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Childhood socioeconomic factors and perinatal characteristics influence development of rheumatoid arthritis in adulthood

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Abstract

Background—Rheumatoid arthritis (RA) has been associated with lower socioeconomic status (SES), but the reasons for this are not known.

Objective—To examine childhood SES measures, SES trajectory and other perinatal factors in relation to RA.

Methods—The sample included 50 884 women, aged 35–74 (84% non-Hispanic white) enrolled 2004–9 in a US national cohort study. In baseline questionnaires, cases (N=424, 0.8%) reported RA diagnosis after age 16, ever use of disease-modifying antirheumatic drugs or steroids for RA and 6 weeks bilateral joint swelling. Childhood SES measures are presented as OR and 95% CI adjusted for age and race/ethnicity. Analyses of perinatal factors also adjusted for childhood SES, and joint effects of childhood and adult SES and smoking exposures were evaluated.

Results—Patients with RA reported lower childhood household education (<12 years vs college degree; OR=1.7; 95% CI 1.1 to 2.5), food insecurity (OR=1.5, 95% CI 1.1 to 2.0) and young maternal age (<20 vs 20–34 years; OR=1.7, 95% CI 1.2 to 2.5), with a trend ($p<0.0001$) for increasing number of adverse factors (OR=3.0; 95% CI 1.3 to 7.0; 4 vs 0 factors) compared with non-cases. High birth weight (>4000 g) and preconception paternal smoking were independently associated with RA. Together, lower childhood SES and adult education (<college degree) were associated with RA (interaction $p=0.03$), with a joint effect magnitude similar to a history of paternal and adult smoking.

Conclusions—RA was associated with low childhood SES sustained into adulthood, with cumulative effects across multiple measures, suggesting the importance of other unmeasured factors linking SES and RA.

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Competing interests None.

Low socioeconomic status (SES) is an established risk factor, with research showing that early life and cumulative life-course SES is associated with adult inflammatory conditions.^{1–4} Rheumatoid arthritis (RA) has been associated with lower adult educational attainment and occupational class,^{5,6} but few studies have examined the role of childhood SES. One described an association of RA with paternal manual occupation,⁷ while another showed no association with relative childhood affluence.⁶ Knowledge is limited on the role of childhood SES in the context of perinatal factors or adult SES.

The developing immune system is especially sensitive to environmental stressors.^{8,9} Childhood-onset autoimmune diseases, such as type-1 diabetes, juvenile arthritis and myositis, have been associated with perinatal factors, including maternal smoking,¹⁰ birth weight¹¹ and birth season.^{12,13} Research on early life risk factors for adult-onset autoimmune diseases is less abundant; for RA, higher birth weight is the most consistently reported,^{7,14} though not seen in all studies.¹⁵ Having been breast fed was protective in one small study,⁷ but not in another larger study.¹⁶ Early life infections and having older siblings were associated with RA in one study.¹⁵

In a large cohort of US women, the Sister Study, we investigated the relationship between childhood socioeconomic factors and adult-onset RA. We also examined associations with perinatal factors in the context of childhood SES and evaluated the combined effects of childhood and adult SES and paternal and adult smoking.

METHODS

Study sample and design

We conducted a case–control analysis using baseline data from the NIEHS Sister Study cohort (N=50 884; enrolled 2004–9), women aged 35–74 with a sister with breast cancer, but without a diagnosis of breast cancer themselves at enrolment.^{17,18} Participants, identified through self-referral after a broad advertising campaign throughout the USA, included women from the South (33%), Midwest (27%), West (22%), Northeast (17%) and Puerto Rico (2%). The Sister Study was approved by the institutional review board of the National Institute of Environmental Health Sciences, NIH. Participants provided written informed consent.

Participants were mailed questionnaires on perinatal factors and encouraged to contact their mother or relatives to assist with questions about early life factors. Sociodemographic data, residential history, lifestyle factors, personal medical history and medication use were collected by telephone interview.

Defining cases and the analysis sample

Women were asked if a doctor had ever diagnosed them with RA. Positive responses were followed with questions about age at diagnosis and symptoms—such as, ‘Have you ever had swelling in your wrist, finger, elbow or knee joints lasting 6 weeks,’ and ‘Have you ever had symptoms on both sides of your body?’ Women were asked about medication use, including current and longest used drug for RA and were referred to a list of disease-modifying antirheumatic drugs (DMARDs).

Excluding women missing data on RA diagnosis or diagnosis age (N=96), 1869 (3.7%) reported RA diagnosed at age 16 (online supplementary figure). Of these, 29% reported DMARD use and 49% reported joint swelling and bilateral symptoms, while 10% also reported another autoimmune disease (lupus, inflammatory bowel disease or multiple sclerosis). We defined cases (n=424; 0.83% of the cohort) as self-reported RA with any current or past DMARD use and bilateral swelling, or steroid use for RA and bilateral swelling in the absence of another autoimmune disease. Median diagnosis age was 47 years; more than 50% reported diagnosis since 1997 and 25% since 2002. All other self-reported RA cases were excluded from analysis. Controls were 48 919 participants reporting no RA, including 188 answering 'don't know.'

Early life factors and other variables

Data on childhood SES included food insecurity ('When you were growing up, were there times your family didn't have enough to eat?'), highest household education level of parent or legally responsible adult when respondent was age 13, single parent household (age 13), self-assessed household income while growing up (well off, middle income, low income or poor) and maternal and paternal age at participants' birth. Mother's age was grouped to reflect younger (<20 years) and older (>34 years) maternal age; father's age used a higher cut-off point for the youngest group (<24 years). A cumulative summary score included four factors initially related to RA: lower education (high school), low income or poor, young maternal age and food insecurity.

Data on perinatal factors included paternal smoking 3 months before conception, prenatal maternal and household smoking, birth weight (pounds and ounces), birth order and breast feeding. Participants unable to report exact birth weight were asked about low birth weight (<5 lb (2270 g)); responses were grouped by standard categories (<2500; 2500–3499; 3400–3999; 4000 g).

Birth date was grouped into four seasons (eg, winter: December–February). Participants born in the USA were asked about their longest residence before age 14 and grouped by state into (1) census regions (West, Midwest, Northeast, Southeast, Puerto Rico) and (2) regions stratified by 40th and 35th parallels. Other factors (multiple birth, gestational age, soy formula use, maternal or gestational diabetes, pregnancy hypertension or pre-eclampsia, DES exposure) were not considered owing to low prevalence or large amounts of missing data.

Additional variables were participant age (baseline), race/ethnicity (non-Hispanic white, black, Hispanic and other), educational attainment (<12 years, high-school degree, some college/associate/technical degree, college graduate/bachelor's degree, graduate/professional degree) and smoking pack-years.

Analyses

Analyses were conducted in SAS (version 9.2, SAS Institute, Cary, North Carolina, USA). For variables with suggestive associations with RA (ie, general association $p < 0.10$), logistic regression was used to estimate OR and 95% CI. Significant findings were those in which the 95% CI excluded the null, corresponding to a two-sided $p < 0.05$. All models were age

adjusted, with covariates prespecified to test for potential confounding by race (for associations with SES factors) and by SES score (for perinatal factors). Both sets of models are presented to show lack of confounding. Analyses excluded subjects with missing values for main variables or covariates in multivariate models. A trend test for childhood SES score was based on an ordinal five-level variable. Analyses did not adjust for adult factors, except for age and when noted to illustrate independence of childhood effects.

We modelled combined effects of lower childhood SES (score of 2) and lower adult SES (<college bachelor's degree) and combined effects of preconception paternal smoking and personal smoking, independently and mutually adjusted for both sets of combined variables, age and race. We tested for interaction of childhood/adult SES, adding a product term to a model including two-level SES and education terms, age, race, paternal smoking and pack-years smoking.

Several sensitivity analyses were conducted: (1) excluding women aged <45 or >64 years, (2) excluding women with sisters in the cohort, (3) limiting the cohort to non-Hispanic whites and (4) using alternate case definitions—for example, including all RA with DMARD or steroid use for RA

RESULTS

Table 1 shows demographics and smoking history by RA status. Several adverse childhood SES factors were more common in RA cases (table 2). In age- and race-adjusted models, RA was associated with lower household education, low or poor household income, food insecurity and young maternal age. A trend was seen for increasing childhood SES score ($p<0.0001$), which remained Significant ($p=0.001$) adjusting for adult education and smoking pack-years (also independently associated with RA; not shown). Older maternal age was modestly associated with RA (35 vs 20–34 years).

Table 3 shows the frequency of perinatal factors by RA status and associations adjusting for age, race and childhood SES score. Paternal smoking 3 months before conception was Significantly associated with RA. A similar association for non-maternal prenatal household smoking was not Significant after adjusting for childhood SES. In participants who never smoked ($n=168$ cases), the association for paternal smoking remained (age and race-adjusted OR=1.4, 95% CI 1.0 to 1.9; $p=0.046$). The RA association with high birth weight remained after adjusting for adult education and smoking (OR=1.5, 95% CI 1.0 to 2.1; $p=0.04$). Sibling number was modestly associated with RA, but the association was attenuated and no longer Significant after adjusting for childhood SES. Being breastfed, birth order, birth season and region or latitude of childhood residence were not associated with RA.

The association of RA with childhood SES score was only seen in those with lower adult educational attainment (<college degree)(table 4). The interaction of childhood SES score and lower adult education was Significant ($p=0.03$), adjusting for age, race, paternal smoking and smoking pack-years. Preconception paternal smoking in the absence of adult smoking was modestly associated with RA and only slightly increased risk of RA associated

with adult smoking, suggesting no interaction. SES and smoking associations were unchanged in a model including both sets of combined variables.

Sensitivity analyses showed no substantial changes for RA associations with early life SES factors, perinatal smoking and birth weight excluding women aged <45 or >65 years (online supplementary table), limited to non-Hispanic whites and excluding women with one or more sisters in the cohort. Similar associations were seen using alternate case definitions.

DISCUSSION

Our findings are consistent with an association of childhood socioeconomic factors and adult diagnosis of RA in this national, volunteer cohort of women. Few previous studies have examined the role of childhood SES in RA and ours is the first to examine multiple measures and consider combined effects with adult SES, reflecting lifetime SES trajectory.

Childhood SES and SES trajectory

The association of RA and low childhood SES is supported by findings with several measures. A graded effect was seen across decreasing household education. For income, the primary difference was between middle and low income. A population-based study in Denmark reported no association of self-assessed childhood affluence and adult RA.⁶ Two studies of parental occupational class have shown significant associations with RA: a Swedish registry study reported an association of adult RA with father's occupation as manual worker,⁷ while childhood RA in Finland was associated with blue collar maternal occupation.¹⁰ Our findings for household education and income may reflect unmeasured factors, including parental occupation and absence of material resources.

Ours may be the first study to examine RA and childhood food insecurity, a relatively new concept reflecting regular access to nutritious foods in developed countries. Childhood food insecurity has been related to a variety of behavioural and health outcomes.¹⁷ In our data, food insecurity was associated with young maternal age, lower household education and income and paternal smoking. However, in a mutually adjusted model, including adult education and smoking, associations persisted for both food deprivation and young maternal age (not shown). Ours may also be the first study to report an association of RA with younger maternal age. A registry-based study of early adult RA (ages 16–29) showed no association with maternal age.¹⁵ In the USA, younger maternal age is a risk factor associated with poverty and may relate to other factors, including prenatal stress. We saw a modest association of RA with older maternal age, which can contribute to a variety of perinatal outcomes, including fetal macrosomia.¹⁸ Adjusting for birth weight did not change our observed effect for older mothers (not shown).

SES is a complex construct, encompassing multiple factors. Lower SES may relate to adversities associated with a lack of material or other resources. Summing across four factors associated with RA risk, we noted an apparent cumulative effect. Educational attainment may predict several aspects of adult SES, including higher income and occupational status, so we modelled SES trajectory using the childhood score stratified by adult education. Our findings indicate that lower childhood SES was associated with RA

primarily in women who remained on a low SES trajectory. Life-course epidemiology suggests various models relating early life factors to outcomes¹⁹; our findings do not support the idea that lower childhood SES alone increases RA risk, but are consistent with a cumulative effect of lower SES throughout the lifespan.

The observed RA/SES association was not due to smoking, an established RA risk factor.²⁰ Adjusting for childhood SES score slightly attenuated associations with maternal and perinatal factors and we cannot rule out the possibility of a role for other SES-related exposures, including environmental pollutants or psychosocial stress.^{21,22} Low SES may increase frequency, intensity, or vulnerability to stress exposures.²³ Low childhood or life-course SES has been related to adult differences in neuroendocrine and proinflammatory signalling,²⁴ diurnal cortisol regulation²⁵ and C-reactive protein levels.² Abnormal hypothalamic pituitary adrenal (HPA) axis function (eg, cortisol response) in RA is well described, though a causal role is unclear.^{26,27} Still, many publications relate HPA function and the sympathetic nervous system to immune dysregulation.²⁸

Paternal smoking and birth weight

Smoking contributes to development of anticitrullinated autoantibodies in RA and may act through other mechanisms to increase the risk of autoimmune diseases.²⁹ Prenatal maternal smoking³⁰ and early postnatal exposure to second-hand smoke³¹ can affect the neonatal and developing immune function. Maternal smoking in pregnancy was associated with childhood RA in one study,¹⁰ but another large study reported no association with living with a parent who smoked.²⁰ In our study, prenatal exposure to non-maternal household smoking and paternal smoking before conception were associated with RA. Mechanisms relating preconception paternal smoking to RA are not known and associations may be difficult to isolate from other prenatal and childhood smoking exposures. Indeed, 96% of cohort participants with prenatal non-maternal household smoking also reported preconception paternal smoking. Most of the non-maternal household smoking is probably due to paternal smoking. However, we viewed paternal preconception smoking as the least confounded marker for early, non-maternal secondhand, smoke since having additional non-parent smokers in the home may be associated with other adverse SES indicators. Given the importance of smoking in RA pathogenesis, these findings support further investigation of early and sustained secondhand smoking in RA.

Our observed association of RA with higher birth weight is consistent with two other studies,^{7,16} and a third showing a non-significant association with large-for-gestational age at birth.¹⁵ The association is probably an underestimate owing to non-differential exposure misclassification. Cortisol dysregulation has been proposed as a mechanism for the effects of birth weight and RA,³² suggesting an interesting link with SES findings

Other risk factors

RA was associated with larger sibships, but not with being firstborn. We saw no association with birth season, which is sometimes considered a proxy for potential infectious exposures in early life; however, analyses considering birth date as a continuous variable may be more sensitive.¹³ In the Nurses' Health Study cohorts, RA was associated with adult residence in

northeastern USA,³³ but we saw only a modest excess in RA for longest childhood residence in the northeast compared with the midwest. We also saw no RA association with latitude, overall or limited to the 47% with residential data within 1 year of birth (not shown).

We saw no age-adjusted association with being breast fed and RA. One study reported an inverse association of RA with breast feeding, but findings in larger studies have been mixed.⁷¹⁶ Breast feeding might interact with other factors affecting breast milk as a source of organic pollutants.³⁴

Limitations

If disease severity were related to lower cohort participation by RA cases with lower SES, then our associations might be underestimates. Because age is a risk factor for RA, we had a higher ratio of controls to cases at younger ages. Age was related to childhood socioeconomic indicators—younger women were less likely to report factors in the childhood SES score (47% of women aged 35–44 had no factors, versus 29% of women d >64—not shown). However, excluding younger (<45) or older (>64) women had no notable impact on our main findings for SES, paternal smoking and birth weight. Sisters may share early life experiences; 19% of the cohort had more than one sister enrolled, but our main findings were unchanged in analyses limited to women without sisters in the cohort (not shown).

False-positive RA self-reporting is common. Although DMARD-based case definitions are more specific, they are not highly sensitive.³⁵ Estimated RA prevalence in this cohort (0.83%) is reasonable compared with population estimates. However, our definition including DMARDs plus joint swelling and bilateral symptoms favoured patients with moderate to severe disease, which might have biased the results if lower SES increases the likelihood of having RA. Similar associations were seen including all cases reporting DMARD or steroid-use for RA. Reliance on DMARDs for case definition may still have excluded some lower SES cases with less access to subspecialty care.

Recall of early life factors is not expected to vary by RA case status; non-differential errors might have biased observed associations towards the null. The extent to which we might have underestimated associations may vary by exposure; self-reporting of fetal smoke exposure has been shown to be a good proxy for maternal report,³⁶ but one study suggested only moderate agreement between paternal social class as recalled in adults compared with measures in early life.³⁷ Preliminary results from a Sister Study comparison of participant response with data collected from their mothers suggested good agreement for the variables examined (personal communication, AAD). Timing of adult education and smoking was not examined relative to RA diagnosis age, though probably occurred before onset in most cases. Breast cancer risk factors may be enriched in the cohort, which might increase the power to detect associations with rare exposures. Multiple testing seems an unlikely reason for the associations noted, given the consistent associations across SES measures and findings on smoking and birth weight supported by existing publications.

CONCLUSIONS

Using multiple indicators of lower childhood SES, we saw individual associations and a dose–response for cumulative SES score with RA. This association was primarily seen in women with lower adult education, supporting the hypothesis that sustained experience of lower SES may be a risk factor for RA. The joint effect of lower childhood SES and adult education was of similar magnitude to having both a paternal and personal smoking history. Lower SES represents a wide range of factors and experiences that may contribute to disease risk. Identifying the role of underlying developmental, environmental and psychosocial factors is an important next step.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic characteristics and smoking history of patients with and without rheumatoid arthritis (RA)

Characteristics	Non-cases* (N=48 919)	Cases (N=424)		p Value [†]
	N (%)	N (%)	N (%)	
Age (at interview), years		Median	Median	<0.0001
36–44	6459 (13)	41 years	27 (6)	42 years
45–54	16 987 (35)	50	117 (28)	51
55–64	17 108 (35)	59	178 (42)	59
65	8361 (17)	68	102 (24)	68
Missing	4	0		
Race/ethnicity				0.04
Non-Hispanic white	41 140 (84)		342 (81)	
Black	4278 (9)		41 (10)	
Hispanic	2214 (5)		31 (7)	
Other	1272 (3)		10 (2)	
Missing	15		0	
Current education				<0.0001
High school or less	7339 (15)		86 (20)	
Some college/technical degree	16 431 (34)		168 (40)	
College BA degree	13 331 (27)		86 (20)	
Graduate or professional degree	11 806 (24)		84 (20)	
Missing	12		0	
Pack-years smoking				<0.0001
Never smoked	26 451 (56)		184 (45)	
Smoked (quintiles pack-years)				
2	4635 (10)		39 (10)	
2–7	4338 (9)		35 (9)	
7–14	3837 (8)		41 (10)	
14–26	4160 (9)		46 (11)	
>26	4111 (9)		50 (14)	
Missing	1387		19	

* Excluding other possible and unlikely cases with self-reported rheumatoid arthritis.

[†] Test of general association, excluding missing responses; percentage with missing data was very low for most covariates, except smoking pack-years (2.8% non-cases and 4.5% cases).

Table 2

Associations of childhood socioeconomic factors with rheumatoid arthritis (RA)

Socioeconomic factors	Non-cases* (N=48 919)	Cases (N=424)	OR (95% CI) [†]	
	N (%)	N (%)	Age-adjusted	Age and race-adjusted
Household education (highest)				
Graduate/professional degree	5136 (11)	30 (7)	Ref	Ref
College graduate (BA)	7999 (16)	56 (13)	1.2 (0.76 to 1.8)	1.2 (0.75 to 1.8)
Some college/technical degree	9196 (19)	67 (16)	1.2 (0.77 to 1.8)	1.2 (0.76 to 1.9)
High-school graduate	17 289 (36)	158 (38)	1.5 (1.0 to 2.2)	1.5 (1.0 to 2.2)
Less than high school	8739 (18)	108 (26)	1.8 (1.2 to 2.7)	1.7 (1.1 to 2.5)
Missing	560	5		
Relative income				
Well off	3143 (6)	24 (6)		
Middle income	29 342 (60)	222 (52)	Ref	Ref
Low income	12 524 (26)	136 (32)	1.3 (1.1 to 1.6) [‡]	1.3 (1.0 to 1.5)
Poor	3793 (8)	41 (10)		
Missing	117	1		
Food insecurity				
No	44 402 (91)	366 (86)	Ref	Ref
Yes	4483 (9)	58 (14)	1.6 (1.2 to 2.1)	1.5 (1.1 to 2.0)
Missing	34	0		
Maternal age, years				
35	8640 (18)	87 (21)	1.3 (1.1 to 2.6)	1.3 (1.0 to 1.7)
20–34	36 690 (77)	291 (71)	Ref	Ref
<20	2250 (5)	33 (8)	1.8 (1.3 to 2.6)	1.7 (1.2 to 2.5)
Missing	1339	13		
Paternal age, years				
35	15 158 (33)	137 (35)	1.2 (0.94 to 1.5)	1.2 (0.93 to 1.4)
24–34	25 414 (56)	202 (52)	Ref	Ref
<24	4965 (11)	51 (13)	1.3 (0.96 to 1.8)	1.3 (0.93 to 1.7)
Missing	3382	34		
Single parent household				
No	44 228 (90)	380 (90)	Ref	Ref
Yes	4680 (10)	44 (10)	1.2 (0.84 to 1.6)	1.1 (0.80 to 1.5)
Missing	11	0		
Number of early life SES factors [§]				
None	17 300 (37)	113 (28)	Ref	Ref
1	15 858 (34)	124 (31)	1.1 (0.88 to 1.5)	1.1 (0.87 to 1.5)
2	10 389 (22)	126 (31)	1.7 (1.3 to 2.2)	1.6 (1.2 to 2.1)
3	3147 (7)	36 (9)	1.6 (1.1 to 2.4)	1.5 (1.0 to 2.2)
4	257 (1)	6 (2)	3.3 (1.4 to 7.5)	3.0 (1.3 to 7.0)

Socioeconomic factors	Non-cases* (N=48 919)	Cases (N=424)	OR (95% CI) [†]	
	N (%)	N (%)	Age-adjusted	Age and race-adjusted
Missing	1968	19		

* Excluding other possible and unlikely cases with self-reported RA; In non-cases, the percentage missing ranged from <0.5% for most variables to 2.7% missing maternal age and 7% missing paternal age; 4% were missing on the summary SES score, which was similar for cases. Percentages shown in the table reflect unadjusted comparisons excluding missing data.

[†] Logistic regression models adjusted for age, or age and race/ethnicity (non-Hispanic white, Hispanic, black, other), excluding missing data.

[‡] No difference low income versus poor, so groups were combined to compare low income/poor versus middle income/well-off.

[§] Summary score: one or more early life factors (high-school household education, low/poor relative household income, young maternal age, food insecurity); p for trend <0.0001 for both models shown.

SES, socioeconomic status.

Table 3

Perinatal and maternal characteristics: associations with RA adjusted for age, race and childhood SES score

Characteristics	Non-cases [*] (N=48 919)	Cases (N=424)	OR (95% CI) [†]	
	N (%)	N (%)	Age, race-adjusted	Also adjusted for childhood SES score
Smoking during pregnancy				
None	14 893 (34)	113 (30)	Ref	Ref
Maternal only	3336 (8)	19 (5)	0.84 (0.51 to 1.4)	0.86 (0.53 to 1.4)
Household only	14 430 (33)	151 (41)	1.3 (1.1 to 1.7)	1.3 (0.98 to 1.6)
Maternal + other household	10 563 (24)	89 (24)	1.2 (0.89 to 1.6)	1.2 (0.88 to 1.6)
Missing	5697	52		
Paternal smoking (3 months before conception)				
No	15 162 (34)	105 (27)	Ref	Ref
Yes	29 738 (66)	284 (73)	1.4 (1.1 to 1.7)	1.3 (1.0 to 1.6)
Missing	4019	35		
Breast fed (ever)				
No	22 779 (51)	171 (45)	Ref	Ref
Yes	21 726 (49)	221 (55)	1.0 (0.84 to 1.3)	1.0 (0.82 to 1.3)
Missing	4414	42		
Birth weight (g)				
<2500	3260 (9)	28 (9)	1.0 (0.66 to 1.5)	1.0 (0.67 to 1.5)
2500–<3000	8271 (24)	65 (22)	0.97 (0.71 to 1.3)	0.95 (0.70 to 1.3)
3000–<3500	13 654 (38)	113 (37)	Ref	Ref
3500–<4000	7208 (19)	52 (17)	0.87 (0.62 to 1.2)	0.90 (0.65 to 1.5)
4000	3374 (9)	43 (14)	1.5 (1.1 to 2.2)	1.5 (1.1 to 2.1)
Missing	13 152	123		
Number of siblings [‡]				
1	5922 (12)	47 (11)	Ref	Ref
2–3	21 226 (44)	174 (42)	1.1 (0.80 to 1.5)	1.1 (0.79 to 1.5)
4–5	11 795 (25)	92 (22)	1.1 (0.74 to 1.5)	1.0 (0.69 to 1.4)
6	9158 (19)	105 (25)	1.5 (1.0 to 2.1)	1.3 (0.94 to 1.9)
Missing	818	6	0.029	0.14
Birth order				
Firstborn	11 042 (24)	111 (28)	Ref	Ref
2nd–3rd	21 593 (47)	165 (42)	0.84 (0.66 to 1.1)	0.85 (0.67 to 1.1)
4th–5th	9062 (20)	73 (19)	0.96 (0.71 to 1.3)	0.95 (0.70 to 1.3)
6th	4320 (9)	44 (11)	1.2 (0.83 to 1.7)	1.1 (0.78 to 1.6)
Missing	2902	31		
Birth season				
Winter (December–February)	11 825 (24)	101 (24)	Ref	Ref
Spring (March–May)	11 806 (24)	104 (24)	1.0 (0.79 to 1.4)	1.0 (0.77 to 1.3)

Characteristics	Non-cases [*] (N=48 919)	Cases (N=424)	OR (95% CI) [†]	
	N (%)	N (%)	Age, race-adjusted	Also adjusted for childhood SES score
Summer (June–Aug)	12 737 (26)	103 (24)	0.95 (0.72 to 1.3)	0.98 (0.74 to 1.3)
Fall (Sept–Nov)	12 551 (26)	116 (27)	1.1 (0.84 to 1.4)	1.1 (0.80 to 1.4)
Childhood residence USA [§]				
West	6844 (14)	59 (14)	1.1 (0.82 to 1.5)	1.1 (0.81, 1.6)
Mid-west	16 944 (36)	127 (30)	Ref	Ref
Northeast	11 735 (25)	112 (27)	1.3 (0.98 to 1.6)	1.3 (0.99, 1.7)
Southeast	11 066 (23)	100 (24)	1.2 (0.90 to 1.5)	1.2 (0.92, 1.6)
Puerto Rico	843 (2)	19 (5)	1.8 (0.87 to 3.5)	1.7 (0.80, 3.6)
Latitude				
At or below 35 degrees	7633 (16)	83 (20)	Ref	Ref
35 up to 40 degrees	11 122 (23)	100 (24)	0.94 (0.69 to 1.3)	0.98 (0.72, 1.3)
Above 40 degrees	28 677 (61)	234 (56)	0.87 (0.66 to 1.1)	0.88 (0.66, 1.2)
Outside USA/missing	1487	7		

^{*} Excluding other possible and unlikely cases with self-reported RA; in non-cases, the percentage with missing data ranged from 1.6% for number of siblings to 8% paternal preconception smoking and 27% for birth weight. The percentage with missing data was similar for cases. Percentages shown in table reflect unadjusted comparisons excluding missing data.

[†] Logistic regression models adjusted for age and race/ethnicity (non-Hispanic white, Hispanic, black, other) and also adjusted for five-level SES score; excluding missing values.

[‡] Trend p=0.028 for age- and race/ethnicity-adjusted model and p=0.14 after also adjusting for SES score.

[§] Self-report for those born in USA and Puerto Rico, based on longest childhood residence before age 14, grouped by census tract region (eg, West, Midwest, etc), or latitude. Missing includes subjects with longest childhood residence outside the USA (n=1126 non-cases, 6 cases) or missing childhood state residence data (n=360 non-cases, 1 case).

SES, socioeconomic status.

Table 4

Joint effects of childhood and adulthood factors

Adult characteristics	Childhood characteristics	OR (95% CI)	
		Age, race-adjusted [*]	Mutually-adjusted for SES and smoking-joint effects [†]
Educational attainment	Childhood SES score		
College degree	None or one	Referent	Referent
	Two or more	1.1 (0.73 to 1.6)	1.1 (0.73 to 1.5)
< College degree	None or one	1.1 (0.87 to 1.5)	1.1 (0.83 to 1.4)
	Two or more	2.0 (1.5 to 2.6)	1.9 (1.4 to 2.5)
Smoking	Father smoked (preconception)		
Never	No	Referent	Referent
	Yes	1.3 (0.95 to 1.9)	1.3 (0.91 to 1.8)
Ever	No	1.6 (1.0 to 2.3)	1.5 (1.0 to 2.3)
	Yes	2.0 (1.4 to 2.7)	1.8 (1.3 to 2.5)

^{*} Age and race- adjusted; n=364 cases and 42 676 non-cases (complete data on SES/smoking variables); individual models for SES and smoking joint effects.

[†] Adjusted for age, race and mutually adjusted for both sets of joint variables.

SES, socioeconomic status.