPIC-Netherlands (2 Dutch cohorts), EPIC-Turin.

inverse associations with the potassium components of PM_{10} and $PM_{2.5}$ and with the zinc component of $PM_{2.5}$ (Tables 6 and 7) We detected the strongest associations with the vanadium components (per $3\,ng/m^3$ increase) of both $PM_{2.5}$ [HR = 1.29 (95% CI: 0.93, 1.78)] and PM_{10} [HR = 1.30 (95% CI: 0.95, 1.77)] (see Tables 6 and 7; see also Figure S2) and with the nickel component of PM_{10} [HR = 1.30 (95% CI: 1.09, 1.55); $I^2 = 0.0$, per $2\,ng/m^3$] (see Tables 6 and 7 and Figure 4), which reached statistical significance, with no heterogeneity in the estimates. Associations with the nickel component of PM_{10} were enhanced when adjusting for PM_{10} [HR = 1.54 (95% CI: 1.11, 2.11); $I^2 = 59.4$, per $2\,ng/m^3$] to account for possible confounding by PM mass (Mostofsky et al. 2012).

Discussion

We found suggestive evidence of an association between long-term exposure to air pollution and incidence of postmenopausal breast cancer in a large, multicenter European study. Associations of breast cancer with NO_x were significant with no heterogeneity between individual cohort estimates and were robust to extensive sensitivity analyses, whereas associations with PM_{coarse}, PM_{10}, and $PM_{2.5}$ were not statistically significant and showed considerable heterogeneity between individual cohort estimates. Secondary analyses with elemental composition of PM showed increased HRs for vanadium and nickel, with the HR for the nickel component of PM_{10} being statistically significant.

Comparison with Previous Studies on Nitrogen Oxides

Our finding of relevance of NO_x for breast cancer is in line with a single study on NO_x and breast cancer incidence, based on the Danish DCH cohort and including 28,435 women from Copenhagen and Aarhus (987 breast cancer cases until 2006, mainly postmenopausal), which detected weak, positive, statistically nonsignificant associations, but comparable to ours in magnitude, considering different units of increase [HR = 1.16 (95% CI: 0.89, 1.51) per $100\,\mu g/m^3$] (Raaschou-Nielsen et al. 2011a). Furthermore, the HR from Raaschou-Nielsen et al. (2011a) is consistent with the HR in the present study for NO_x [HR = 1.03 (95% CI: 0.95, 1.11) per $20\,\mu g/m^3$] (Figure 2) based on the Copenhagen part of the DCH study and with extended breast cancer follow-up until 2013. It should be noted that the DCH is also included in this meta-analysis and that this is not an independent finding. Our results are not in line with those of a case–control study (301 cases and 220 controls) that detected a statistically significantly increased risk of postmenopausal breast cancer [odds ratio (OR) = 2.58 (95% CI: 1.15, 5.83)] when comparing the highest to the lowest quartile of traffic emissions at residence at first birth (Nie et al. 2007) or with the results of a Canadian case–control study from Montreal, Quebec, which found a strong and statistically significant association between traffic-related NO_2 and postmenopausal breast cancer [OR = 1.30 (95% CI: 1.00, 1.71) per 5 ppb $\sim 7.5\,\mu g/m^3$] among 383 breast cancer cases and 416 controls (Crouse et al. 2010). However, a larger Canadian study in 10 Canadian provinces (1,039 postmenopausal

Table 7. Association between exposure to elemental components of PM_{10} and breast cancer incidence in 11 European cohorts with available data

Exposure	Fixed increase	*n* cohorts	*n*	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	I^2 (*p*-value)[a]
PM_{10} Cu	$20\,ng/m^3$	10[b]	51,937	1.07 (0.96, 1.19)	1.05 (0.94, 1.18)	1.07 (0.93, 1.22)	14.9 (0.32)
PM_{10} Fe	$500\,ng/m^3$	10[b]	51,937	1.08 (0.96, 1.22)	1.07 (0.94, 1.22)	1.08 (0.92, 1.28)	24.6 (0.25)
PM_{10} K	$100\,ng/m^3$	9[c]	50,006	0.89 (0.72, 1.10)	0.89 (0.72, 1.10)	0.89 (0.72, 1.10)	54.3 (0.07)
PM_{10} Ni	$2\,ng/m^3$	6[d]	44,009	1.40 (1.00, 1.95)	1.27 (1.02, 1.59)	1.30 (1.09, 1.55)	0.0 (0.76)
PM_{10} S	$200\,ng/m^3$	10[b]	51,937	1.11 (0.82, 1.51)	1.11 (0.82, 1.51)	1.11 (0.82, 1.50)	18.7 (0.29)
PM_{10} Si	$500\,ng/m^3$	10[b]	51,937	1.15 (0.96, 1.37)	1.14 (0.95, 1.37)	1.16 (0.95, 1.42)	32.7 (0.19)
PM_{10}V	$3\,ng/m^3$	10[b]	51,937	1.39 (1.03, 1.87)	1.25 (0.91, 1.70)	1.30 (0.95, 1.77)	0.0 (0.92)
PM_{10} Zn	$20\,ng/m^3$	10[b]	51,937	1.00 (0.85, 1.17)	0.99 (0.83, 1.17)	1.01 (0.81, 1.26)	42.5 (0.12)

Note: CEANS, Cardiovascular Effects of Air Pollution and Noise in Stockholm; CI, confidence interval; Cu, copper; DCH, Danish Diet, Health and Cancer cohort; EPIC, European Prospective Investigation into Cancer and Nutrition; EPIC-E3N, French cohort of the Etude Epidemiologique de Femmes de la Mutuelle Générale de l'Education Nationale; Fe, iron; HR, hazard ratio; HUBRO, Oslo Health Study; K, potassium; Ni, nickel; PH, proportional hazard; PM_{10}, particulate matter <10 μm; S, sulfur; Si, silicon; V, vanadium; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme; Zn, zinc. CEANS consists of 4 Stockholm, Sweden, cohorts: SNAC-K, SALT/TwinGene, 60YO/IMPROVE, and SDPP; EPIC-Netherlands consists of 2 Dutch cohorts: EPIC MORGEN and EPIC Prospect.
[a]Cochran's test for heterogeneity for Model 3 of effect estimates between the cohorts.
[b]Ten cohorts: HUBRO, CEANS (4 Swedish cohorts pooled), DCH, EPIC-Netherlands (2 Dutch cohorts), VHM&PP, and EPIC-Turin.
[c]Nine cohorts: CEANS (4 Swedish cohorts pooled), DCH, EPIC-Netherlands (2 Dutch cohorts), VHM&PP, and EPIC-Turin.
[d]Six cohorts: HUBRO, DCH, EPIC-Netherlands (2 Dutch cohorts), VHM&PP, and EPIC-Turin.

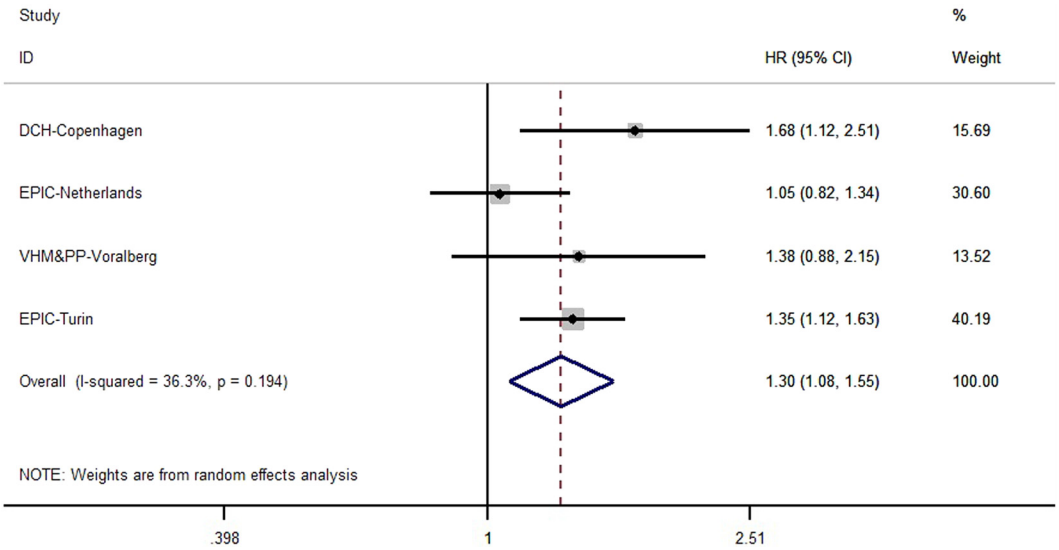

Figure 4. Adjusted associations (Model 3) between breast cancer and the nickel component of particulate matter <10 μm (PM_{10}) in 5 European cohorts [European Prospective Investigation into Cancer and Nutrition (EPIC)-Netherlands consists of two Dutch cohorts: EPIC-MORGEN and EPIC-Prospect]: Results from cohort-specific analyses and random-effects analyses.

breast cancer cases and 1,139 controls) detected weak and statistically nonsignificant associations with NO_2, with ORs ranging from 1.07–1.10 per 10 ppb $\sim 19\,\mu g/m^3$ (Hystad et al. 2015), which is closer to our findings for NO_2 (Table 3, Figure 2). NO_2 and NO_x are closely related traffic pollutants with correlation coefficients in our study ranging from 0.79 in EPIC-NL (see Table S8) to 0.99 in EPIC-Umeå (see Table S3), except for 0.51 in VHM&PP (see Table S9). We found no association between NO_2 and breast cancer [HR = 1.02 (95% CI: 0.98, 1.07) per $10\,\mu g/m^3$] (Table 3; see also Figure S1), which is consistent with the findings of two recent cohort studies with data on NO_2 (but no data on NO_x): The Sister Study cohort (United States and Puerto Rico) with 47,591 women (1,749 breast cancer cases, 5 y of follow-up), which reported an HR for NO_2 of 1.02 [(95% CI: 0.97, 1.07) per 5.8 ppb] (Reding et al. 2015), and the Danish Nurse Cohort study with 22,877 women (1,145 breast cancer cases, 16 y of follow-up), which found an HR for NO_2 of 1.00 [(95% CI: 0.94, 1.07) per $7.4\,\mu g/m^3$] (Andersen et al. 2016). Furthermore, our findings are in accord with those of a number of ecological studies that have detected correlations between trends in NO_x emissions or other traffic-related pollutants (motor vehicle density, consumption of gasoline) over time and breast cancer incidence (Chen and Bina 2012; Wei et al. 2012; Park et al. 2014). Our estimate of a 4% increase in risk of breast cancer for each $20\,\mu g/m^3$ increase in NO_x levels at the residence presents a modest risk but is comparable to that for NO_x and lung cancer, as found in a recent meta-analysis [HR = 1.03 (95% CI: 1.01, 1.05) per $10\,\mu g/m^3$] (Hamra et al. 2015). NO_x represents the total concentration of nitric oxide (NO) and NO_2 produced from the reactions among nitrogen, oxygen, and hydrocarbons at high temperatures, such as combustion processes, with the major source in urban areas coming from motorized traffic. NO_x is marker of primary vehicle emissions, and NO_2 also contains a secondary component. Thus, NO_x is likely to be more related to ultrafine particles (PM with diameter <0.1 μm), and our finding of a stronger association for NO_x than for NO_2 potentially suggests the relevance of this fraction of PM and other unmeasured particle metrics. A study from Copenhagen, Denmark, reported a high correlation coefficient (>0.85) between ultrafine particles and NO_x and traffic volume, supporting the hypothesis that NO_x can be used as a tracer to estimate particle number and size emission factors (Wang et al. 2010). A study from Salzburg, Austria, reported a stronger correlation between ultrafine particles and NO_x than NO_2 (Kwasny et al. 2010). The stronger association found for NO_x than for NO_2 in the present study is not explained by the better LUR model performance for NO_x, which was the case in 8 out of the 15 cohorts included in this meta-analysis; in 4 cohorts, the LUR model performance for NO_2 was better, and in 3 cohorts, the models for both pollutants performed equally well.

Our suggestive finding of the relevance of air pollution to breast cancer is supported by findings that exposure to benzene, which is present in traffic exhaust, led to the development of mammary tumors in mice (Huff et al. 1989). PAHs, mainly originating from traffic, were linked to breast cancer (Mordukhovich et al. 2010, 2015), with the strongest associations found in women with select biologically plausible DNA repair genotypes (Mordukhovich et al. 2016). Potentially plausible biological mechanisms for the association between PAHs and air pollution and breast cancer incidence include aberrant methylation (White et al. 2016) and DNA damage via the formation of adducts and via oxidative stress (Mordukhovich et al. 2016). It has also been suggested that air pollution may increase breast cancer risk by increasing mammographic breast density, one of the strongest biomarkers of breast cancer risk (Boyd 2013). However, of two studies on air pollution and mammographic density, one detected a positive association (Yaghjyan et al. 2017), and the other detected no association (Huynh et al. 2015).

Comparison with Previous Studies on Particles

We found positive but statistically nonsignificant associations of PM_{10}, PM_{coarse}, and $PM_{2.5}$ with postmenopausal breast cancer (Table 3, Figure 3). Summary estimates for PM proxies were moderately heterogeneous, particularly for $PM_{2.5}$, ranging from a statistically significant inverse association in VHM&PP [HR = 0.65 (95% CI: 0.47, 0.88)] to a positive association in EPIC-Oxford [HR = 1.54 (95% CI: 0.77, 3.10) per $5\,\mu g/m^3$] (Figure 3). Difference in the sources and in the compositions of $PM_{2.5}$ may explain the variation in the magnitude and direction of estimates for $PM_{2.5}$, or these findings may be due to chance. The results for $PM_{2.5}$ were more variable in different sensitivity

analyses (Tables 4 and 5) than those for NO_x, possibly because of the different sources of $PM_{2.5}$ in different cities and locations other than traffic, which is a main source of NO_x. LUR model performance for NO_x was better than that for $PM_{2.5}$ in the majority of the cohorts (all but HUBRO and CEANS) (Raaschou-Nielsen et al. 2013). Excluding VHM&PP from analyses of $PM_{2.5}$ enhanced the HR from 1.08 to 1.28 (95% CI: 0.99, 1.65) and eliminated heterogeneity ($I^2 = 0.0$) (Table 5). VHM&PP had the least detailed confounder information, but we included the VHM&PP cohort in our main analysis because of our *a priori* analysis plan and to maintain consistency with previous ESCAPE analyses. Furthermore, there was little evidence of confounding when we compared fully adjusted and age-sex–adjusted HRs.

Our results are in accord with those of three cohort studies with data on PM and breast cancer incidence, which did not observe associations and which detected HRs above and below 1 (Andersen et al. 2016; Hart et al. 2016; Reding et al. 2015). The Sister Study reported HRs for $PM_{2.5}$ and PM_{10} of 1.03 [(95% CI: 0.94, 1.07) per $3.6\,\mu g/m^3$] and 0.99 [(95% CI: 0.98, 1.00) per $5.8\,\mu g/m^3$], respectively (Reding et al. 2015); the Danish Nurse Study reported HRs for $PM_{2.5}$ and PM_{10} of 1.00 [(95% CI: 0.91, 1.09) per $3.3\,\mu g/m^3$] and 1.02 [(95% CI: 0.94, 1.11) per $2.9\,\mu g/m^3$], respectively (Andersen et al. 2016); and the Nurses' Health Study II [United States; 115,921 women (1,296 postmenopausal breast cancer cases, 18 y of follow-up)] found HRs for $PM_{2.5}$, $PM_{2.5-10}$, and PM_{10} (per $10\,\mu g/m^3$) of 0.76 (95% CI: 0.61, 0.95), 1.07 (95% CI: 0.92, 1.25), and 0.97 (95% CI: 0.86, 1.09), respectively. The lack of association observed in our study and in three other cohorts (Andersen et al. 2016; Hart et al. 2016; Reding et al. 2015) may be due to use of recent PM exposures (several years prior to breast cancer diagnoses) and lack of data on exposures early in life. An early case–control study detected an association between TSP levels at birth [OR = 2.42 (95% CI: 0.97, 6.09), $>140\,\mu g/m^3$ vs. $<84\,\mu g/m^3$] and postmenopausal breast cancer, but none with exposures later in life (at first birth, 10 y and 20 y before cancer diagnosis) (Bonner et al. 2005), indicating a need for more (preferably cohort) studies with data on early-life exposures.

Premenopausal versus Postmenopausal Breast Cancer

Of the existing studies on air pollution and breast cancer, one focused on postmenopausal women only (Crouse et al. 2010), whereas the majority included data on both pre- and postmenopausal women (Andersen et al. 2016; Bonner et al. 2005; Hart et al. 2016; Hystad et al. 2015; Lewis-Michl et al. 1996; Nie et al. 2007; Reding et al. 2015; Raaschou-Nielsen et al. 2011b). It remains unclear whether associations between air pollution and breast cancer differ by menopausal status because three studies found stronger associations with postmenopausal breast cancer (Bonner et al. 2005; Lewis-Michl et al. 1996; Nie et al. 2007), three found stronger associations with premenopausal breast cancer (Andersen et al. 2016; Hart et al. 2016; Hystad et al. 2015), and two studies did not report air pollution estimates separately by menopausal status (Reding et al. 2015; Raaschou-Nielsen et al. 2011b).

Particle Composition Findings

We present a novel finding of the relevance of the nickel and possibly the vanadium components of PM to breast cancer development (Tables 6 and 7, Figure 4; see also Figure S2). Nickel and vanadium are heavy metals, originating mainly from mixed oil-burning and industrial production emissions. The nickel component of PM_{10} was also the element that showed the strongest association with lung cancer incidence [HR = 1.59 (95% CI: 1.12, 2.26) per $2\,ng/m^3$] in a related ESCAPE study in 14 European cohorts (Raaschou-Nielsen et al. 2016). Furthermore, our finding is consistent with those of an Italian study examining the effects of living near incinerators, which detected an increased risk of breast cancer mortality [OR = 2.00 (95% CI: 1.00, 3.99)] among women living in areas with the highest ($>2\,ng/m^3$) compared with the lowest ($<0.5\,ng/m^3$) concentration of heavy metals combined, including not only nickel and vanadium but also lead, cadmium, mercury, antimony, arsenic, chromium, cobalt, copper, and manganese (Ranzi et al. 2011). Nickel has been hypothesized to play a role in breast cancer development by acting as a metalloestrogen, a heavy metal that binds to estrogen receptors, mimicking actions of estrogen (Aquino et al. 2012). A study of 112,379 women from the California Teachers Study in the United States (5,361 of whom developed breast cancer) failed to find an association between any of 11 estrogen disruptors (modeled at the participants' residences) and breast cancer risk but found some evidence of association between inorganic arsenic and breast cancer in nonsmoking nonmovers and between cadmium and ER − /PR − breast cancer (Liu et al. 2015). A related study in the same cohort examined the role of modeled levels of 24 mammary gland carcinogens (MGCs) at the residence and found associations between propylene oxide and vinyl chloride and overall breast cancer risk, as well as associations for acylamide, benzidine, carbon tetrachloride, ethylidene dichloride, and vinyl chloride with ER + /PR + breast cancer and for benzene with ER − /PR − breast cancer (Garcia et al. 2015). More studies with data on elemental components of PM exposures and breast cancer are needed to further explore the relevance of specific chemical compounds to breast cancer risk.

Strengths and Limitations

Our study benefited from a multicenter design and from a large number of women recruited from general populations from around Europe with large variations in air pollution levels, well-defined information on the most important breast cancer risk factors, and a standardized definition of breast cancer from national and regional cancer registries. Breast cancer diagnoses available from the national registry have been validated in Denmark against clinical records in a study that found that incidence data were complete, with no tumors missing and with correct data on malignancy and date of diagnosis (Jensen et al. 2002); national and regional cancer registries in other similar European countries likely have data of similar quality. The major strength of our study is the standardized exposure assessment and standardized statistical analyses across all cohorts. The air pollution LUR models have been validated and were previously linked to lung cancer (Raaschou-Nielsen et al. 2013). We adjusted the analyses for a number of potential confounders but found little evidence of confounding in air pollution estimates, minimizing the possibility of residual confounding in cohorts that had missing data on the confounders, typically on reproductive factors or HT use.

A weakness of our study is the lack of data on breast cancer subtypes by ER and PR status: A recent study found that association with NO_2 was limited to ER + /PR + breast cancer [HR = 1.10 (95% CI: 1.02, 1.19) per $3.6\,\mu g/m^3$] (Reding et al. 2015), and a similar trend, although without statistically significant effect modification, was found for PM exposures (Hart et al. 2016). We lacked data on premenopausal breast cancer, and some of the most recent studies suggest stronger associations for air pollution and premenopausal breast cancer than for postmenopausal breast cancer (Andersen et al. 2016; Hart et al. 2016; Hystad et al. 2015). We lacked information on mammographic screening participation, but the screening-related bias in breast

cancer epidemiology (the timing of breast cancer diagnoses) is more relevant for premenopausal breast cancer. Breast cancer screening affects the timing of breast cancer diagnosis and results in an increased rate of diagnosis in the early period, the so-called incidence peak, which is compensated by lower incidence in the later period of screening after screening age. In 2003, the European Commission recommended breast cancer screening for women 50–69 y old, and in 2007, organized breast cancer screening was in place in all of the countries included in this analysis (initiated in 1974 in Austria; in the 1990s in the United Kingdom, Sweden, and Netherlands; and between 2004 and 2007 in France, Italy, and Denmark) (Altobelli and Lattanzi 2014). Screening participation in 2014 varied between 57% and 80% in these countries (Altobelli and Lattanzi 2014). It is not known whether women who participated in breast cancer screening would have had higher or lower air pollution at their residences, although a single Canadian study with data on mammographic screening participation found higher levels of NO_2 among women who participated in screening (Hystad et al. 2015). That study also found an attenuation of associations with NO_2 in women participating in screening programs, but for premenopausal women only, suggesting that lack of adjustment for breast cancer screening participation would not change our results in postmenopausal women. Furthermore, we lacked data on detailed occupational exposures to chemicals that may be related to breast cancer risk apart from a crude definition of night-shift work (defined as occupation as nurse or physician) that was available in only one cohort (see Table S1). We used exposure levels in adulthood, assessed close to the time of the breast cancer diagnosis, and we lack data on early-life exposures to air pollution, specifically before and around first childbirth, which have been found to be relevant in studies on air pollution (Bonner et al. 2005; Nie et al. 2007). Notably, active tobacco smoking early in life, particularly before first childbirth, has recently been established as a risk factor for breast cancer (Dossus et al. 2014), increasing the plausibility that exposure to air pollution early in life, when mammary tissue is still in development and not fully differentiated, could be a critical factor for breast cancer carcinogenesis. Similarly, a study on occupational exposures and postmenopausal breast cancer also found that exposures to some compounds before 36 y of age were most relevant (Labrèche et al. 2010).

In this study, we used LUR models that were developed on air pollution measurements obtained between 2008 and 2011, but we applied them to baseline addresses typically 10 to 15 y earlier, which likely resulted in some exposure misclassification. Several studies have documented stable spatial contrast of NO_2 over study periods of 10–15 y (Cesaroni et al. 2012; Eeftens et al. 2011; Gulliver et al. 2013). A study found stable traffic intensities on Dutch streets over a 10-y period (Beelen et al. 2007), and spatial models for black smoke in the United Kingdom provided reasonable predictions going back to the 1960s (Gulliver et al. 2011). In analyses of nonmovers, we found identical associations with NO_x (Table 4) to those found in the main analyses but with high heterogeneity between the individual cohort estimates. This finding is likely explained by the smaller exposure misclassification in nonmovers, which, as expected, resulted in detecting stronger associations than in the entire cohort, but in cohorts with HRs >1 and in two cohorts with HRs <1, which contributed to an increase in the range of HRs and to higher heterogeneity. Exposure misclassification may have also resulted from using predicted concentrations of the pollutants and from a lack of information about participants' activity patterns. Finally, we had no data to examine associations between air pollution and breast cancer in men, limiting the generalizability of the results.

Conclusion

In a large, multicenter European study on long-term exposure to ambient air pollution and postmenopausal breast cancer incidence, we found suggestive evidence of an association between air pollution and incidence of postmenopausal breast cancer.

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