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EXTENDED REPORT

Oral contraceptives, breastfeeding and the risk of developing rheumatoid arthritis: results from the Swedish EIRA study

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211620).

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Received 10 April 2017
Revised 15 June 2017
Accepted 24 June 2017
Published Online First 28 July 2017

ABSTRACT

Objectives To study whether oral contraceptive (OC) use or breastfeeding (BF) influence the risk of rheumatoid arthritis (RA), stratifying the cases by presence/absence of anticitrullinated protein antibodies (ACPA), and whether these factors interact with known risk factors in the development of ACPA-positive RA.

Methods Women aged ≥18 years, participants in the population-based case–control Swedish Epidemiological Investigation of RA study (2641 cases/4251 controls), completed an extensive questionnaire regarding OC, BF and potential confounders. We calculated ORs, with 95% CIs, adjusted for age, residential area, smoking and alcohol consumption. Attributable proportion due to interaction (AP) was estimated to evaluate presence of interaction.

Results Compared with never users, ever and past OC users had a decreased risk of ACPA-positive RA (OR=0.84 (95% CI 0.74 to 0.96); OR=0.83 (95% CI 0.73 to 0.95), respectively). No significant associations were found for ACPA-negative RA. Long duration of OC use (>7 years vs never use) decreased the risk of both ACPA-positive (p=0.0037) and ACPA-negative RA (p=0.0356). A history of long BF decreased the risk only of ACPA-positive RA in a dose-dependent manner (p=0.0086), but this trend did not remain after adjustments. A significant interaction was observed between the lack of OC use and smoking (AP=0.28 (95% CI 0.14–0.42)) on the risk of ACPA-positive RA. No interactions were found for BF.

Conclusions OC decreased the risk of RA, especially ACPA-positive RA, where an interaction with smoking was observed. A long duration of OC use decreased the risk of both disease subsets. We could not confirm an association between BF and a decreased risk of either ACPA-positive or ACPA-negative RA.

INTRODUCTION

Rheumatoid arthritis (RA) is among the most common autoimmune diseases, with a complex interplay of genetic and environmental factors involved in its aetiology.[1 2] Since the disease is two to three times more common among women as compared with men,[3–5] it has been suggested that hormonal and reproductive factors might partly explain this sex difference.

Regarding oral contraceptive (OC) use and the risk of RA, some studies have shown an inverse association,[6–11] but the majority of reports have been unable to demonstrate an association.[12–23] Only a few previous reports have taken seropositivity into account, either exploring the classic rheumatoid factor (RF)[6 9 11 15 21] or presence/absence of anticitrullinated protein antibodies (ACPA).[12 14] Furthermore, disparate results so far might be explained by methodological issues, such as the use of prevalent cases for analysis,[14] inclusion of non-population controls[9 11] or relatively few cases.[11 12 21]

Breastfeeding (BF) has been associated with a decreased risk of RA,[13 15 24 25] and a long duration of BF seems to have the strongest association.[15 24] However, some studies have found an increased RA risk.[12 26] Analyses taking seropositivity into account have yielded disparate results.[12 13 15 26] Among these, Berglin *et al* reported that a longer BF history provided a higher risk of RA among those carrying the *PTPN22* 1858T variant or were positive for ACPA or RF.[12] Apart from these studies, the influence of BF on ACPA-positive/ACPA-negative RA has not been further investigated.

For the ACPA-positive subgroup of RA, several risk factors have been identified, including smoking, the *PTPN22*R620W* (1858 C/T) risk allele and the *HLA-DRB1* shared epitope (SE) allele.[1 27–31] In contrast, for the ACPA-negative subgroup of RA, only a few risk factors have been identified.[2 31] ACPA-status and the classic RF highly correlate, and risk factors for seropositive/negative RA behave similarly.[2 30 32]

The aim of this study was to investigate the association between both OC use and total history of BF among parous women, and the risk of developing RA stratifying the cases by ACPA-status (positive/negative), using data from a large population-based case–control study. Moreover, the aim was to explore potential additive interactions between BF and OC, respectively, in regard to known risk factors for ACPA-positive disease, namely smoking status, presence of SE alleles and *PTPN22* gene.

METHOD

Study design

This study was based on data from the Swedish Epidemiological Investigation of RA (EIRA) comprising women above 18 years, living in defined geographical areas of Sweden, between 1996 and 2014. The general design of the EIRA study has been described in detail elsewhere.[33] Incident cases of RA were diagnosed by rheumatologists and included if they fulfilled either the American College of Rheumatology 1987 criteria[34] or the

To cite: Orellana C, Saevarsdottir S, Klareskog L, *et al*. *Ann Rheum Dis* 2017;**76**:1845–1852.

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latest 2010 RA criteria.[35] Twenty-four cases were diagnosed according to the new criteria alone. Controls were randomly selected from the national population register and matched to the cases by age (5-year group) and residential area. For further details, see online supplementary text (online supplementary file 1). All participants provided written informed consent, and ethical approval was obtained from the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden.

Data collection

Participants completed an extensive questionnaire regarding lifestyle and environmental exposures, including OC use, BF and potential confounders. Information about OC use was available for the entire study period, whereas information on BF history among parous women was only available from 2006.

Between 1996 and 2014, a total of 2809 cases and 5312 controls were identified; of these, 2676 cases (95%) and 4251 controls (80%) answered the questionnaire. Blood samples were available from all participating cases.

Antibody assays and genotyping

Blood samples were assayed for ACPA-status using the Immunoscan-RA Mark2 ELISA test (Euro-Diagnostica, Malmö, Sweden).[36 37] The cut-off value for ACPA-positive RA was 25 U/mL. A total of 35 and 13 cases lacking information on ACPA-status were excluded from the OC and BF analyses, respectively.

Genotyping of the *PTPN22* and *HLA-DRB1* genes was conducted as previously described.[38 39] Among *HLA-DRB1* genes, *DRB1*01*, *DRB1*04* and *DRB1*10* genes were defined as SE alleles. Any genotype containing 1 or 2 of these genes was considered as having 'any SE allele', versus those not having any of the genes ('no SE alleles').

Exposures

The year in which the first symptoms of RA occurred was defined as the index-year for each case. Controls were then assigned the same index-year as their matched case.

Current users of OCs were defined as those who were currently using OCs during the index-year and who had started at least the year before index-year. Participants who started OC use during index-year (four cases/seven controls) and those with missing information on OC use (59 cases/115 controls) were excluded from the analyses. Past users were defined as those who used OCs in the past and had stopped at least the year before the index-year. Ever users were defined as current and past users while never users were women who had not used OCs at any time before the index-year.

Parous women were defined as those who had given birth before or during the index-year. Total BF history among parous women was calculated as the sum of the duration of BF for each child born and categorised as 0–6, 7–12 and ≥13 months, according to quartile distribution among controls. Participants with missing information on BF history (78 cases/148 controls) were excluded from analyses. Parous women who did not breast feed (two cases/14 controls) were included in the reference category.

Statistical analysis

Odds ratios (OR) with 95% confidence intervals (CI) of RA overall, ACPA-positive and ACPA-negative RA, associated with OC use and BF were calculated by means of unconditional logistic regression. Regarding OC use, current/past/ever users were compared with never users. Duration of OC use was categorised according to the median value among controls (≤7/>7 years). For the BF analyses, the shortest duration of BF (0–6 months) was used as the reference category.

All analyses were adjusted for the matching variables (age and residential area). We conducted additional adjustments (each variable was investigated separately) for parity (yes/no), number of children (1, 2, 3 and ≥4), body mass index (<25/≥25 kg/m^2), menopausal status, use of postmenopausal hormone therapy (ever/never), age at menarche (≤11, 12, 13 and ≥14 years), age at first birth (<22, 22–24, 25–29 and >29 years), time between last delivered child and the index-year (0–24, 25–30, 31–37 and >37 years), index-year intervals, university education (yes/no), pack-years of cigarette smoking (0–<10, ≥10–<20 and ≥20) and alcohol consumption (low (including non-drinkers), medium and high). We also adjusted for OC use when analysing BF as the main exposure and vice versa. Only smoking and alcohol consumption made a change in the ORs and were retained in the final analyses.

Potential interaction was estimated using departure from additivity of effects (additive interaction), as suggested by Rothman.[40] We tested for interactions in the same manner for both OC use and BF with well-established risk factors of RA: smoking, SE alleles and *PTPN22* risk allele.

To evaluate interaction, the attributable proportion due to interaction (AP) was calculated together with the 95% CI.[41] The AP is the proportion of the incidence among people exposed to two interacting factors, indicating their joint effect apart from the sum of their independent effects. For further details, see online supplementary text.

All analyses were carried out using the Statistical Analysis System (SAS) V.9.4.

RESULTS

In total, 2641 cases and 4251 controls were available for the OC analyses. Overall, 1756 (66.5%) cases were ACPA-positive and the mean time between symptom onset and diagnosis was 10 months for both ACPA subsets. A total of 2578 cases and 4129 controls were included in the OC analyses after all exclusions. For BF, a total of 1242 cases and 2658 controls were available for analysis (for the period 2006–2014), of which 884 cases and 1949 controls where parous women with available BF history. Baseline characteristics of participants are presented in table 1.

OC use and risk of RA

Ever users of OCs had a decreased odds of developing RA overall compared with never users (OR=0.87, 95% CI 0.78 to 0.97). The OR for current and past users were 0.85 (95% CI 0.68 to 1.06) and 0.87 (95% CI 0.78 to 0.98), respectively. The association between ever and past OC use was significant for ACPA-positive, but not for the smaller subset of ACPA-negative RA, and remained significant after adjustment for pack-years of smoking and alcohol consumption (table 2).

A longer duration of ever OC use (above the median value of 7 years) was associated with a decreased risk of RA overall (OR=0.81, 95% CI 0.71 to 0.92). The trend with a longer duration was significant for both ACPA-positive (p=0.0037) and ACPA-negative RA (p=0.0356). Similar result was observed for past OC use except for ACPA-negative RA, probably due to lack of power (table 3). Separate analyses for OC using RF yielded similar results (data not shown).

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Table 1 Characteristics of cases and controls. EIRA, Sweden, 1996–2014

	Cases (n=2641) N (%), mean±SD		Controls (n=4251) N (%), mean±SD
	ACPA-positive RA 1756 (66.5%)	ACPA-negative RA 885 (33.5%)	
Age at inclusion (years)	50.9±13.0	52.0±13.5	51.4±13.4
Age at menarche (years)	13.2±1.4	13.2±1.4	13.1±1.5
Parous	1375 (78.3)	718 (81.1)	3376 (79.4)
Number of children	2.2±1.2	2.2±0.8	2.2±0.9
Age at first birth (years)	24.8±4.9	24.5±4.9	25.6±5.0*
Age at menopause (years)	49.6±5.6	49.8±5.3	50.0±5.4
Oral contraceptive use†			
Ever	1135 (64.7)	582 (65.8)	2862 (67.4)‡
Current	134 (7.6)	61 (6.9)	331 (7.8)
Past	1001 (57.1)	521 (58.9)	2531 (59.6)‡
Never	572 (32.6)	289 (32.7)	1267 (29.9)
Missing	46 (2.6)	13 (1.5)	115 (2.7)
Breast feeding (months)§			
None	1 (0.1)	1 (0.3)	14 (0.7)
1–6	193 (28.7)	80 (27.6)	519 (24.7)
7–12	192 (28.6)	83 (28.6)	574 (27.4)
≥13	234 (34.8)	100 (34.5)	842 (40.1)
Missing	52 (7.7)	26 (9.0)	148 (7.1)
Total duration of breast feeding (months) according to parity§			
One child	6.4±5.6	4.8±2.7	6.9±5.4
Two children	11.7±8.2	11.7±8.1	12.4±8.3
Three children or more	22.5±18.1	19.5±12.9	20.7±13.9
Ever use of PMH¶	117 (26.3)	67 (29.7)	412 (29.5)
BMI ≥25 kg/m^2	749 (42.7)	409 (46.2)	1704 (40.1)‡
University degree	469 (26.7)	251 (28.4)	1425 (33.5)*
Ever smoker	1175 (66.9)	531 (60.0)	2266 (53.3)*
Pack-years			
Never smokers	571 (32.5)	348 (39.3)	1943 (45.7)
0–10	367 (20.9)	185 (21.0)	963 (22.7)‡
10–20	316 (18.0)	132 (14.9)	531 (12.5)*
≥20	409 (23.3)	149 (16.8)	530 (12.5)*
Other	82 (4.7)	63 (7.1)	243 (5.7)‡
Missing	11 (0.6)	8 (0.9)	41 (0.9)
Alcohol consumption			
Non-drinkers	213 (12.1)	100 (11.3)	330 (7.8)*
Low	892 (50.9)	418 (47.3)	1991 (46.9)
Moderate	408 (23.3)	228 (25.8)	1045 (24.6)
High	235 (13.4)	138 (15.6)	864 (20.4)*
Missing	5 (0.3)	0 (0)	14 (0.3)

Baseline characteristics among participants who replied to the questionnaire, excluding cases lacking ACPA-status (35 cases).
Information on age at menarche and age at menopause available for 1211 cases/2596 controls and 757 cases/1548 controls, respectively.
A pack-year is defined as 20 cigarettes smoked every day for 1 year. The category 'Other' includes those smoking other tobacco than cigarettes (eg, cigarillos, cigars or pipe tobacco).
Alcohol consumption defined as number of drinks per week (one drink=12 g of alcohol) and categorised according to the quartile distribution among the controls. The two lowest categories (non-drinkers and low consumption) were merged for analyses.
*p Value <0.0001 for the difference between cases and controls.
†Oral contraceptive use after exclusion of four cases/seven controls who initiated use during the index-year. Ever oral contraceptive use is the sum of current and past use.
‡p Value <0.05 for the difference between cases and controls.
§Information on breastfeeding available for 884 cases and 1949 controls (all parous women) from 2006. Quartile distribution among controls, with the two highest categories merged into one.
¶Only among postmenopausal women.
ACPA, anticitrullinated protein antibodies; BMI, body mass index; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; PMH, postmenopausal hormone therapy; RA, rheumatoid arthritis.

BF and risk of RA

Compared with women who breast fed for 0–6 months, those who breast fed their children for 7–12 months had an OR of 0.93 (95% CI 0.75 to 1.14) of developing RA overall, whereas BF for 13 months or more had an OR of 0.77 (95% CI 0.63 to 0.94). This declining trend was statistically significant for

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Table 2 ORs of developing RA overall and ACPA-positive/ACPA-negative RA according to oral contraceptive use. EIRA, Sweden, 1996–2014

ACPA status	Oral contraceptive use*	Ca/Co	OR (95% CI)†	OR (95% CI)‡
RA overall	Ever	1717/2862	0.87 (0.78 to 0.97)	0.87 (0.78 to 0.98)
	Current	195/331	0.85 (0.68 to 1.06)	0.89 (0.71 to 1.12)
	Past	1522/2531	0.87 (0.78 to 0.98)	0.87 (0.78 to 0.98)
	Never	861/1267	1.0	1.0
	Missing	59/115	–	–
ACPA-positive	Ever	1135/2862	0.84 (0.74 to 0.95)	0.84 (0.74 to 0.96)
	Current	134/331	0.86 (0.67 to 1.11)	0.92 (0.71 to 1.19)
	Past	1001/2531	0.84 (0.74 to 0.95)	0.83 (0.73 to 0.95)
	Never	572/1267	1.0	1.0
	Missing	46/115	–	–
ACPA-negative	Ever	582/2862	0.94 (0.80 to 1.10)	0.93 (0.79 to 1.10)
	Current	61/331	0.83 (0.59 to 1.17)	0.81 (0.57 to 1.16)
	Past	521/2531	0.95 (0.80 to 1.12)	0.94 (0.79 to 1.11)
	Never	289/1267	1.0	1.0
	Missing	13/115	–	–

*Participants who started OC use during index-year (four cases/seven controls) were excluded from the analysis. Ever is the sum of current and past OC users.
†Adjusted for age and residential area.
‡Adjusted for age, residential area, smoking (pack-years) and alcohol consumption (low (including non-drinkers), medium and high).
ACPA, anticitrullinated protein antibodies; Ca/Co, number of cases/controls; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; OC, oral contraceptive; RA, rheumatoid arthritis.

ACPA-positive, but not for ACPA-negative RA. These estimates were attenuated after adjustment for smoking and alcohol consumption (table 4). Analyses using RF instead of ACPA gave similar results (data not shown).

Interaction analyses

Never OC use among never smokers was not associated with risk of ACPA-positive RA (OR=0.99, 95% CI 0.81 to 1.21). Compared with never smoking women which had used OCs, women who had smoked and used OCs had an OR=1.71 (95% CI 1.47 to 1.99), whereas women who had smoked and never used OCs had an OR=2.34 (95% CI 1.95 to 2.82) (table 5). Moreover, a significant interaction on the additive scale was found between smoking and never use of OCs (AP=0.28, 95% CI 0.14 to 0.42) regarding the risk of ACPA-positive RA, indicating that among smokers the risk was more pronounced in never OC users than in ever OC users. No significant interactions were found between OC use and SE alleles, the *PTPN22* gene or between BF and any of the three factors explored (data not shown).

DISCUSSION

In this large population-based case–control study of incident RA, with careful matching between cases and controls and extensive exposure information, we found that women who had ever used OCs had a significantly decreased risk of developing RA. The estimates were similar for current and past use, although only significant in the larger group of past users. When stratifying by ACPA-status, the association was only significant for ACPA-positive RA in both crude and adjusted models. A significant

Table 3 ORs of developing RA overall and ACPA-positive/ACPA-negative RA according to duration of oral contraceptive use. EIRA, Sweden, 1996–2014

		Ever OC use		Current OC use		Past OC use	
ACPA-status	Duration of OC use*	Ca/Co	OR (95% CI)†	Ca/Co	OR (95% CI)†	Ca/Co	OR (95% CI)†
RA overall	Never	852/1245	1.0	852/1245	1.0	852/1245	1.0
	≤7 years	865/1348	0.94 (0.83 to 1.07)	59/85	1.16 (0.77 to 1.76)	806/1263	0.93 (0.82 to 1.06)
	>7 years	835/1481	0.81 (0.71 to 0.92)	134/242	0.99 (0.74 to 1.33)	701/1239	0.81 (0.71 to 0.93)
	p-trend		0.0014		0.9982		0.0021
ACPA-positive	Never	565/1245	1.0	565/1245	1.0	565/1245	1.0
	≤7 years	556/1348	0.89 (0.76 to 1.03)	39/85	1.18 (0.73 to 1.90)	517/1263	0.88 (0.75 to 1.02)
	>7 years	570/1481	0.80 (0.69 to 0.93)	95/242	0.95 (0.69 to 1.32)	475/1239	0.80 (0.68 to 0.93)
	p-trend		0.0037		0.8011		0.0039
ACPA-negative	Never	287/1245	1.0	287/1245	1.0	287/1245	1.0
	≤7 years	309/1348	1.04 (0.86 to 1.25)	20/85	1.15 (0.61 to 2.18)	289/1263	1.04 (0.86 to 1.25)
	>7 years	265/1481	0.82 (0.67 to 0.99)	39/242	1.09 (0.68 to 1.74)	226/1239	0.83 (0.67 to 1.01)
	p-trend		0.0356		0.7056		0.0636

26 cases and 55 controls lacked information on duration of oral contraceptive use.
*Duration of OC use categorised according to median value among controls.
†Adjusted for age, residential area, smoking (pack-years) and alcohol consumption (low (including non-drinkers), medium and high).
ACPA, anticitrullinated protein antibodies; Ca/Co, number of cases/controls; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; OC, oral contraceptives; RA, rheumatoid arthritis.

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Table 4 ORs of developing RA overall and ACPA-positive/ACPA-negative RA according to breastfeeding. EIRA, Sweden, 2006–2014

ACPA-status	Breastfeeding*	Ca/Co	OR (95% CI)†	OR (95% CI)‡
RA overall	≤6 months	275/533	1.0	1.0
	7–12 months	275/574	0.93 (0.75 to 1.14)	0.99 (0.80 to 1.23)
	≥13 months	334/842	0.77 (0.63 to 0.94)	0.88 (0.71 to 1.08)
	Missing	78/148	–	–
	p-value trend	–	0.0075	0.1919
ACPA-positive	≤6 months	194/533	1.0	1.0
	7–12 months	192/574	0.91 (0.72 to 1.15)	0.99 (0.78 to 1.26)
	≥13 months	234/842	0.74 (0.59 to 0.93)	0.86 (0.68 to 1.09)
	Missing	52/148	–	–
	p-value trend	–	0.0086	0.2096
ACPA-negative	≤6 months	81/533	1.0	1.0
	7–12 months	83/574	0.97 (0.70 to 1.35)	1.01 (0.72 to 1.42)
	≥13 months	100/842	0.83 (0.60 to 1.15)	0.91 (0.65 to 1.27)
	Missing	26/148	–	–
	p-value trend	–	0.2405	0.5446

*Breastfeeding duration categorised according to quartiles values among controls, merging the two highest categories.
†Adjusted for age and residential area.
‡Adjusted for age, residential area, smoking (pack-years) and alcohol consumption (low (including non-drinkers), medium and high).
ACPA, anticitrullinated protein antibodies; Ca/Co, number of cases/controls; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; RA, rheumatoid arthritis.

dose–response association was observed for duration of ever OC use both for ACPA-positive and ACPA-negative RA. Non-use of OC significantly interacted with smoking regarding the risk of ACPA-positive RA. Furthermore, BF also decreased the risk of RA in a dose-dependent manner (total duration), but this trend was only significant for ACPA-positive RA and did not maintain after adjustments.

EIRA has the advantage of being one of the largest population-based case–control studies comprising incident cases of RA with concordant information on environmental and genetic factors. The selection of controls (randomly and continuously from the same study base as the cases) minimises the possible selection bias in this step. Another major strength of our study was the possibility to adjust our results with respect to several potential confounders.

Several limitations of our study should be mentioned. First, although the participation proportion among controls was high (80%), selection bias may have occurred if the controls did not

Table 5 ORs of developing ACPA-positive RA for subjects exposed to OC and ever smoking/HLA-DRB1 SE alleles/PTPN22 in women aged 18 years or above. EIRA, Sweden, 1996–2014

OC use*	Smoking	Ca/Co	OR (95% CI)†	OR (95% CI)‡
Ever	Never	358/1205	1.0	1.0
Never	Never	201/684	1.05 (0.86 to 1.28)	0.99 (0.81 to 1.21)
Ever	Ever	771/1632	1.61 (1.39 to 1.87)	1.71 (1.47 to 1.99)
Never	Ever	364/563	2.33 (1.94 to 2.80)	2.34 (1.95 to 2.82)
AP§	–	–	0.29 (0.15 to 0.43)	0.28 (0.14 to 0.42)
OC use*	**SE alleles**	**Ca/Co**	**OR (95% CI)†**	**OR (95% CI)‡**
Ever	None	113/449	1.0	1.0
Never	None	60/215	1.24 (0.86 to 1.77)	1.26 (0.87 to 1.83)
Ever	Any	657/531	4.99 (3.93 to 6.33)	5.11 (4.00 to 6.54)
Never	Any	348/243	6.62 (5.03 to 8.70)	6.28 (4.73 to 8.34)
AP§			0.21 (0.04 to 0.38)	0.14 (–0.05 to 0.34)
OC use*	**PTPN22 alleles**	**Ca/Co**	**OR (95% CI)†**	**OR (95% CI)‡**
Ever	None	578/840	1.0	1.0
Never	None	311/389	1.32 (1.09 to 1.60)	1.27 (1.04 to 1.55)
Ever	Any	249/239	1.50 (1.22 to 1.85)	1.53 (1.23 to 1.90)
Never	Any	115/108	1.84 (1.37 to 2.47)	1.76 (1.30 to 2.39)
AP§			0.0007 (–0.32 to 0.33)	–0.02 (–0.37 to 0.33)

*Since ever OC use was associated with a decreased risk of ACPA-positive RA, the risk category included non-OC users for each interaction analysis, which was separately conducted for smoking, SE alleles and *PTPN22*.
†Adjusted for matching variables (age and residential area) and alcohol consumption.
‡Adjusted for matching variables (age and residential area), pack-years of smoking and alcohol consumption (low (including non-drinkers), medium and high).
§The AP estimates the proportion of the excess risk that is due to the interaction *per se* (factor A + factor B) according to the formula $RR_{AB} - RR_A - RR_B + 1 / R_{RAB}$ (where RR=relative risk).
ACPA, anticitrullinated protein antibodies; AP, attributable proportion due to interaction; Ca/Co, number of cases/controls; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; OC, oral contraceptives; RA, rheumatoid arthritis; SE, shared epitope.

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reflect the exposure frequency in the study base. However, both BF and ever OC use among controls were very similar to the high frequency of BF[42] and reported OC use[43] among Swedish women, respectively. Second, we did not have detailed information regarding OC preparations or doses, being only able to conduct analyses on OC use as a whole.

Regarding OC use, our finding of a decreased risk of developing RA is in accordance with previous reports.[6–11] Although most previous studies have not observed a statistically significant association,[12–21] some results have suggested a protective effect, but the sample size might have been inadequate to reach definite conclusions. Only borderline associations have been observed in a few recent meta-analyses.[22 23] Our results are in agreement with those from Doran *et al*,[6] who reported a decreased risk among ever (OR=0.57 (95% CI 0.35 to 0.91) but not among current (OR=1.0 (95% CI 0.4 to 2.52) OC users. Another case–control study performed in Sweden showed a non-significant association for ever (OR=0.70, 95% CI 0.40 to 1.24) and current (OR=1.21, 95% CI 0.58 to 2.52) OC users, but the association for past users was significant (OR=0.37, 95% CI 0.16 to 0.86).[8] These findings are in line with our results, although they used old criteria (year 1958) for RA diagnosis. In line with our findings, Berglin *et al* found a protective effect with OC use >7 years.[12]

Previous reports taking seropositivity into account have yielded contradictory results.[6 9 11 12 14 15 21] Doran *et al* found a protective effect of OC exposure on the risk of RF-positive (OR=0.36, 95% CI 0.18 to 0.72) but not RF-negative RA (OR=0.982, 95% CI 0.46 to 2.10).[6] By contrast, Pedersen *et al* reported an increased risk of ACPA-positive RA among ever users of OC (OR=1.65, 95% CI 1.06 to 2.57).[14] However, the inclusion of prevalent cases (diagnosed within 5 years) might entail bias. Our result was notably mainly restricted to ACPA-positive RA and estimates only slightly modified after adjustments. Similar results using RF instead of ACPA-status corroborate the high correlation between ACPA-status and the classic RF.

The current knowledge on the association between BF and RA has not reached firm conclusions. In a large cohort study, Karlson *et al* found a decreased risk of RA among women who breast fed for more than 12 months, with a significant trend with increased duration of BF.[15] Restricting the analyses to RF positive patients, a similar reduction was found for a total BF duration of ≥24 months. In line with these results, a study conducted in Sweden showed a decreased risk of RA among women who breast fed their children for more than a year, with similar trends for RF-negative/RF-positive RA.[13] A similar result was obtained by a recent cross-sectional study in an Asian population.[24] Our estimates were attenuated after adjustments for smoking and alcohol consumption, which indicates their role as important confounders in this study. Analyses using RF yielded similar results as those for ACPA-status. However, in a nested case–control study, Berglin *et al* found a strong association between BF and later development of RA (OR=4.8, 95% CI 1.43 to 15.8) with a higher risk with increasing time of BF and greater among ACPA-positive cases.[12] Similar findings were reported by Brennan and Silman, with a higher risk for RF-positive RA among women who breast fed.[26] These opposite results might be explained by methodological issues (small number of cases (70) and recruitment via a media campaign, respectively). Finally, a recently published systematic review and meta-analysis reported a decreased risk of RA, whether with a longer or shorter duration of BF.[25] Our study confirms and extends these findings by adding the stratification according to ACPA-status, which to our knowledge has not been explored using a large dataset as in our present study.

To the best of our knowledge, no previous study has found evidence of interaction between OC and/or BF and smoking habits or major genetic risk factors of RA, respectively. The significant interaction between lack of OC use and smoking indicates that the risk of ACPA-positive RA associated with smoking is higher among women who never used OCs than among those who did. However, since both smoking and the use of OC have been linked to an increased predisposition to venous thrombotic events (VTE), women with a history of VTEs (especially if they smoke) might be recommended not to use OC by their physician. We can therefore not exclude the possibility that our findings on an interaction between non-OC use and smoking merely reflects that smoking women, who have an increased RA risk, do not receive OC prescription as often. The physiopathology of RA is complex and not fully understood, but our findings may contribute to the knowledge regarding mechanisms of importance for the development of RA.

The postpartum period soon after delivery has been described as a time of higher risk for the onset of RA.[19] The immunostimulating effect of the hormone prolactin, levels of which are elevated during BF, might explain this increased risk immediately after childbirth.[44] However, recent findings indicate that prolactin might act more as a regulator of inflammation, with protective and regenerative functions.[45] Since elevated prolactin levels do not support our findings, a potential biological mechanism might be a prolonged anti-inflammatory effect of progesterone. It has been shown that elevated progesterone levels during pregnancy remain high during BF through expression of progesterone receptors in lymphocytes.[46] Finally, another potential mechanism might be an anti-inflammatory effect of cortisol, which has been found to be significantly higher among postmenopausal women with a history of BF.[47]

The potential effect of hormones contained in OC preparations might vary according to dose and type. Although such information was not available in the present study, the protective effect seems to differ between ACPA-subsets and with a longer duration of OC use, supporting the hypothesis of a dose–response effect.

The protective effect of OC use on the risk of ACPA-positive RA is in line with our previous finding of a reduced risk of ACPA-positive RA, among women who used postmenopausal hormone therapy.[48] On the other hand, the finding of a protective effect of BF on the risk of ACPA-positive (in the crude model), but not ACPA-negative RA, is in line with our previous finding of a risk of ACPA-negative but not ACPA-positive RA during the postpartum period.[49] All of these findings together support the notion of RA as two different disease entities with different risk factors patterns.

In summary, we found an inverse relationship between OC use and the subsequent development of RA, especially ACPA-positive RA. An interaction between never OC use and smoking was also observed for this subgroup of disease, implying that among smokers, the risk was more pronounced in never OC users than in ever OC users. A trend was observed for longer duration of BF and decreased risk of ACPA-positive RA, although not significant after adjustments. In this large population-based study, we were able to address these questions more thoroughly than has been possible before, by examining disease subsets separately, in the context of other risk factors and by considering many potential confounders. Further research is required to explore the biological mechanisms behind our findings and whether hormonal factors have different impact on the ACPA-subsets of RA.

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Acknowledgements We would like to thank Marie-Louise Serra and Lena Nise for excellent assistance with the collection of data. We would also like to thank all cases and controls who participated in the study as well as the clinicians and nurses in the EIRA study group.

Contributors CO conducted the statistical analyses and drafted the manuscript; CB initiated the study and was responsible for the analysis, interpreting the results and revising the manuscript; LA, LK and CB contributed to study design; and LA, LK, EWK and SS contributed to data interpretation and critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript.

Funding This study was supported by grants from the Swedish Medical Research Council, the Swedish Research Council for Health, Working Life and Welfare, King Gustav Vâ€™s 801-year foundation, Vinnova, the Swedish Foundation for Strategic Research, the Swedish Rheumatic Foundation, the Stockholm County Council, the Insurance Company AFA, the Innovative Medicines Initiative 1 supported BTCure project and the National Institutes of Health (NIH, AR047782). The funding sources had no role in the reporting of the study or in the decision to submit the manuscript for publication.

Competing interests No, there are no competing interests.

Patient consent Obtained.

Ethics approval This study was approved by the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden.

Provenance and peer review Not commissioned; externally peer reviewed.

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Oral contraceptives, breastfeeding and the risk of developing rheumatoid arthritis: results from the Swedish EIRA study

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Ann Rheum Dis 2017 76: 1845-1852 originally published online August 17, 2017
doi: 10.1136/annrheumdis-2017-211620

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