Original Article: Passive Smoking Throughout the Life Course and the Risk of Incident Rheumatoid Arthritis in Adulthood Among Women

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ABSTRACT (Word count = 264; max 250 structured in A&R)

Objective

To investigate passive smoking throughout the life course and the risk of rheumatoid arthritis (RA), while accounting for personal smoking.

Methods

We analyzed the Nurses' Health Study II prospective cohort, using information collected via biennial questionnaires. We assessed the influence of (1) maternal smoking during pregnancy (*in utero* exposure), (2) childhood parental smoking, and (3) years lived with smokers since age 18. Incident RA and serostatus was determined by medical record review. Using the marginal structural model framework, we estimated the controlled direct effect of each passive smoking exposure on adult incident RA risk by serologic phenotype, controlling for early-life and time-updated adult factors including personal smoking.

Results

Among 90,923 women, we identified 532 incident RA cases (66% seropositive) during 27.7 years (median) of follow-up. Maternal smoking during pregnancy was associated with RA after confounding adjustment (HR 1.25 [95% CI 1.03, 1.52]), but not after accounting for subsequent smoking exposures. Childhood parental smoking was associated with seropositive RA after adjusting for confounders (HR 1.41 [95% CI 1.08, 1.83]). In the controlled direct effect analyses, childhood parental smoking was associated with seropositive RA (HR 1.75 [95% CI 1.03, 2.98]) after controlling for adult personal smoking, which was accentuated among ever smokers (HR 2.18 [95% CI 1.23, 3.88]). There was no significant

association of adult passive smoking with RA (20+ years lived smoker: HR 1.30 [95% CI 0.97, 1.74] vs. none).

Conclusion

We found a potential direct influence of childhood parental smoking on adult-onset incident seropositive RA even after controlling for adult personal smoking.

INTRODUCTION

Rheumatoid arthritis (RA) is a debilitating systemic inflammatory disease characterized by prominent polyarthritis with associated morbidity and mortality (1–3). In its pathogenesis, considered an interplay of genetic and environmental exposures (4), lung inflammation is strongly implicated as an initial site of immune dysregulation and RA-related autoantibody production (5–7). Thus, smoking, personal (active) and passive, has been of interest as a major modifiable environmental risk factor for seropositive RA, characterized by autoantibodies such as rheumatoid factor (RF) and anticitrullinated peptide antibodies (ACPAs), particularly among genetically predisposed individuals (4,8).

Personal (active) smoking is the most well-established environmental risk factor for development of rheumatoid arthritis (RA) as demonstrated in multiple epidemiological studies (9–13). The potential link between passive smoking and incident RA is less established (14). This is partly due to the challenge of having a sufficiently large longitudinal database with adequately granular data to capture passive smoking and incident RA. Among the few existing cohort studies of passive smoking and RA risk are a birth cohort study of maternal smoking during pregnancy and childhood polyarthritis (15), an analysis of Nurses' Health Study (NHS) on years living with smokers and adult incident RA (11), and a population registry-based study of childhood passive smoking and adult incident RA (16). No single study to date has provided a comprehensive view on the link between passive smoking over the life course (maternal smoking during pregnancy while *in utero*, childhood passive smoking, and adult passive smoking) and incident RA during adulthood.

Therefore, we aimed to examine the influence of passive smoking at several stages of one's life course while accounting for personal smoking behavior using a framework from the life-course epidemiology literature (17). We analyzed the Nurses' Health Study II (NHSII) prospective cohort, which provided both passive smoking exposure spanning participants' life course and confirmed diagnoses of adult incident RA with serostatus. We hypothesized that early-life passive smoking exposure would increase seropositive RA risk.

METHODS

Participants and eligibility

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We performed a cohort study based on the prospectively collected data in the NHSII. Briefly, the NHSII enrolled 116,429 female registered nurses aged 25–42 years in 1989. Since then, the prospective follow-up has continued every two years to date through mailed questionnaires with >90% follow-up rates. The questionnaires collect information on sociodemographics, anthropometrics, behaviors, medications, dietary intake, and health conditions. For the current study, we excluded those who self-reported prevalent RA or connective tissue diseases before the 1989 baseline questionnaire to focus on incident RA during follow-up. Subjects missing childhood parental smoking status or adult passive smoking information were excluded. The study protocol was approved by the institutional review board of Mass General Brigham.

Passive smoking exposure variables of interest

We examined three passive smoking exposures of interest: (1) maternal smoking during pregnancy as an *in utero* exposure, (2) parental smoking during childhood as a childhood exposure, and (3) adult passive smoking as an adult exposure. All these passive smoking variables were collected in additional smoking behavior questionnaire items in 1999 when women ranged in age from 35–52. Maternal smoking during pregnancy was then categorized into three categories: yes, no, and missing/do not know. For childhood parental smoking, we compared any childhood parental smoking (either one or both of parents) vs. no childhood parental smoking. Adult passive smoking was asked as years lived since age 18 with household smokers. In 1999 when the passive smoking questionnaire was administered, participants were aged 35–52 years old. We categorized the adult passive smoking exposure levels to zero, 1-19 years, and 20+ years.

Identification of incident RA outcome

Participants who self-reported a new physician diagnosis of RA in the main NHSII questionnaires received a validated follow-up questionnaire for connective tissue disease screening (18). For participants screening positive, medical records were requested and independently reviewed by two physicians to confirm RA presence and date of clinical onset based on the 1987 American College of Rheumatology (ACR) (19) or 2010 ACR/European League Against Rheumatism (20) classification criteria. RA cases were further determined as seropositive (positivity of RF and/or ACPA, if available) and seronegative from the results of clinical testing in the medical record. RA cases were identified up to and including the 2017 questionnaire cycle.

Accounting for personal (active) smoking exposure in the life-course analysis framework

Our interest was in the *direct* influence of passive smoking on incident RA. Thus, we needed to adequately control for personal smoking exposure. Additionally, as personal smoking behaviors temporally lie *after* earlier life passive smoking behavior, personal smoking may serve as a "mediator".

That is, earlier-life experience of passive smoking might have influenced the uptake of later-life personal smoking, as suggested by previous studies (21–23). Such increased uptake of personal smoking due to earlier-life experience could then affect the adult incident RA risk (**sFigure 1**).

In the life-course analysis framework for early-life exposure that may influence later-life exposure as well as adult health outcomes, several forms of hypotheses can be formed (17). On one extreme is the "social trajectory" model, which hypothesizes that early-life passive smoking is *only* important through promoting later-life uptake of personal smoking but does not cause harm by itself. The other extreme is the "cumulative exposure" model, in which passive and active cigarette smoke inhalation increases the risk of RA by cumulative dose-response. The distinction can be made if we examine the "direct effect" of early-life passive smoking controlling for later personal smoking. If such an association is observed, early-life passive smoking is demonstrated not to follow the pure "social trajectory" model. Additionally, if the early life is a particularly heightened risk period regarding smoking's link to later-life incident RA, the direct effect may be observed even when adult personal smoking is absent.

We conceptualized our direct effect of interest as the "controlled direct effect" in the causal inference literature (24,25). A controlled direct effect of earlier-life passive smoking is the direct impact of earlier-life passive smoking when everybody is hypothetically forced to follow the same later-life personal smoking pattern (e.g., everybody is forced to remain never personal smokers, everybody is forced to take up personal smoking). As everybody is controlled to have the same later-life personal smoking pattern, the direct effect of earlier-life passive smoking is isolated.

Covariates

Variables that may affect passive and/or personal smoking exposure and incident RA risks are considered confounders. A variable that lies temporally prior to a smoking exposure can be a confounder but not a mediator. However, because we have smoking exposures spanning the life course, the same covariate may be temporally ordered after an earlier smoking exposure (potential mediator), but temporally ordered before a later smoking exposure (potential confounder). Thus, from the larger set of covariates, we defined a timeline ordering the passive smoking exposures of interest, personal smoking, and additional covariates related to RA risk (**Figure 1**). For example, personal smoking during late adolescence could be considered a mediator occurring after the *in utero* smoking exposure, but be considered as a confounder for the adult passive smoking exposure.

For the *in utero* passive smoking exposure of maternal smoking during pregnancy, we considered participant's race/ethnicity, maternal and paternal education level, maternal and paternal occupation, home ownership, U.S. state at birth, and family history of RA as confounders. For the childhood parental

smoking exposure, we additionally considered preterm birth status, birthweight, breastfeeding status, and maternal smoking during pregnancy as confounders. For the adult passive smoking exposure, we additionally accounted for age at menarche, body mass index (BMI) at age 18, childhood parental smoking, personal smoking by age 19, and time-varying covariates up until 1999 (ascertainment of adult passive smoking) as confounders. Earlier exposures were considered confounders with respect to later exposures as they could be associated with later exposure and incident RA.

We additionally incorporated time-varying covariates measured during the NHSII cohort follow-up beginning in 1989, such as menopausal status and postmenopausal hormone use. Participants' personal parity and breastfeeding were self-reported. BMI was calculated from self-reported weight in kilograms / height in meters squared. Weekly hours of moderate to vigorous physical activity were calculated from a validated survey (26,27). Using the food-frequency questionnaires (28), we calculated the Alternate Healthy Eating Index (AHEI) (29,30). US residence regions were classified as New England, Mid-Atlantic, Midwest, South, and West based on zip code. Median household income was derived from the participant's address and US Census tract-level data by zip code.

Statistical analyses and modeling strategies
Participant characteristics at baseline, stratified by the categories in each of the 3 passive smoking exposure variables, were summarized by means and standard deviations and proportions as appropriate.

We employed several regression approaches to examine the total effect of passive smoking regardless of adult personal smoking and the direct effect of passive smoking accounting for adult personal smoking. We considered three separate outcomes in each analysis: all RA, seropositive RA, and seronegative RA.

First, we fit the base model using Cox proportional hazards models accounting only for the age and questionnaire cycle (calendar time). Second, we fit the confounder-adjusted models using the aforementioned passive smoking exposure-specific set of covariates that were deemed temporally preceding using Cox proportional hazards models.

Third, we accounted for the personal smoking variables in two ways: (a) the conventional time-varying regression model and (b) inverse probability weighted controlled direct effect model (a type of marginal structural model (31)). Model (b) is considered less biased and preferred in estimating the controlled direct effect although it tends to give a wider confidence interval. Both model (a) and model (b) adjusted for the personal smoking variables, but they accounted for the time-varying confounders of personal smoking variables differently. In model (a), time-varying covariates were also included in the regression model as further adjustment variables. Model (a) tends to give a more precise confidence interval, but it

can result in an estimate biased toward null due to overadjustment. We fit model (a) with the pooled logistic regression approach to ensure comparability to model (b). This approach approximates Cox regression with a rare outcome such as incident RA. The adult pack-year variable was incorporated as a 4-level ordinal time-varying covariate (zero, >0 to 10 pack-years, >10 to 20 pack-years, or >20 pack-years).

In model (b), these time-varying covariates were handled through stabilized inverse probability weights, (32) which aimed to eliminate their confounding upon the subsequent personal smoking variables while allowing for their mediating roles with respect to preceding passive smoking variables. We constructed stabilized inverse probability weights for each smoking variable using a weight denominator model, including all covariates preceding the smoking variable (including those prior to birth), and a weight numerator model, including only the covariates prior to birth. Both weight models were used to predict the probability of the smoking variable as actually observed. Adult personal smoking during the cohort follow-up was modeled as a pack-year ordinal variable (zero, >0 to 10 pack-years, >10 to 20 pack-years, or > 20 pack-years) in ordinal logistic regression models. The final stabilized inverse probability weights were constructed as the cumulative product of the stabilized inverse probability weights over time. To avoid extreme weights, we conducted "weight truncation" at 1st and 99th percentiles. (32) We fit a weighted pooled logistic regression for the incident RA outcome using the generalized estimating equation procedure.

For both models (a) and (b), we also conducted analyses stratified by the personal smoking status (life-long never smoker stratum vs. any personal smoking stratum) for passive smoking exposures that demonstrated associations with the incident RA outcome in the overall unstratified analyses. For the adult passive smoking exposure, we additionally conducted a sensitivity analysis excluding participants who were under 28 years old in 1989 as they could not have been in the 20+ years category. Analyses were conducted in SAS 9.4 (33). We provided point estimates and their 95% confidence intervals (CI).

RESULTS

Participants and descriptive analyses

Our analysis sample had n = 90,923 participants. **Table 1** shows the cohort grouped by the childhood parental smoking for major participant adult characteristics at the 1989 baseline questionnaire as well as during childhood. Mean age at baseline was 34.5 years (SD 4.7). The characteristics were mostly similar between those reporting no childhood parental smoking and any childhood parental smoking. Smoking-related variables did exhibit some differences. Personal smoking at baseline was higher among those reporting any childhood parental smoking (current and past smoking 38% vs. 26%). Maternal smoking during pregnancy was reported in 38% among those who reported any childhood parental smoking but only 1.4% among those who reported no childhood parental smoking. See **sTable**

1-3 for the full listings of characteristics stratified by each passive smoking exposure. During a median of 27.7 years of follow-up since 1989, there were a total of 532 confirmed incident RA cases. Of these, 352 incident RA cases were determined as seropositive, whereas the remaining 180 were seronegative.

Exposure (1) Maternal smoking during pregnancy (in utero exposure):

Table 2 presents the results for maternal smoking during pregnancy. This exposure was associated with all incident RA after adjustment for temporally preceding confounder variables (HR 1.25 [95% CI 1.03, 1.52]). The HR was slightly higher for the seropositive incident RA (HR 1.34 [95% CI 1.06, 1.70]). Accounting for the later-life personal smoking further reduced the point estimates toward null in all incident RA and in seropositive incident RA. Estimates were similarly unremarkable for the seronegative incident RA analyses. These direct effect estimates were similar across the conventional approach (more precise) and the controlled direct effect approach (considered less biased and preferred).

Exposure (2) Childhood parental smoking:

Table 3 presents the results for childhood parental smoking. This exposure was associated with seropositive incident RA after adjustment for temporally preceding confounder variables (HR 1.41 [95% CI 1.08, 1.83]). There was no association for all RA (1.18 [95% CI 0.96, 1.46]). Accounting for the later-life personal smoking by the conventional approach gave 1.30 [95% CI 0.99, 1.70]. On the other hand, the controlled direct effect analysis indicated a potential direct influence (1.75 [95% CI 1.03, 2.98]). These approaches gave similar non-significant results for the seronegative incident RA.

We further conducted analyses stratified by adult personal smoking status: life-long never personal smokers (n = 58,707) and ever personal smoking at any time (n = 32,216). We conducted both the conventional and controlled direct effect analyses in these two strata (**Table 4**). Increased risk for incident RA was not detected among the life-long never personal smokers. On the other hand, the controlled direct effect analyses among the adult personal smokers gave a statistically significant increased risk for seropositive incident RA (2.18 [95% CI 1.23, 3.88]), also controlling for smoking pack-years. The corresponding conventional analyses were not statistically significant.

Exposure (3) Adult passive smoking:

Table 5 presents the results for adult passive smoking as recorded as years lived with household smokers since age 18 through 1999 (aged 35–52). This exposure at the level of 1-19 years had no association with all RA or seropositive RA after adjustment for temporally preceding confounder variables. At the level of 20+ years, the point estimates were increased, but not significant. Accounting for the later-life personal smoking by the conventional approach and controlled direct effect gave null results for

both exposed levels. A sensitivity analysis excluding participants who were under 28 years old in 1989 (n=83,336) gave similar results (**sTable 4**).

DISCUSSION

In this large cohort study of women, we found that passive smoking exposure during childhood was associated with adult-onset seropositive RA, suggesting a direct influence of early-life exposures on RA risk. We performed our study using a statistical framework that accounted for the complex confounding or mediating relationships of variables occurring throughout the life course. To our knowledge, ours is the first study to comprehensively apply the life-course epidemiology framework (17,25,31) to examine RA risk using a large prospective cohort with repeated measures of exposures and covariates, and lengthy follow-up. These findings suggest that early-life inhaled exposures such as passive cigarette smoking could predispose individuals to develop RA not explained by later personal smoking behaviors. These results add to the mucosal paradigm of RA pathogenesis (5–7), where inhalants in pulmonary mucosa may trigger biologic processes that contribute to RA-related autoantibody production years before clinical RA symptoms emerge.

Personal smoking is one of the most well-established modifiable risk factors for incident RA, whereas the influence of passive smoking is less well understood (14). In a prospective cohort study utilizing the Finish Medical Birth Registry, Jaakkola and Gissler (15) examined the association of maternal smoking during pregnancy and incident RA and other polyarthritis defined as health care utilization with relevant ICD9 codes during the first 7 years of life. They found an elevated odds ratio (2.10 [95% CI 1.30, 3.40]). There was no consideration of childhood parental smoking, which could be another major source of passive smoking. Although we did examine maternal smoking during pregnancy as one of the exposures of interest, a direct comparison to Jaakkola and Gissler's study is difficult as our outcome was later-life incident RA, which does not overlap with the early-life incident RA outcome of Jaakkola and Gissler's study. In our analysis, maternal smoking during pregnancy as an *in utero* exposure was almost exclusively found among those who reported childhood parental smoking. The lack of clear association between maternal smoking and later-life incident RA in our study after accounting for childhood passive smoking and personal smoking may be partly due to the strong correlation of these two early-life passive smoking exposures. Since maternal smoking during pregnancy affects the fetus through placental transfer and not through direct inhalation, this may also explain some of the differences of this passive smoking exposure compared to the others.

In a past study utilizing the NHS prospective cohort, Costenbader et al (11) examined the association between years lived with smokers and adult all incident RA, adjusting for variables including personal smoking pack-years. They found suggestive results among both life-long never smokers (HR 1.46 [95%

CI 0.92, 2.32] for 30+ years lived with smokers) and ever adult smokers (HR 1.59 [95% CI 0.92, 2.74] for 30+ years lived with smokers). Childhood parental smoking was not associated with incident RA in this study using conventional analysis since personal smoking was the exposure of interest. As the study utilized the older NHS cohort (age 30–55 in 1976; age 36-61 at passive smoking assessment in 1982), the childhood parental exposure came from 1930–1950's, which was different from the life experience of the more contemporary NHSII cohort whose childhood parental exposure came from 1960–1970's when the negative health effects of smoking were more widely accepted. Such societal change may explain the difference between the results from the two cohorts. Also, our study had a shorter duration of years lived with a smoker due to the earlier age of assessing this exposure (age 35–52). For the exposure of years lived with smokers (20+ years category), we did have elevated point estimates in the controlled direct effect analyses (1.26 [95% CI 0.73, 2.17] for all RA and 1.62 [95% CI 0.84, 3.15] for seropositive RA), although they also did not reach statistical significance.

Another more recently published prospective cohort study utilized the French E3N cohort, a general population cohort of 98,995 French women convened in 1990 (age range at baseline 40–65 years) (16). Seror et al. examined the association of childhood and adulthood passive smoking exposures with RA defined as self-report (collected in 2008, 2011, and 2014) with billing code confirmation. To account for adult personal smoking, they stratified the analyses into life-long never smokers and ever smokers. Compared to the reference group of no passive or personal smoking exposure, the life-long never smoker with childhood passive smoking exposure had a HR of 1.43 [95% CI 0.97, 2.11]. The ever-smoker with childhood passive smoking exposure had a HR of 1.67 [95% CI 1.17, 2.39], whereas the ever-smoker without childhood passive smoking exposure had a HR of 1.38 [95% CI 1.10, 1.74]. Within the ever-smoker stratum, the comparison of childhood passive smoking exposure vs. none should give a HR of 1.67 / 1.38 = 1.21. Similar to our results, adult passive smoking was not associated with RA. Their results are in alignment with ours in that childhood passive smoking exposure in conjunction with adult personal smoking are associated with the most evidently increased risk of RA, whereas the childhood passive smoking exposure alone is less clearly associated. Our study's contribution is clarifying that the association was significant only for seropositive RA, which we ascertained through detailed medical record review, in addition to the more formal evaluation through the controlled direct effect approach.

A case-control study from the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) examined the association of passive smoking and RA (34) among life-long never smokers only. They did not find a significant association. The distinction between childhood and adulthood passive smoking was not made clearly although distinction was made between passive smoking within or before 10 years of diagnosis of RA. Our findings suggest little influence of adult passive smoking (from age 18 up to age 35–52) on RA risk when accounting for preceding confounding factors. Another case-control study used the

Mayo Clinic Biobank repository (Minnesota and Florida, USA) to study the association of RA outcome and several exposures, including passive smoking (35). Although the association of passive smoking and incident RA was not evident, they found the highest pack-years of passive smoking exposure may subject individuals at elevated incident RA risk. Our study adds to this literature by investigating more granular passive smoking information over participants' life course using repeated measures of variables collected from a prospective cohort and using causal inference methods. The potential biologic effects underpinning the association between early-life passive smoking exposures to adult-onset RA deserve future study. One possibility could be that passive smoking results in epigenetic modifications as a "first-hit" in individuals genetically predisposed to develop RA and subsequent triggers, including personal smoking, that influence immune tolerance loss, and RA-related autoantibody production years before clinical RA symptoms develop. Our controlled direct effect analyses are particularly appropriate for examining this because it enabled us to examine the influence of early-life passive smoking while conceptually intervening on the later-life personal smoking status.

A hypothetical, perfectly designed observational cohort study investigating passive smoking's direct influence on incident RA would enroll participants at conception and record passive and personal smoking status as well as other covariates in granular detail as they occur during the entire childhood and adulthood of participants. No such study exists to date and this is unlikely to happen in the future. Our study has several limitations compared to such hypothetical perfection. One is the adult cohort nature of the NHSII, which enrolled subjects at age 25–42. As our ability to ascertain incident RA is limited to the period after enrollment, we could not study early-life RA cases. This limitation is the case for all existing studies (11,16,34,35), except one (15), which did not study adult RA cases since this would have required very lengthy surveillance. Our window of observation does capture the age range in which adult incidence of RA progressively increases (36). One limitation of our adult passive smoking exposure analysis was the time point of exposure assessment at ages 35–52 since NHSII only included these questions on a single questionnaire. Longer duration of passive smoke exposure could be associated with increased RA risk. Also, post-exposure enrollment poses a potential for selection or recall bias, that is, earlier exposure could theoretically bias enrollment of exposed and unexposed individuals if the exposure affects early deaths and attitudes for participations. As deaths attributable to passive smoking before our enrollment are likely rare and the NHSII was not initially a study about smoking (rather it was initiated to study oral contraceptives), we consider such biased enrollment to be minimal. The determination of serostatus of RA cases were based on medical record review of routine care laboratory data. As such, we could not conduct an analysis that distinguished RF-positive RA and CCP-positive RA among seropositive RA since the cases diagnosed with RA prior to the 2000s did not have CCP checked for clinical purposes. Therefore, it is unclear whether the association of passive smoking with seropositive RA may have been different if examining by RF or CCP serostatus separately.

The NHSII's major strength is in the detailed collection of adult personal smoking level (pack-years of smoking collected every two years) as well as other known risk factors, such as diet and BMI. This enabled us to conduct the controlled direct effect analysis that accounted for such a rich set of time-varying variables in the inverse probability weight construction. The benefit of this analytical approach appeared in the childhood parental smoking analysis where conventional time-varying regression model produced borderline results, likely due to overadjustment by including mediators in the model, whereas the controlled direct effect approach depicted a clearer picture of the increased risk of incident RA associated with childhood parental smoking controlling for adult smoking status and pack-years. However, the potential for residual confounding still exists in our observational study.

To summarize, we found an increased risk of medical record-confirmed incident seropositive RA due to early-life passive smoking from childhood parental smoking when combined with adult personal smoking even after controlling for adult smoking pack-years. Our observations are most compatible with the "cumulative exposure" model in life-course epidemiology, in which both childhood parental smoking and later-life personal smoking increase the risk of adult incident seropositive RA. In particular, childhood passive smoking may be a risk factor that further amplifies the influence of adult personal smoking.

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Table 1. Characteristics of Women in the Nurses' Health Study II (n = 90,923) by Childhood Parental Smoking.

	Overall (n = 90,923)	No Childhood Parental Smoking (n = 32,064)	Any Childhood Parental Smoking (n = 58,859)
Adult variables at baseline in 1989			
Age, year (means (SD))	34.47 (4.66)	33.95 (4.71)	34.76 (4.60)
White race, %	92.98	91.85	93.57
Household income, %			
Quartile 1 (lowest income)	21.09	21.30	20.98
Quartile 2	34.61	35.13	34.34
Quartile 3	21.95	21.88	22.00
Quartile 4 (highest income)	22.34	21.69	22.68
Body mass index, kg/m² (mean (SD))	24.01 (4.99)	23.57 (4.69)	24.25 (5.12)
Physical activity, %*			
< 3 METs/week	14.73	14.59	14.81
≥ 3 METs/week	85.27	85.41	85.19
Menopausal status and PMH use, %			
Premenopausal	97.81	98.20	97.61
Postmenopausal and never PMH use	0.10	0.09	0.11
Postmenopausal and any PMH use	2.09	1.71	2.28
Smoking status, %			

	Overall (n = 90,923)	No Childhood Parental Smoking (n = 32,064)	Any Childhood Parental Smoking (n = 58,859)
Never smoker	65.88	73.67	61.65
Past smoker	21.64	18.25	23.48
Current smoker	12.47	8.08	14.87
Pack-years among ever smokers (Mean [SD])	11.30 (8.14)	9.6 (7.56)	11.88 (8.2)
—Childhood variables—			
Mother's occupation, %			
Professional	9.62	10.29	9.24
Other	70.98	71.05	70.97
Missing	19.40	18.67	19.79
Father's occupation, %			
Professional	23.08	25.83	21.55
Other	57.16	55.15	58.28
Missing	19.75	19.02	20.16
Maternal smoking during pregnancy, %			
No	64.98	94.56	48.84
Yes	24.87	1.39	37.78
Don't know/Missing	10.15	4.05	13.38

Abbreviations: RA: rheumatoid arthritis; SD: standard deviation; IQR: interquartile range; PMH: postmenopausal hormone use. METs: metabolic equivalents.

* Missing < 1% See **sTable 2** for the full listing of the variables.

Table 2. Hazard Ratios for rheumatoid arthritis, overall and by serologic phenotype, according to **maternal smoking during pregnancy (*in utero* exposure)** among women in the Nurses' Health Study II (n=90,923)

	RA cases/Person-years	Base model*	+Confounders**	+Adult personal smoking and covariates (conventional)†	Controlled direct effect‡
All RA					
No maternal smoking	325/1,524,879	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Maternal smoking	153/578,896	**1.23 (1.02, 1.49)**	**1.25 (1.03, 1.52)**	1.14 (0.92, 1.41)	1.10 (0.76, 1.57)
Don't know/Missing	54/236,559	1.03 (0.77, 1.37)	1.04 (0.78, 1.39)	0.98 (0.73, 1.32)	1.01 (0.64, 1.58)

Seropositive RA					
No maternal smoking	209/1,523,144	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Maternal smoking	104/578,180	**1.31 (1.03, 1.66)**	**1.34 (1.06, 1.70)**	1.12 (0.86, 1.46)	1.04 (0.67, 1.61)
Don't know/Missing	39/236,345	1.16 (0.82, 1.64)	1.21 (0.86, 1.70)	1.07 (0.75, 1.52)	1.01 (0.58, 1.75)
Seronegative RA					
No maternal smoking	116/1,521,421	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Maternal smoking	49/577,267	1.09 (0.78, 1.53)	1.10 (0.78, 1.53)	1.17 (0.79, 1.72)	1.23 (0.65, 2.32)
Don't know/Missing	15/235,895	0.79 (0.46, 1.35)	0.75 (0.44, 1.30)	0.80 (0.46, 1.39)	1.00 (0.47, 2.14)

* Adjusted for age and questionnaire cycle.

** Additionally adjusted for race/ethnicity, maternal and paternal education, maternal and paternal occupations, home ownership, state born, and family history of RA (temporally preceding confounders for the maternal smoking during pregnancy exposure).

† Additionally adjusted for adult personal smoking pack-years, childhood parental smoking, adult passive smoking (years lived with a smoker since age 18), and temporally preceding covariates (birthweight, preterm birth, breastfeeding, age at menarche, body mass index at age 18, menopausal status and hormone use, parity/breastfeeding, body mass index, physical activity, alternate healthy eating index, residence, and census income).

‡ Controlling for adult personal smoking pack-years, childhood parental smoking, adult passive smoking (years lived with a smoker since age 18) via conditioning and inverse probability weighting using temporally preceding covariates among birthweight, preterm birth, breastfeeding, age at menarche, body mass index at age 18, menopausal status and hormone use, parity/breastfeeding, body mass index, physical activity (≥ 3 metabolic equivalent), alternate healthy eating index, residence, and census income.

Table 3. Hazard ratios for incident rheumatoid arthritis, overall and by serologic phenotype, according to **childhood parental smoking at home** among women in the Nurses' Health Study II (n=90,923).

	RA cases/Person-years	Base model*	+Confounders**	+Adult personal smoking and covariates (conventional)†	Controlled direct effect‡
All RA					
No parent smoked	160/829,934	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Any parent smoked	372/1,510,400	**1.24 (1.03, 1.49)**	1.18 (0.96, 1.46)	1.11 (0.90, 1.38)	1.27 (0.84, 1.92)
Seropositive RA					
No parent smoked	95/829,037	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Any parent smoked	257/1,508,631	**1.46 (1.15, 1.84)**	**1.41 (1.08, 1.83)**	1.30 (0.99, 1.70)	**1.75 (1.03, 2.98)**

Seronegative RA					
No parent smoked	65/828,417	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Any parent smoked	115/1,506,166	0.93 (0.68, 1.26)	0.86 (0.60, 1.22)	0.85 (0.60, 1.21)	0.77 (0.40, 1.45)

* Adjusted for age and questionnaire cycle.

** Additionally adjusted for race/ethnicity, maternal and paternal education, maternal and paternal occupations, home ownership, state born, family history of RA, birthweight, preterm birth, breastfeeding, and maternal smoking during pregnancy (temporally preceding confounders for the childhood parental smoking exposure).

† Additionally adjusted for adult personal smoking pack-years and adult passive smoking (years lived with a smoker since age 18) and their preceding covariates (birthweight, preterm birth, breastfeeding, age at menarche, body mass index at age 18, menopausal status and hormone use, parity/breastfeeding, body mass index, physical activity, alternate healthy eating index, residence, and census income).

‡ Controlling for adult personal smoking pack-years and adult passive smoking (years lived with a smoker since age 18) via conditioning and inverse probability weighting using their temporally preceding covariates (birthweight, preterm birth, breastfeeding, age at menarche, body mass index at age 18, menopausal status and hormone use, parity/breastfeeding, body mass index, physical activity (≥ 3 metabolic equivalent), alternate healthy eating index, residence, and census income).

Table 4. Hazard ratio estimates for the **childhood parental smoking at home** stratified by adult personal smoking status among women in the Nurses' Health Study II.

	Life-long never personal smokers* n = 58,707			Ever personal smokers** n = 32,216		
	RA cases/Person-years	+Adult covariates (conventional)†	Controlled direct effect‡	RA cases/Person-years	+Adult personal smoking and covariates (conventional)†	Controlled direct effect‡
All RA						
No parent smoked	115/604, 161	1.00 (ref)	1.00 (ref)	45/225,773	1.00 (ref)	1.00 (ref)
Any parent smoked	188/915,414	0.99 (0.75, 1.31)	0.84 (0.41, 1.70)	184/594,986	1.35(0.94, 1.92)	1.43 (0.89, 2.32)
Seropositive RA						
No parent smoked	67/603,473	1.00 (ref)	1.00 (ref)	28/225,565	1.00 (ref)	1.00 (ref)
Any parent smoked	128/914,492	1.15 (0.81, 1.65)	0.90 (0.31, 2.61)	129/594,139	1.55 (0.99, 2.43)	**2.18 (1.23, 3.88)**
Seronegative RA						

No parent smoked	48/603,055	1.00 (ref)	1.00 (ref)	17/225,362	1.00 (ref)	1.00 (ref)
Any parent smoked	60/913,236	0.76 (0.48, 1.21)	0.79 (0.43, 1.45)	55/592,930	1.02 (0.56, 1.84)	0.74 (0.33, 1.66)

* In this stratum, no adjustment for the level of personal smoking was required as it uniformly remained zero.

** In this stratum, further adjustment for the level of adolescent and adult personal smoking was conducted.

† Adjusted for age, questionnaire cycle, race/ethnicity, maternal and paternal education, maternal and paternal occupations, home ownership, state born, family history of RA, birthweight, preterm birth, breastfeeding, and maternal smoking during pregnancy, adult personal smoking pack-years (only among adult personal smokers), adult passive smoking (years lived with a smoker since age 18) and their preceding covariates (menopausal status and hormone use, parity/breastfeeding, body mass index, physical activity (≥ 3 metabolic equivalent), alternate healthy eating index, residence, and census income).

‡ Controlling for adult personal smoking and adult passive smoking (years lived with a smoker since age 18) via conditioning and inverse probability weighting using the same covariates listed above for †.

Table 5. Hazard ratios for rheumatoid arthritis, overall and by serologic phenotype, according to **years lived with a smoker since age 18** among women in the Nurses' Health Study II (n=90,923).

	RA cases/Person-years	Base model*	+Confounders**	+Adult personal smoking and covariates†	Controlled direct effect‡
All RA					
None	267/1,314,937	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1-19 years	194/821,678	1.12 (0.93, 1.35)	1.00 (0.82, 1.23)	0.92 (0.75, 1.13)	1.00 (0.69, 1.44)
20+ years	71/203,719	**1.59 (1.22, 2.08)**	1.30 (0.97, 1.74)	0.99 (0.73, 1.35)	1.26 (0.73, 2.17)
Trend p		**p < 0.001**	p = 0.10	p = 0.91	p = 0.40
Seropositive RA					
None	169/1,313,506	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1-19 years	136/820,861	**1.26 (1.00, 1.58)**	1.07 (0.84, 1.37)	1.00 (0.78, 1.28)	1.15 (0.76, 1.75)
20+ years	47/203,301	**1.74 (1.25, 2.42)**	1.34 (0.94, 1.93)	1.05 (0.72, 1.53)	1.62 (0.84, 3.15)
Trend p		**p < 0.001**	p = 0.11	p = 0.82	p = 0.15
Seronegative RA					
None	98/1,312,174	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1-19 years	58/ 819,399	0.89 (0.65, 1.24)	0.87 (0.61, 1.24)	0.79 (0.54, 1.14)	0.77 (0.38, 1.57)
20+ years	24/203,011	1.36 (0.86, 2.14)	1.24 (0.76, 2.05)	0.89 (0.52, 1.54)	0.79 (0.31, 1.98)
Trend p		p = 0.32	p = 0.50	p = 0.61	p = 0.61

* Adjusted for age and questionnaire cycle.

** Additionally adjusted for race/ethnicity, maternal and paternal education, maternal and paternal occupations, home ownership, state born, family history of RA, birthweight, preterm birth, breastfeeding, maternal smoking during pregnancy, childhood parental smoking, age at menarche, body mass index at age 18, personal smoking by age 19, and adult covariates during NHSII follow-up (menopause and hormone use, parity/breastfeeding, BMI, physical activity, Alternative Healthy Eating Index, residence, census tract income; all updated until 1999).

† Additionally adjusted for adult personal smoking pack-years and preceding covariates during NHSII follow-up (fully time-updated).

‡ Controlling for adult personal smoking via conditioning and inverse probability weighting using the covariates listed above for ** and †.

Figure 1. Timeline of passive and personal smoking variables and covariates in the Nurses' Health Study II.

Our exposures of interest were passive smoking exposures spanning participants life course: (1) maternal smoking during pregnancy (*in utero* passive smoking); (2) childhood parental smoking (childhood passive smoking); and (3) years lived with smokers since age 18 to year 1999 (ages 35–52; adult passive smoking). In assessing the influence of passive smoking exposures, we accounted for personal (active) smoking variables, including the childhood and adolescence personal smoking and adult personal smoking in pack-years. Covariates incorporated into the analyses are shown at the bottom of the figure.

Abbreviations: NHS II: Nurses' Health Study II; RA: rheumatoid arthritis; pkyr: pack-years of personal smoking.