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AMBIENT AIR POLLUTION EXPOSURES AND RISK OF RHEUMATOID ARTHRITIS: RESULTS FROM THE SWEDISH EIRA CASE-CONTROL STUDY

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Abstract

Objective—Environmental factors may play a role in the development of rheumatoid arthritis (RA). We examined whether long-term exposures to air pollution were associated with risk of RA in the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) Study.

Methods—We studied 1,497 incident RA cases and 2,536 controls. Local levels of particulate matter (PM₁₀) and gaseous pollutants (SO₂ and NO₂) from traffic and home heating were predicted for all residential addresses. We examined the association of an interquartile range increase (2μg/m³ for PM₁₀, 8μg/m³ for SO₂, and 9μg/m³ for NO₂) in each pollutant at different time points prior to symptom onset and average exposure with the risk of all RA and the risk of the rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) RA phenotypes.

Results—There was no evidence of an increased risk of RA with PM₁₀. Total RA risks were modestly elevated for the gaseous pollutants, but were not statistically significant after adjustment for smoking and education (odds ratio (OR)=1.18 [95% confidence interval (CI): 0.97–1.43] and OR=1.09 [95% CI: 0.99–1.19] for SO₂ and NO₂ in the 10th year before onset). Stronger elevated risks were observed for individuals with less than a university education and with the ACPA- RA phenotype.

Conclusion—No consistent overall associations between air pollution in the Stockholm area and risk for RA were observed. However, there was a suggestion of increased risks of RA incidence with increases in NO₂ from local traffic and SO₂ from home heating sources with stronger associations for the ACPA- phenotype.

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Air pollution exposures and risk of RA in EIRA

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Keywords

air pollution; rheumatoid arthritis; traffic pollution; home heating pollution

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting approximately 1% of the adult population.[1–4] Epidemiologic studies have revealed that risk of developing RA is associated with exposures to silica, mineral oil, and cigarette smoke,[5–19] suggesting that respiratory exposures activating the immune system may lead to RA, in particular the subset of RA that is characterized by the presence of antibodies to citrullinated protein antigens (ACPA+ RA).[20–22] Air pollution is an environmental factor that has been hypothesized to be associated with an increased risk of RA due to its ability to increase systemic inflammation.[23, 24] In a previous analysis in a cohort of US women, we observed a 30% increased risk of RA in women with residential addresses within 50m of a major roadway,[24] suggesting a possible association with air pollution. In the current analysis we investigate the association of specific air pollutants related to local traffic and home heating sources and onset of RA in the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) case-control study to determine if specific air pollutants are associated with an increased risk of RA.

MATERIALS AND METHODS

Study Population and Outcome Assessment

EIRA is a population-based case-control study throughout the middle and southern portions of Sweden. Case-control selection was described in detail previously.[14] Briefly, each case was defined as a person 18–70 years of age who, between 1996 and 2008, received a diagnosis of RA for the first time. All potential cases were examined and diagnosed by a rheumatologist at the rheumatology unit entering the case into the study and all fulfilled the American College of Rheumatology (ACR) 1987 criteria for RA. The time of onset of RA was defined as the time of the first symptom of the disease. For 85% of the cases the time between onset and inclusion in the study was less than one year. Each case was further classified by autoantibody phenotypes according to the presence of rheumatoid factor [RF] or anti-citrullinated peptide antibodies [ACPA]. Controls were identified from the national population register and were selected with consideration for the age, and gender of the cases. All cases and controls consented to the study after receiving written information, and all aspects of the study were approved by the ethics committee of Karolinska Institutet. For this analysis, only cases and controls residing in Stockholm County (where the pollution estimates were available) at the time of enrollment, a geographic region of 6,488 square kilometers, were included resulting in a total of 1,497 cases and 2,536 controls.

Exposure Assessment

All addresses occupied for at least two years in the residential history of each EIRA participant from 1968 onward were geocoded through Statistics Sweden to obtain latitude and longitude. Prediction models were used to estimate annual air pollution levels from local sources of traffic (particulate matter 10 microns in aerodynamic diameter (PM_{10}), particulate matter 2.5 microns in aerodynamic diameter ($PM_{2.5}$), nitrogen dioxide (NO_2), and oxides of nitrogen (NO_x)) and home heating (sulfur dioxide, SO_2) for each home address. These estimates were available for all addresses in Stockholm County 1968–1998 based on models developed and described in detail for previous studies.[25–27] Briefly, these models combined information from the emissions inventories (available each decade

since 1960), annual changes in road traffic, and annual changes in residential heating and fuel sulfur content with dispersion modeling to determine the levels of pollution at each address in each year. We assumed that the levels of pollution were constant after the last available exposure predictions. Due to the modeling process and similar patterns in dispersion, there is a high level of correlation between PM₁₀ and PM_{2.5} and between NO₂ and NO_x, therefore we have chosen to only present models using the predictions for PM₁₀ and NO₂.

We created a variety of exposure metrics as appropriate to examine different potential important periods of exposure. To explore the effects of timing of exposure prior to disease incidence, we created metrics to examine the annual exposure in the 5th-, 10th-, and 20th- years prior to onset of RA symptoms or the index date for the corresponding controls, where the index date for a control is the date of onset of RA for the case that the control was originally matched to. These windows of exposure were chosen based on previous studies demonstrating that autoantibodies are elevated 5–10 years prior to diagnosis with RA.[28–30] As it is also plausible that long-term exposure to air pollution is the exposure of interest, we calculated the average exposure from either birth or the start of air pollution predictions (whichever was later) to diagnosis for all addresses in Stockholm Country.

Additional Covariates

Information on potential confounders is available from mailed questionnaires that were completed by incident RA cases and controls. Incomplete questionnaires were completed with the assistance of trained staff over the phone or via mail. We adjusted for age and gender to account for the matching in the initial design of the study and examined possible confounding by smoking status (current/former/never), and level of educational attainment as a marker of individual socioeconomic status (SES). As used previously in this study,[31] education was based on categories used by Statistics Sweden: compulsory school, vocational upper secondary school, theoretical upper secondary school, other education, and university degree.

Statistical Analysis

Since matching was broken for this analysis because of the availability of cases and controls with air pollution data, logistic regression models were used to assess the relationship of total RA, RF+ and RF– RA and ACPA+ and ACPA– RA with exposures to each of the pollutants in separate models. All models were controlled for the original matching factors - age and gender. To allow comparability between pollutants, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated based on an interquartile range increase (IQR, difference between the 75th and 25th percentiles in the distribution) of the average exposure for each pollutant (2μg/m³ for PM₁₀, 8μg/m³ for SO₂, and 9μg/m³ for NO₂). To test for deviations from linearity for each dose-response we used cubic splines and only present linear results if there were no statistically significant departures from linearity. To determine if educational attainment was an effect modifier, we performed stratified analyses in cases and controls with and without a university degree to obtain category specific odds ratios. In previous analyses in EIRA, smoking has been shown to be an important effect modifier, therefore we also performed analyses stratified by ever/never smoking status. To test for statistical significance (p<0.05) of the effect modifiers we included multiplicative interaction terms in the multivariable analyses of the full study. All statistical analyses were performed in SAS version 9.1.3 (Cary, NC).[32]

RESULTS

The EIRA cases/controls both had a mean (SD) age of 51.5 (12.6) at enrollment (Table 1). Seventy-three percent of the cases and 71% of the controls were female, and 28.1% and 34.9% respectively were never smokers. Twenty-two percent of the cases and 16% of the controls had a compulsory school education, while 24% of the cases and 30% of the controls had a university education. Overall, the median levels of air pollution were similar between cases and controls. For PM₁₀ there was little difference in the median levels across the different time windows examined, however for NO₂ and SO₂, the levels tended to be higher in cases than in controls, and exposures were higher in windows that included exposures further back in time.

The results for the EIRA models including all RA cases are presented in Table 2. Overall, there was no evidence of an association of RA with exposures to PM₁₀ in any time period and the odds ratios (OR) were mostly below 1 with wide confidence intervals. In models adjusted for age and gender (Model 1), exposure to SO₂ and NO₂ did appear to be associated with a modest increased risk of RA. The elevated risks with exposure to the gaseous pollutants were mainly observed with exposure in the 10th- and 20th-years prior to onset. Models additionally adjusted for smoking status were generally attenuated (Model 2) and the point estimates for the gaseous pollutants were generally elevated but not statistically significant after additional adjustment for education level (Model 3). We did not see an association with RA risk for any of the pollutants with the average exposure metric.

Results for the ACPA+ and ACPA- RA phenotypes are presented in Table 3 and the results for RF+ and RF- RA are presented in the Supplemental Appendix. Overall, the patterns in the specific antibody subtypes were similar to those seen for all RA cases. However, the effects of SO₂ and NO₂ did appear to be strongest in models restricted to the ACPA- cases, with elevations, but few statistically significant associations, observed for ACPA+, RF+ or RF- RA. The age, gender, and smoking adjusted OR for each interquartile range increase in SO₂ in the 10th year prior to symptom onset was 1.44 (95%CI: 1.10–1.90) for ACPA- RA and for NO₂ was 1.18 (95%CI: 1.03–1.34). Further adjustment for education modestly strengthened the associations. Odds ratios were slightly lower for the gaseous pollutants in the 5th and 20th year prior to symptom onset and again were not elevated for the measure of average exposure.

In stratified models (Figure 1), ORs for all RA, ACPA+ RA and ACPA- RA were elevated in participants without a university education compared to those with a university education, although elevated ORs were observed in both groups for the gaseous pollutants. Most interaction terms for all RA and ACPA+ were significant at the p<0.05 level with the exception of three SO₂ interactions (10th year before onset: p-for-interaction=0.69 for all RA, p-for-interaction=0.56 for ACPA+ RA; 20th year before onset p-for-interaction=0.09 for all RA) and the interaction of PM₁₀ in the 20th year before onset for ACPA+ RA (p-for-interaction=0.16). No interaction terms were statistically significant for ACPA- RA, possibly due to the smaller strata-specific sample sizes. In models stratified by smoking (Figure 2), total RA odds ratios were generally higher for never smokers compared to ever smokers, however, none of the smoking-pollution interaction terms were statistically significant.

DISCUSSION

In the EIRA case-control study, exposures to gaseous pollutants from local sources from traffic (NO₂) and home heating (SO₂) in the 5th, 10th and 20th year prior to RA symptom onset were positively, but in most cases not statistically significantly, associated with overall

RA risk. Significant but still weak associations were observed between exposure to certain gaseous pollutants and all RA in certain strata of the population in particular. When subdivided by serology (RF and ACPA), the adverse effects of NO₂ and SO₂ were stronger and more often statistically significant for ACPA- RA cases compared to the results in all RA cases combined, while similar trends but no statistically significant associations were observed in the ACPA+, RF+ or RF- analyses. These findings are in contrast to associations demonstrated for other airway environmental exposures, cigarette smoking and silica dust, where the strongest associations are seen for ACPA+ RA.[20–22, 33] We found little evidence of adverse effects of increases in particulate matter, PM₁₀, on the risk of RA or with average exposure measurement. To the best of our knowledge, this is the first study to examine the association of exposure to specific air pollutants and the risk of RA.

RA is an inflammatory autoimmune disease and various air pollutants have been linked with other diseases of pulmonary and systemic inflammation.[23] The current study does not provide strong evidence for an association of air pollution with the risk of RA. This is in contrast, to, our previous study in US women, showing a 30% elevated risk of RA with residence within 50 m of a major roadway.[24] In the current study, NO₂ and PM₁₀ were explicitly modeled based only on local traffic sources; however, we only saw an increased risk of RA with NO₂. NO₂ is often considered an ideal marker of traffic pollution and increased exposure has been linked with a variety of adverse health effects and increases in systemic inflammation, particularly in European studies.[34–39] SO₂ was modeled to reflect the impact of local home heating sources. Long-term exposures to SO₂ have not been consistently associated with chronic diseases or all cause mortality,[40–45] but more acute exposures to SO₂ have been related to cardiovascular deaths and/or hospital admissions.[46] It is possible that in this study SO₂ is a proxy for other exposures that may be etiologically relevant for RA. Our results suggest that exposures in the specific years prior to symptom onset may be more strongly associated with the development of RA, than with the long term average exposures. Recent studies have suggested that autoantibodies such as ACPA have been found to precede the onset of RA by up to 14 years [28–30] and an etiology for RA has been proposed that builds on the exposure in the lungs to irritants/adjuvants such as smoking and silica.[22, 47] Our initial hypothesis was that if this was the primary biologic mechanism affected by air pollution (another lung irritant), the strongest effects would be observed in ACPA+ cases. This mechanism would not explain our stronger findings in the ACPA- cases, which may indicate the role of other etiological mechanisms.

This analysis has several important limitations, as well as strengths. Although exposure data in EIRA is available over a 30-year period (1968–1998) allowing us to examine the impacts of exposure at various time points before RA onset, this study is restricted to a small geographic area, Stockholm County. We are only examining the contribution of local sources of pollution, in an area with comparatively low background levels; therefore, the range of each pollutant is quite tight, making it difficult to observe effects. Our measures of air pollution are indicators of complex mixtures, and since our estimates of NO₂ and PM₁₀ are both describing air pollution from traffic, they are highly correlated (correlations~0.95 within each period of exposure). However, the range of PM₁₀ was much smaller (2 µg/m³) than that of NO₂ (9 µg/m³), possibly explaining the differences in the findings between the two pollutants. The exposure models used are imperfect predictors of personal exposures and we do not have information on the amount of time that each participant spent at the actual home address, or time spent inside or outside the home. This would most likely lead to non-differential misclassification of our air pollution exposure measures, and would bias our results towards finding no association. Lastly, we lack information on exposure to these pollutants at locations other than the residence and we do not have information on occupational PM₁₀, SO₂, or NO₂ exposures. This prevents us from examining the impact of exposures from all sources on the incidence of RA.

Socioeconomic status (SES) was an important confounder and a significant modifier in our EIRA analyses. In the air pollution literature, it has been hypothesized that individuals with lower SES may be particularly susceptible to the effects of air pollution, or that they may experience higher indoor levels of ambient air pollution due to the conditions of poor housing stock.[48] Low SES also could be a marker for residential exposure to air pollution, as individuals with higher SES tend to live in areas with lower levels of pollution.[48] In the EIRA participants, levels of pollution were modestly higher for individuals with less than a university education, compared to those with a university education, and results from stratified analyses indicated that the effect of air pollution is most pronounced for those with less than a university education. In contrast, although smoking status was an important confounder in our analyses, there was little evidence of effect modification. However, results tended to be slightly stronger among never smokers, who may be more susceptible to the effects of air pollution than smokers consistently exposed to cigarette smoke.

In conclusion, we do not find any consistent overall associations between air pollution in the Stockholm area and risk for RA. There was a suggestion of increased risks of RA incidence with increases in NO₂ from local traffic and SO₂ from home heating sources with stronger associations for the ACPA- phenotype. Socioeconomic status appeared to be an important confounder and effect modifier, suggesting that further study is needed in populations with a wide range of socioeconomic status. As this is, to the best of our knowledge, the first study to examine this association, further research into whether particulate matter or gaseous pollutants are associated with RA risk is needed, particularly in locations with a wider range of pollution exposures.

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Figure 1. The Effect of Educational Attainment on Incident RA Risk (Panel A), ACPA+ RA Risk (Panel B), and ACPA- RA Risk (Panel C) Associated with an Interquartile Range Increase in Ambient Air Pollution in the EIRA study (Odds Ratios and 95% Confidence Intervals). All models are adjusted for age, gender, and smoking

Figure 2. The Effect of Smoking Status on Incident RA Risk (Panel A), ACPA+ RA Risk (Panel B), and ACPA- RA Risk (Panel C) Associated with an Interquartile Range Increase in Ambient Air Pollution in the EIRA study (Odds Ratios and 95% Confidence Intervals). All models are adjusted for age, gender, and educational attainment

Table 1

Characteristics of the EIRA cases and controls

	Cases	Controls
N (%)	1,497	2,536
RF+	982 (66%)	N/A
ACPA+	991 (66%)	N/A
ACPA–	505 (34%)	N/A
Age at enrollment, mean (SD)	51.5 (12.6)	51.5 (12.6)
Gender (%)		
Male	27.7	28.7
Female	72.3	71.3
Smoking status at enrollment (%)		
Never	27.9	35.5
Current	26.9	18.6
Non Regular	10.5	10.0
Former	30.9	25.7
Missing	3.8	10.3
Education (%)		
Compulsory school	21.8	16.1
Vocational upper secondary school	12.7	9.5
Theoretical upper secondary school	12.1	11.7
Other education	24.9	21.7
University degree	24.3	30.2
Missing	4.2	10.9
Air pollution in the 5 th Year Before RA Onset (median, IQR)		
PM ₁₀ (µg/m ³)	2.0 (2.6)	2.1 (2.6)
SO ₂ (µg/m ³)	1.7 (2.4)	1.8 (2.2)
NO ₂ (µg/m ³)	5.8 (7.5)	5.6 (7.6)
Air pollution in the 10 th Year Before RA Onset (median, IQR)		
PM ₁₀ (µg/m ³)	1.9 (2.5)	2.0 (2.5)
SO ₂ (µg/m ³)	2.7 (3.7)	2.4 (3.4)
NO ₂ (µg/m ³)	7.4 (9.1)	7.0 (9.1)
Air pollution in the 20 th Year Before RA Onset (median, IQR)		
PM ₁₀ (µg/m ³)	1.9 (2.3)	1.9 (2.3)
SO ₂ (µg/m ³)	9.1 (10.0)	8.1 (9.3)
NO ₂ (µg/m ³)	10.8 (12.9)	10.4 (12.5)
Average air pollution (median, IQR) ^a		
PM ₁₀ (µg/m ³)	2.2 (2.0)	2.3 (2.1)
SO ₂ (µg/m ³)	7.7 (7.8)	7.6 (8.4)
NO ₂ (µg/m ³)	9.6 (8.8)	9.7 (8.8)

^a Average pollution calculated from the later of 1968 or date of birth to index date

N/A= not applicable

Table 2

Odds Ratios (OR) and 95% Confidence Intervals (CI) of Incident RA Risk Associated with an Interquartile Range Increase in Ambient Air Pollution

Timing Relative to Onset of RA	PM ₁₀ (2 µg/m ³) OR (95%CI)	SO ₂ (8 µg/m ³) OR (95%CI)	NO ₂ (9 µg/m ³) OR (95%CI)
5th Year Before Onset , (1,307 cases, 2,197 controls)			
Model 1 ^a	0.96 (0.90–1.03)	1.17 (0.83–1.65)	1.07 (0.96–1.19)
Model 2 ^b	0.96 (0.89–1.03)	1.04 (0.74–1.48)	1.03 (0.92–1.15)
Model 3 ^c	0.98 (0.91–1.05)	1.12 (0.79–1.59)	1.07 (0.95–1.19)
10th Year Before Onset , (1,276 cases, 2,138 controls)			
Model 1 ^a	0.98 (0.91–1.05)	1.28 (1.06–1.55)	1.10 (1.00–1.20)
Model 2 ^b	0.97 (0.90–1.05)	1.15 (0.95–1.39)	1.06 (0.96–1.16)
Model 3 ^c	0.99 (0.92–1.07)	1.18 (0.97–1.43)	1.09 (0.99–1.19)
20th Year Before Onset , (1,168 cases, 1,916 controls)			
Model 1 ^a	1.01 (0.94–1.09)	1.12 (1.05–1.21)	1.03 (0.97–1.10)
Model 2 ^b	1.00 (0.93–1.08)	1.07 (0.99–1.15)	1.01 (0.94–1.08)
Model 3 ^c	1.02 (0.94–1.10)	1.08 (1.00–1.16)	1.02 (0.95–1.09)
Average Exposure (1,497 cases, 2,536 controls)			
Model 1 ^a	0.95 (0.87–1.03)	1.02 (0.95–1.10)	0.99 (0.91–1.08)
Model 2 ^b	0.94 (0.87–1.02)	0.99 (0.92–1.07)	0.96 (0.89–1.05)
Model 3 ^c	0.96 (0.88–1.04)	1.01 (0.93–1.09)	0.98 (0.90–1.07)

^aModel 1 = Adjusted for age and gender

^bModel 2 = Adjusted for age, gender, smoking status

^cModel 3 = Adjusted for age, gender, smoking status, and educational attainment

Table 3

Odds Ratios (OR) and 95% Confidence Intervals (CI) of ACPA Positive and ACPA Negative RA Risk Associated with an Interquartile Range Increase in Ambient Air Pollution in EIRA

Timing of Pollution Relative to Onset of RA	ACPA Positive RA			ACPA Negative RA		
	PM ₁₀ (2 µg/m ³)	OR (95%CI) SO ₂ (8 µg/m ³)	NO ₂ (9 µg/m ³)	PM ₁₀ (2 µg/m ³)	OR (95%CI) SO ₂ (8 µg/m ³)	NO ₂ (9 µg/m ³)
5th Year Before		789 cases, 2,197 controls			448 cases, 2,197 controls	
Model 1 ^a	0.95 (0.88–1.04)	1.09 (0.73–1.64)	1.06 (0.93–1.21)	1.01 (0.91–1.13)	1.45 (0.87–2.42)	1.17 (1.00–1.37)
Model 2 ^b	0.95 (0.87–1.03)	0.94 (0.62–1.42)	1.02 (0.89–1.16)	1.01 (0.91–1.12)	1.26 (0.75–2.10)	1.13 (0.97–1.32)
Model 3 ^c	0.97 (0.89–1.06)	1.01 (0.67–1.52)	1.05 (0.92–1.20)	1.04 (0.94–1.16)	1.40 (0.84–2.33)	1.19 (1.01–1.40)
10th Year Before		771 cases, 2,138 controls			436 cases, 2,138 controls	
Model 1 ^a	0.97 (0.89–1.06)	1.18 (0.94–1.48)	1.08 (0.97–1.21)	1.02 (0.92–1.14)	1.64 (1.26–2.15)	1.22 (1.07–1.39)
Model 2 ^b	0.97 (0.89–1.05)	1.00 (0.80–1.27)	1.03 (0.92–1.15)	1.02 (0.92–1.13)	1.44 (1.10–1.90)	1.18 (1.03–1.34)
Model 3 ^c	0.99 (0.90–1.08)	1.03 (0.82–1.30)	1.06 (0.95–1.18)	1.05 (0.94–1.17)	1.48 (1.13–1.95)	1.22 (1.07–1.40)
20th Year Before		698 cases, 1,916 controls			404 cases, 1,916 controls	
Model 1 ^a	1.00 (0.92–1.09)	1.13 (1.04–1.23)	1.03 (0.96–1.12)	1.02 (0.91–1.14)	1.20 (1.09–1.32)	1.06 (0.97–1.17)
Model 2 ^b	0.99 (0.90–1.08)	1.05 (0.96–1.14)	1.00 (0.92–1.08)	1.01 (0.90–1.13)	1.13 (1.02–1.25)	1.04 (0.95–1.15)
Model 3 ^c	1.00 (0.92–1.10)	1.06 (0.97–1.15)	1.02 (0.94–1.10)	1.03 (0.92–1.15)	1.14 (1.03–1.26)	1.06 (0.96–1.17)
Cumulative Average		991 cases, 2,536 controls			505 cases, 2,536 controls	
Model 1 ^a	0.94 (0.86–1.04)	1.01 (0.92–1.10)	0.98 (0.89–1.08)	1.00 (0.88–1.13)	1.06 (0.96–1.18)	1.06 (0.93–1.19)
Model 2 ^b	0.94 (0.85–1.03)	0.97 (0.89–1.07)	0.95 (0.86–1.05)	1.00 (0.88–1.13)	1.04 (0.94–1.16)	1.03 (0.91–1.17)
Model 3 ^c	0.96 (0.87–1.06)	0.98 (0.89–1.07)	0.97 (0.87–1.07)	1.02 (0.90–1.16)	1.09 (0.97–1.21)	1.07 (0.94–1.21)

^aModel 1 = Adjusted for age and gender

^bModel 2 = Adjusted for age, gender, smoking status

^cModel 3 = Adjusted for age, gender, smoking status, and educational attainment