Arthritis & Rheumatology
Vol. 73, No. 12, December 2021, pp 2219–2228
DOI 10.1002/art.41939

American College of Rheumatology
Empowering Rheumatology Professionals

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

Kazuki Yoshida,[1] Jiaqi Wang,[2] Susan Malspeis,[2] Nathalie Marchand,[1] Bing Lu,[1] Lauren C. Prisco,[2] Lily W. Martin,[2] Julia A. Ford,[3] Karen H. Costenbader,[1] Elizabeth W. Karlson,[1] and Jeffrey A. Sparks[1]

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 were 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 factors and time-updated adulthood factors including personal smoking.

Results. Among 90,923 women, we identified 532 incident RA cases (66% seropositive) during a median of 27.7 years of follow-up. Maternal smoking during pregnancy was associated with RA after adjustment for confounders, with a hazard ratio (HR) of 1.25 (95% confidence interval [95% CI] 1.03–1.52), but not after accounting for subsequent smoking exposures. Childhood parental smoking was associated with seropositive RA after adjustment 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 adulthood personal smoking, and the association was accentuated among ever smokers (HR 2.18 [95% CI 1.23–3.88]). There was no significant association of adulthood passive smoking with RA (HR 1.30 for ≥20 years of living with a smoker versus none [95% CI 0.97–1.74]).

Conclusion. We found a potential direct influence of childhood parental smoking on adult-onset incident seropositive RA even after controlling for adulthood 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, which is characterized

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Supported by a Rheumatology Research Foundation R Bridge Award and the NIH (awards L30-AR-066953, K24-AR-052403, R01-AR-049880, R01-AR-057327, R01-AR-119246, R01-HL-034594, P30-AR-070253, P30-AR-072577, P30-AR-069625, UM1-CA-186107, U01-HG-008685, 1OT2-OD-026553, and R03-AR-075886). The Nurses' Health Study II was supported by the NIH (awards U01-CA-176726, R01-CA-67262, and U01-HL-145386). Dr. Yoshida's work was supported by a Rheumatology Research Foundation K Bridge Award, a Brigham and Women's Hospital Department of Medicine Fellowship Award, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (award K23-AR-076453). Dr. Sparks' work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (award K23-AR-069688).

[1]Kazuki Yoshida, MD, ScD, Nathalie Marchand, ScD, Bing Lu, MD, DrPH, Karen H. Costenbader, MD, MPH, Elizabeth W. Karlson, MD, Jeffrey A. Sparks, MD, MMSc: Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [2]Jiaqi Wang, MS, Susan Malspeis, MS, Lauren C. Prisco, BA, Lily W. Martin, BS: Brigham and Women's Hospital, Boston, Massachusetts; [3]Julia A. Ford, MD: University of Michigan, Ann Arbor.

Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.41939&file=art.41939-sup-0001-Disclosureform.pdf.

Address correspondence to Kazuki Yoshida, MD, ScD, Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, 60 Fenwood Road, no. 6016Q, Boston, MA 02115 (email: kazukiyoshida@mail.harvard.edu); or to Jeffrey A. Sparks, MD, MMSc, Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, 60 Fenwood Road, no. 6016U, Boston, MA 02115 (email: jsparks@bwh.harvard.edu).

Submitted for publication April 7, 2021; accepted in revised form July 29, 2021.

by the presence of autoantibodies such as rheumatoid factor (RF) and anti–citrullinated protein antibodies (ACPAs), particularly among genetically predisposed individuals (4,8).

Personal (active) smoking is the most well-established environmental risk factor for the development of RA, as demonstrated in multiple epidemiologic 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 years living with smokers and adult incident RA in the Nurses' Health Study (NHS) (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 of the link between passive smoking over the life course (maternal smoking during pregnancy while in utero, childhood passive smoking, and adulthood passive smoking) and incident RA during adulthood.

Therefore, we aimed to examine the influence of passive smoking at several stages of the life course while accounting for personal smoking behavior using a framework from the life-course epidemiology literature (17). We analyzed the NHSII prospective cohort, which provided data on both passive smoking exposure spanning the 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.

SUBJECTS AND METHODS

Participants and eligibility. We performed a cohort study based on the prospectively collected data in the NHSII. Briefly, the NHSII enrolled 116,429 female registered nurses ages 25–42 years in 1989. Since then, the prospective follow-up has continued every 2 years to date through mailed questionnaires, with >90% response rates. The questionnaires collect information on sociodemographic characteristics, anthropometrics, behaviors, medications, dietary intake, and health conditions. For the present 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 adulthood 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 3 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) adulthood passive smoking as an adulthood exposure. Information on all of these passive smoking variables was collected through additional smoking behavior questionnaire items in 1999, when women ranged in age from 35–52 years. Maternal smoking during pregnancy was then classified into 3 categories: yes, no, and missing/don't know. For childhood parental smoking, we compared any childhood parental smoking (either or both parents) versus no childhood parental smoking. Adulthood passive smoking was asked as years lived since age 18 with household smokers. In 1999, when the passive smoking questionnaire was administered, participants were ages 35–52 years old. We categorized the adulthood passive smoking exposure levels as 0 years, 1–19 years, or ≥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 who screened positive, medical records were requested and independently reviewed by 2 physicians to confirm the RA diagnosis and date of clinical onset based on the American College of Rheumatology (ACR) 1987 classification criteria (19) or the ACR/European Alliance of Associations for Rheumatology 2010 classification criteria (20). RA cases were further classified as seropositive (positivity for RF and/or ACPA, if available) or seronegative based on the results of clinical testing found in the medical record. RA cases were identified using all questionnaire cycles 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, since personal smoking behaviors temporally occur *after* earlier-life passive smoking exposure, personal smoking may serve as a "mediator". That is, the 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 risk of adult incident RA (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41939/abstract).

In the life-course analysis framework for early-life exposure that may influence later-life exposure as well as adulthood health outcomes, several types of hypotheses can be formed (17). On one extreme is the "social trajectory" model, which hypothesizes that early-life passive smoking is important *only* in that it promotes later-life uptake of personal smoking, and it 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 adulthood 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 or everybody is forced to take up personal smoking). Since 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 smoking exposures span 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 a confounder for the adulthood passive smoking exposure.

For the in utero passive smoking exposure of maternal smoking during pregnancy, we considered the participant's race and ethnicity, maternal and paternal education level, maternal and paternal occupation, home ownership, US state of birth, and family history of RA as confounders. For the childhood parental smoking exposure, we additionally considered preterm birth status, birth weight, breastfeeding status, and maternal smoking during pregnancy as confounders. For the adulthood 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 adulthood passive smoking) as confounders. Earlier exposures were considered confounders with respect to later exposures since 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 as 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 (29,30). US residence regions were classified

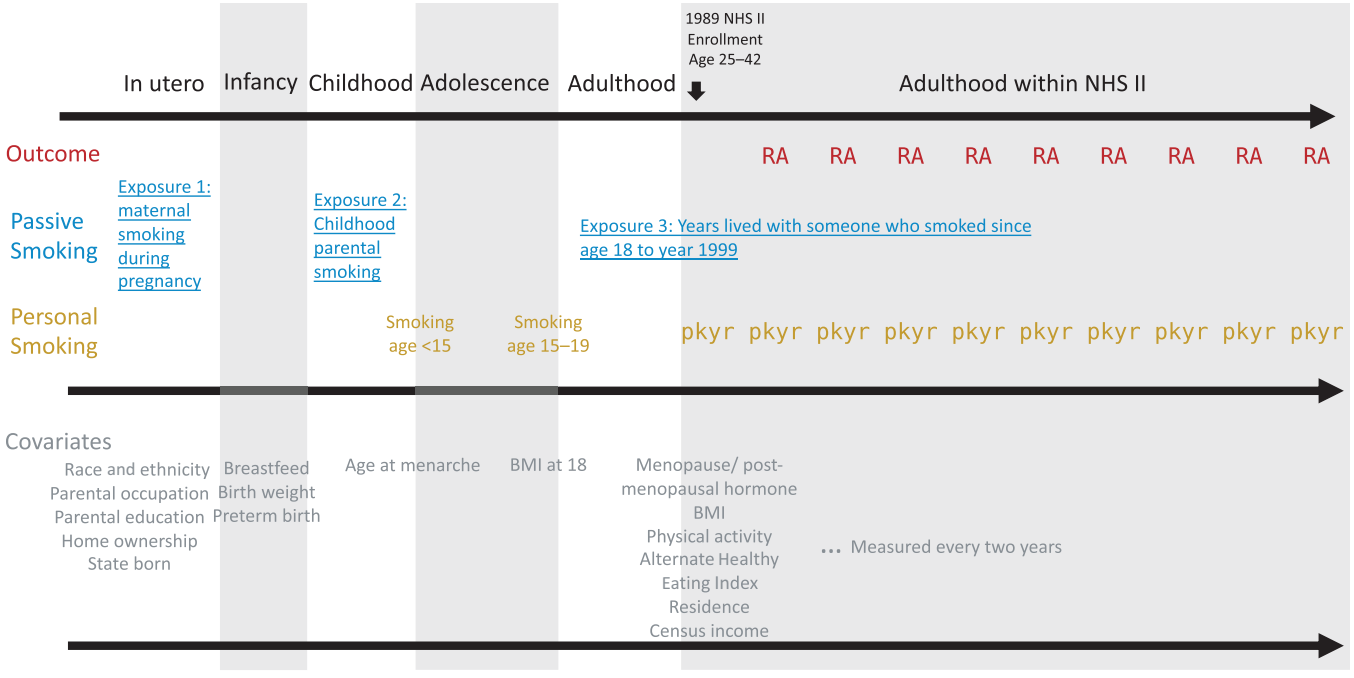

Figure 1. Time line of passive and personal smoking variables and covariates in the Nurses' Health Study II (NHSII). Exposures of interest were passive smoking exposures spanning the participants' life course: 1) maternal smoking during pregnancy (in utero passive smoking), 2) childhood parental smoking (childhood passive smoking), and 3) years lived with smokers from age 18 to 1999 (ages 35–52 years; adulthood passive smoking). In assessing the influence of passive smoking exposures on the development of rheumatoid arthritis (RA), we accounted for personal (active) smoking variables, including childhood and adolescent personal smoking and adulthood personal smoking in pack-years (pkyr). Covariates incorporated into the analyses are shown at the bottom of the figure. BMI = body mass index.

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 analysis and modeling strategies. Participant characteristics at baseline, stratified by the categories in each of the 3 passive smoking exposure variables, are summarized as the mean ± SD or proportion as appropriate.

We employed several regression approaches to examine the total effect of passive smoking regardless of adulthood personal smoking and the direct effect of passive smoking accounting for adulthood personal smoking. We considered 3 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 to be temporally preceding the exposure using Cox proportional hazards models. Third, we accounted for the personal smoking variables in 2 ways: using the conventional time-varying regression model (model A), and using the inverse probability–weighted controlled direct effect model (a type of marginal structural model [31]) (model B). Model B is considered less biased and is preferred for estimating the controlled direct effect, although it tends to yield 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 yield 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

Table 1. Childhood and baseline adulthood characteristics of women in the Nurses' Health Study II (n = 90,923), according to childhood parental smoking*

	Overall (n = 90,923)	No childhood parental smoking (n = 32,064)	Any childhood parental smoking (n = 58,859)
Adulthood variables at baseline in 1989			
Age, mean ± SD years	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
BMI, mean ± SD kg/m^2	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 used PMH	0.10	0.09	0.11
Postmenopausal and any PMH use	2.09	1.71	2.28
Smoking status, %			
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

* See Supplementary Table 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41939/abstract, for a complete list of variables. BMI = body mass index; METs = metabolic equivalents; PMH = postmenopausal hormone use.
† Data were missing for <1% of subjects.

regression approach to ensure comparability to model B. This approach approximates Cox regression with a rare outcome such as incident RA. The adulthood pack-year variable was incorporated as a 4-level ordinal time-varying covariate (0 pack-years, >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, which included all covariates preceding the smoking variable (including those prior to birth), and a weight numerator model, which included only the covariates prior to birth. Both weight models were used to predict the probability of the smoking variable as actually observed. Adulthood personal smoking during the cohort follow-up was modeled as a pack-year ordinal variable (0 pack-years, >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 the 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 (lifelong never smoker stratum versus any personal smoking stratum) for passive smoking exposures that demonstrated associations with the incident RA outcome in the overall unstratified analyses. For the adulthood passive smoking exposure, we additionally conducted a sensitivity analysis excluding participants who were younger than 28 years in 1989, since they could not have been in the ≥20 years category. Analyses were conducted in SAS version 9.4 (33). We provided point estimates and their 95% confidence intervals (95% CIs).

RESULTS

Participants and descriptive analyses. Our analysis sample included 90,923 participants. Table 1 shows adulthood (1989 baseline questionnaire) and childhood characteristics of the participants according to childhood parental smoking. The mean ± SD age at baseline was 34.5 ± 4.7 years. The characteristics were mostly similar between those reporting no childhood parental smoking and those exposed to any childhood parental smoking. Smoking-related variables did exhibit some differences. Personal smoking at baseline was higher among those reporting any childhood parental smoking (38% were current or past smokers versus 26% of those with no childhood parental smoking). Maternal smoking during pregnancy was reported for 38% of those who reported any childhood parental smoking but only 1.4% of those who reported no childhood parental smoking. See Supplementary Tables 1–3, available on the *Arthritis & Rheumatology* website at http://

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

	No. of RA cases/ no. of person-years	Base model†	Confounders‡	Adulthood personal smoking and covariates (conventional model)§	Controlled direct effect model¶
All RA					
No maternal smoking	325/1,524,879	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
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 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
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 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
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)

* Except where indicated otherwise, values are the hazard ratio (95% confidence interval).
† Adjusted for age and questionnaire cycle.
‡ Additionally adjusted for race and ethnicity, maternal and paternal education, maternal and paternal occupations, home ownership, US state of birth, and family history of rheumatoid arthritis (RA; temporally preceding confounders for the maternal smoking during pregnancy exposure).
§ Additionally adjusted for adulthood personal smoking pack-years, childhood parental smoking, adulthood passive smoking (years lived with a smoker since age 18), and temporally preceding covariates (birth weight, preterm birth, breastfeeding, age at menarche, body mass index [BMI] at age 18, menopausal status and hormone use, parity/breastfeeding, BMI, physical activity [≥3 metabolic equivalents], Alternate Healthy Eating Index, residence, and census income).
¶ Controlling for adulthood personal smoking pack-years, childhood parental smoking, adulthood passive smoking (years lived with a smoker since age 18) via conditioning and inverse probability weighting using temporally preceding covariates (birth weight, preterm birth, breastfeeding, age at menarche, BMI at age 18, menopausal status and hormone use, parity/breastfeeding, BMI, physical activity [≥3 metabolic equivalents], Alternate Healthy Eating Index, residence, and census income).
# $P < 0.05$.

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

	No. of RA cases/ no. of person-years	Base model†	Confounders‡	Adulthood personal smoking and covariates (conventional model)§	Controlled direct effect model¶
All RA					
No parent smoked	160/829,934	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
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 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
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 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
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)

* Except where indicated otherwise, values are the hazard ratio (95% confidence interval).
† Adjusted for age and questionnaire cycle.
‡ Additionally adjusted for race and ethnicity, maternal and paternal education, maternal and paternal occupations, home ownership, US state of birth, family history of rheumatoid arthritis (RA), birth weight, preterm birth, breastfeeding, and maternal smoking during pregnancy (temporally preceding confounders for the childhood parental smoking exposure).
§ Additionally adjusted for adulthood personal smoking pack-years and adulthood passive smoking (years lived with a smoker since age 18) and temporally preceding covariates (birth weight, preterm birth, breastfeeding, age at menarche, body mass index [BMI] at age 18, menopausal status and hormone use, parity/breastfeeding, BMI, physical activity [≥3 metabolic equivalents], Alternate Healthy Eating Index, residence, and census income).
¶ Controlling for adulthood personal smoking pack-years and adulthood passive smoking (years lived with a smoker since age 18) via conditioning and inverse probability weighting using temporally preceding covariates (birth weight, preterm birth, breastfeeding, age at menarche, BMI at age 18, menopausal status and hormone use, parity/breastfeeding, BMI, physical activity [≥3 metabolic equivalents], Alternate Healthy Eating Index, residence, and census income).
# $P < 0.05$.

onlinelibrary.wiley.com/doi/10.1002/art.41939/abstract, for a full listing 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 to be seropositive, whereas the remaining 180 were seronegative.

Maternal smoking during pregnancy (in utero exposure) (exposure 1). 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 (hazard ratio [HR] 1.25 [95% CI 1.03–1.52]). The HR was slightly higher for seropositive incident RA (HR 1.34 [95%

Table 4. Hazard ratios for incident RA, overall and by serologic phenotype, among women in the Nurses' Health Study II (n = 90,923), according to childhood parental smoking stratified by adulthood personal smoking status*

	Lifelong never personal smokers (n = 58,707)†			Ever personal smokers (n = 32,216)‡		
	No. of RA cases/no. of person-years	Adulthood covariates (conventional model)§	Controlled direct effect model¶	No. of RA cases/no. of person-years	Adulthood personal smoking and covariates (conventional model)§	Controlled direct effect model¶
All RA						
No parent smoked	115/604,161	1.00 (referent)	1.00 (referent)	45/225,773	1.00 (referent)	1.00 (referent)
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 (referent)	1.00 (referent)	28/225,565	1.00 (referent)	1.00 (referent)
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 (referent)	1.00 (referent)	17/225,362	1.00 (referent)	1.00 (referent)
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)

* Except where indicated otherwise, values are the hazard ratio (95% confidence interval).
† No adjustment for the level of personal smoking was required since it uniformly remained 0.
‡ Further adjustment for the level of adolescent and adulthood personal smoking was conducted.
§ Adjusted for age, questionnaire cycle, race and ethnicity, maternal and paternal education, maternal and paternal occupations, home ownership, US state of birth, family history of rheumatoid arthritis (RA), birth weight, preterm birth, breastfeeding, maternal smoking during pregnancy, adulthood personal smoking pack-years (only among adulthood personal smokers), adulthood passive smoking (years lived with a smoker since age 18), and temporally preceding covariates (menopausal status and hormone use, parity/breastfeeding, body mass index, physical activity [≥3 metabolic equivalents], Alternate Healthy Eating Index, residence, and census income).
¶ Controlling for adulthood personal smoking and adulthood passive smoking (years lived with a smoker since age 18) via conditioning and inverse probability weighting using the same covariates listed above for the conventional model.
# $P < 0.05$.

CI 1.06–1.70]). Accounting for 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).

Childhood parental smoking (exposure 2). 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 later-life personal smoking by the conventional approach resulted in an HR of 1.30 for seropositive incident RA (95% CI 0.99–1.70). In contrast, the controlled direct effect analysis indicated a potential direct influence (HR 1.75 [95% CI 1.03–2.98]). Both approaches gave similar nonsignificant results for seronegative incident RA.

We further conducted analyses stratified by adulthood personal smoking status: lifelong 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 2 strata (Table 4). Increased risk of incident RA was not detected among the lifelong never personal smokers. In contrast, controlled direct effect analysis indicated a significantly increased risk of seropositive incident RA among the adulthood personal smokers (2.18 [95% CI 1.23–3.88]), also controlling for smoking pack-years. Results of the corresponding conventional analyses were not significant.

Adulthood passive smoking (exposure 3). Table 5 presents the results for adulthood passive smoking, defined as years lived with household smokers from age 18 through 1999 (ages 35–52 years). 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 were not significant. Accounting for later-life personal smoking using the conventional approach and the controlled direct effect model gave null results for both exposure levels. A sensitivity analysis that included only participants who were ≥28 years old in 1989 (n = 83,336) yielded similar results (Supplementary Table 4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41939/abstract).

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

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

No. of years lived with a smoker	No. of RA cases/ no. of person-years	Base model†	Confounders‡	Adulthood personal smoking and covariates (conventional model)§	Controlled direct effect model¶
All RA					
None	267/1,314,937	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
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)
P for trend	–	<0.001	0.10	0.91	0.40
Seropositive RA					
None	169/1,313,506	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
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)
P for trend	–	<0.001	0.11	0.82	0.15
Seronegative RA					
None	98/1,312,174	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
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)
P for trend	–	0.32	0.50	0.61	0.61

* Except where indicated otherwise, values are the hazard ratio (95% confidence interval).
† Adjusted for age and questionnaire cycle.
‡ Additionally adjusted for race and ethnicity, maternal and paternal education, maternal and paternal occupations, home ownership, US state of birth, family history of rheumatoid arthritis (RA), birth weight, preterm birth, breastfeeding, maternal smoking during pregnancy, childhood parental smoking, age at menarche, body mass index (BMI) at age 18, personal smoking by age 19, and adulthood covariates during the Nurses' Health Study II follow-up (menopause and hormone use, parity/breastfeeding, BMI, physical activity [≥3 metabolic equivalents], Alternative Healthy Eating Index, residence, and census income; all updated until 1999).
§ Additionally adjusted for adulthood personal smoking pack-years and temporally preceding covariates during the Nurses' Health Study II follow-up (fully time-updated).
¶ Controlling for adulthood personal smoking via conditioning and inverse probability weighting using the covariates listed above for the model including confounders and the conventional model.
# $P < 0.05$.

framework that accounted for the complex confounding or mediating effects of variables that occur 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. Our 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 with incident RA and other polyarthritis, defined as health care utilization with relevant International Classification of Diseases, Ninth Revision codes during the first 7 years of life. They found an elevated odds ratio of developing disease (2.10 [95% CI 1.30–3.40]) for those exposed to maternal smoking during pregnancy. 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 in the present study, a direct comparison to the study by Jaakkola and Gissler is difficult, since our outcome was later-life incident RA, which does not overlap with the early-life incident RA outcome used in their study. In our analysis, maternal smoking during pregnancy as an in utero exposure was almost exclusively reported by those who reported childhood parental smoking. The lack of a clear association between maternal smoking and later-life incident RA, after accounting for childhood passive smoking and personal smoking, in our study may be partly due to the strong correlation of these 2 early-life passive smoking exposures. The fact that maternal smoking during pregnancy affects the fetus through placental transfer, and not through direct inhalation, may also explain some of the differences between this passive smoking exposure and 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 for both lifelong 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 using conventional analysis in that study, since personal smoking was the exposure of interest.

Since the study by Costenbader et al utilized the older NHS cohort (ages 30–55 years in 1976; ages 36–61 years at passive smoking assessment in 1982), childhood parental smoking exposure in that study occurred in the 1930s–1950s, which was different from the life experience of the more contemporary NHSII cohort, whose childhood parental smoking exposure occurred in the 1960s–1970s, when the negative health effects of smoking were more widely accepted. Such societal change may explain the difference in results between the 2 cohorts. Also, our study had a shorter possible duration of years lived with a smoker due to the earlier age at assessment of this exposure (ages 35–52 years). For the exposure "years lived with a smoker" (≥20 years category), we did find 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 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 by self-report (collected in 2008, 2011, and 2014) with billing code confirmation. To account for adulthood personal smoking, they stratified the analyses into lifelong never smokers and ever smokers. Compared to the reference group of no passive or personal smoking exposure, the lifelong never smoker with childhood passive smoking exposure had an HR of 1.43 [95% CI 0.97–2.11]. The ever-smoker with childhood passive smoking exposure had an HR of 1.67 [95% CI 1.17–2.39], whereas the ever-smoker without childhood passive smoking exposure had an HR of 1.38 [95% CI 1.10–1.74]. Within the ever-smoker stratum, the comparison of childhood passive smoking exposure versus none should yield an HR of 1.67/1.38 = 1.21.

Similar to our results, adulthood passive smoking was not associated with RA in the study by Seror et al (16). Their results are consistent with ours, in that childhood passive smoking exposure in conjunction with adulthood personal smoking were associated with the most evidently increased risk of RA, whereas the childhood passive smoking exposure alone was 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 examined the association of passive smoking and RA (34) among only lifelong never smokers. The authors did not find a significant association. The distinction between childhood and adulthood passive smoking was not made clearly, although a distinction was made between passive smoking within or before 10 years of the diagnosis of RA. Our findings suggest little influence of adulthood passive smoking (from age 18 years up to ages 35–52 years) on RA risk when accounting

for preceding confounding factors. Another case–control study used the Mayo Clinic Biobank repository (Minnesota and Florida) to study the association between RA outcome and several exposures, including passive smoking (35). Although the association of passive smoking and incident RA was not evident, they found that the highest pack-years of passive smoking exposure may subject individuals to an elevated risk of incident RA. 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 and adult-onset RA deserve further study. One possibility could be that passive smoking results in epigenetic modifications as a "first-hit" in individuals genetically predisposed to develop RA, and that subsequent triggers, including personal smoking, influence loss of immune tolerance and the production of RA-related autoantibodies years before clinical RA symptoms develop. Our controlled direct effect analyses are particularly appropriate for examining this possibility, 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 the direct influence of passive smoking 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 occurred 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 ages 25–42 years. Since our ability to ascertain incident RA was 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 analysis of adulthood passive smoking exposure was the time point of exposure assessment at ages 35–52 years, since the NHSII only included these questions on a single questionnaire. Longer duration of passive smoking exposure could be associated with increased RA risk. Also, postexposure 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 toward participation. Since deaths attributable to passive smoking before our enrollment are likely rare and the NHSII was not initiated to study smoking (but rather to study oral contraceptives), we consider such biased enrollment to be minimal.

The determination of RA serostatus was based on medical record review of routine care laboratory data. As such, we could not conduct an analysis that distinguished patients with RF-positive RA from patients with ACPA–positive RA among those with seropositive RA, since patients diagnosed as having RA prior to the 2000s did not have ACPA checked for clinical purposes. Therefore, it is unclear whether the association of passive smoking with seropositive RA may have been different if RF and ACPA serostatus were analyzed separately.

The major strength of the NHSII is in the detailed collection of data on adulthood personal smoking (pack-years of smoking collected every 2 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 the 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 adulthood 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 associated with early-life passive smoking from childhood parental smoking when combined with adulthood personal smoking, even after controlling for adulthood 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 adulthood personal smoking.

ACKNOWLEDGMENTS

The authors thank the participants of the NHSII for their dedicated participation in this longitudinal study, as well as the NHS staff members at the Channing Division of Network Medicine (Department of Medicine, Brigham and Women's Hospital and Harvard Medical School) for their assistance.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Yoshida had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Yoshida, Prisco, Martin, Sparks.

Acquisition of data. Yoshida, Wang, Malspeis, Marchand, Lu, Prisco, Martin, Ford, Costenbader, Karlson, Sparks.

Analysis and interpretation of data. Yoshida, Wang, Malspeis, Marchand, Lu, Costenbader, Karlson, Sparks.

REFERENCES

1. Benn RT, Wood PH. Mortality in rheumatoid arthritics. Br J Prev Soc Med 1972;26:60.
2. Kirwan JR. Links between radiological change, disability, and pathology in rheumatoid arthritis [review]. J Rheumatol 2001;28: 881–6.
3. Yoshida K, Lin TC, Wei MY, Malspeis S, Chu SH, Camargo CA, et al. Accrual of multimorbidity after incident rheumatoid arthritis and matched comparators using a large prospective cohort with 30 years of follow-up [abstract]. Arthritis Rheumatol 2019;71 Suppl 10. URL: https://acrabstracts.org/abstract/accrual-of-multimorbidity-after-incident-rheumatoid-arthritis-and-matched-comparators-using-a-large-prospective-cohort-with-30-years-of-follow-up/.
4. Sparks JA, Costenbader KH. Genetics, environment, and gene-environment interactions in the development of systemic rheumatic diseases [review]. Rheum Dis Clin North Am 2014;40:637–57.
5. Demoruelle MK, Solomon JJ, Fischer A, Deane KD. The lung may play a role in the pathogenesis of rheumatoid arthritis. Int J Clin Rheumatol 2014;9:295–309.
6. Sparks JA, Karlson EW. The roles of cigarette smoking and the lung in the transitions between phases of preclinical rheumatoid arthritis [review]. Curr Rheumatol Rep 2016;18:15.
7. Demoruelle MK, Wilson TM, Deane KD. Lung inflammation in the pathogenesis of rheumatoid arthritis [review]. Immunol Rev 2020;294:124–32.
8. Sparks JA, Chen CY, Jiang X, Askling J, Hiraki LT, Malspeis S, et al. Improved performance of epidemiologic and genetic risk models for rheumatoid arthritis serologic phenotypes using family history. Ann Rheum Dis 2015;74:1522–9.
9. Voigt LF, Koepsell TD, Nelson JL, Dugowson CE, Daling JR. Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis. Epidemiology 1994;5:525–32.
10. Criswell LA, Merlino LA, Cerhan JR, Mikuls TR, Mudano AS, Burma M, et al. Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal women: results from the Iowa Women's Health Study. Am J Med 2002;112:465–71.
11. Costenbader KH, Feskanich D, Mandl LA, Karlson EW. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. Am J Med 2006;119:503–11.
12. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies [review]. Ann Rheum Dis 2010;69:70–81.
13. Di Giuseppe D, Discacciati A, Orsini N, Wolk A. Cigarette smoking and risk of rheumatoid arthritis: a dose-response meta-analysis. Arthritis Res Ther 2014;16:R61.
14. Prisco LC, Martin LW, Sparks JA. Inhalants other than personal cigarette smoking and risk for developing rheumatoid arthritis [review]. Curr Opin Rheumatol 2020;32:279–88.
15. Jaakkola JJ, Gissler M. Maternal smoking in pregnancy as a determinant of rheumatoid arthritis and other inflammatory polyarthropathies during the first 7 years of life. Int J Epidemiol 2005;34:664–71.
16. Seror R, Henry J, Gusto G, Aubin HJ, Boutron-Ruault MC, Mariette X. Passive smoking in childhood increases the risk of developing rheumatoid arthritis. Rheumatology (Oxford) 2019;58:1154–62.
17. Liu S, Jones RN, Glymour MM. Implications of lifecourse epidemiology for research on determinants of adult disease [review]. Public Health Rev 2010;32:489–11.