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Gender-specific association between childhood trauma and rheumatoid arthritis: A case–control study

Carsten Spitzer [a,*], Stefanie Wegert [b], Jürgen Wollenhaupt [b], Katja Wingenfeld [c], Sven Barnow [d], Hans Joergen Grabe [e]

[a] Asklepios Fachklinikum Tiefenbrunn, Göttingen, Germany
[b] Department of Rheumatology and Clinical Immunology, Schön Klinik Hamburg-Eilbek Hamburg, Germany
[c] Department of Psychiatry and Psychotherapy, Campus Benjamin Franklin, Charité-Universitätsmedizin Berlin, Berlin, Germany
[d] Institute of Psychology, Ruprecht-Karls University, Heidelberg, Germany
[e] Department of Psychiatry and Psychotherapy, Ernst-Moritz-Arndt-University, Greifswald, Germany

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ABSTRACT

Objective: Rheumatoid arthritis (RA) has been associated with a variety of emotional stressors, but findings remain inconclusive if RA is related to childhood trauma, which is known to have long-lasting negative consequences for physical health decades into adulthood. We investigated the association between childhood trauma and RA by comparing histories of child abuse and neglect between RA patients and adults from the general population in a cross-sectional case–control study.
Methods: 331 patients with definite RA and 662 gender- and age-matched adults from the general population were administered the self-report Childhood Trauma Questionnaire (CTQ) for the assessment of emotional, physical and sexual abuse as well as emotional and physical neglect.
Results: Adjusting for gender and current depression, RA patients scored significantly higher in all CTQ subscales apart from sexual abuse and physical neglect than the controls. Adjusted odds ratios for these types of childhood trauma were higher in the RA group than in controls ranging from 2.0 for emotional neglect (95% confidence interval [CI]: 1.4–3.0) to 2.6 for emotional abuse (95% CI: 1.4–4.7). Gender-specific analyses revealed basically the same pattern for women, but not for men.
Conclusion: Our findings suggest an association between childhood trauma and development of RA, particularly in women. This relationship may be mediated by dysregulations of neuro-endocrine-immune networks, but larger prospective studies are needed to clarify the association between early life stress and the risk for RA in genetically susceptible individuals.

Introduction

Rheumatoid arthritis (RA) represents a chronic, systemic, inflammatory, autoimmune disorder affecting the synovial membrane of multiple joints in a symmetrical fashion. It may cause joint damage, disability, decreased quality of life, and cardiovascular and other comorbidities. In developed countries, RA affects 0.5 to 1.0% of adults, and is most typical in women and elderly people [1]. Although its precise etiology is not yet known, there is mounting evidence that the complex interactions of genetic susceptibility, immunological and inflammatory processes as well as environmental factors contribute to the risk for and course of RA [1]. Among the environmental factors, psychosocial stress is of major importance, and the impact of stressful events on the course of the disease, e.g. clinical exacerbations and disease activity, is undisputed [2–8]. In contrast, the role of stress as a trigger or risk factor in the development of RA remains controversial [3, 6–8]. For example, in line with prior research [9] a recent longitudinal study based on the follow-up of nationwide and population-based cohorts did not find that the death of a child as a severe stressor increased the risk for RA in bereaved parents [10]. However, several other investigations have indicated an association between stress and the development of RA [8, 11, 12].

Childhood trauma represents one of the most extreme forms of stress, and is known to have long-lasting negative consequences for both mental and physical health decades into adulthood [13–17]. Adverse childhood experiences are related to a number of chronic somatic conditions involving inflammatory processes, particularly cardiovascular and autoimmune diseases such as multiple sclerosis or RA [15, 18, 19]. Additionally, traumatic stress in general and childhood trauma in particular are independently associated with a pro-inflammatory state in later life [20,21], which may contribute to the complex pathogenesis of autoimmune diseases [5]. Correspondingly, a cross-sectional general population study reported that adults with two or more childhood

* Corresponding author at: Asklepios Fachklinikum Tiefenbrunn, D-37124 Rosdorf, Germany. Tel.: +49 551 5005 247; fax: +49 551 5005 301.
E-mail address: c.spitzer@asklepios.com (C. Spitzer).

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adversities had a 100% increased risk of rheumatic diseases including RA [18]. In an independent investigation, childhood physical abuse was associated with a 50% increased risk of arthritic disorders such as RA [15]. A large prospective cohort study also found a moderate increase in the risk of self-reported arthritis among subjects with traumatic experiences in childhood [22]. In clinical samples of adult RA patients, prevalence of retrospectively recorded childhood abuse including sexual molestation, penetration and physical assault ranged between 13 and 50% [23,24], which exceeds figures from the general population [17,19,25,26]. However, a community based, case–control study did not find an association between traumatic childhood experiences and the risk of RA [9]. These inconsistent findings can be attributed to methodological limitations, e.g. vague disease definitions such as self-reported arthritis [15,22], number of cases with RA below 100 [9,18,23,24] or disregard of the socioeconomic status (SES), which is relevant both in RA and childhood trauma [14,27,28]. More importantly, none of the above mentioned studies controlled for depression although adult retrospective reports of childhood trauma may be biased by depressive mood, which is frequent in RA patients and may lead to mood-congruent memory distortions [29–31]. Finally, while RA is more frequent in women, and girls and boys are differentially exposed to various types of childhood adversities [1,32], gender differences in the assumed relationship between childhood trauma and RA have not yet been investigated.

Taking these findings and considerations into account, the objective of our study was twofold: (i) to investigate the association between childhood trauma and RA by comparing histories of child abuse and neglect between RA patients and individuals from the general population in a case–control design, controlling for sociodemographic factors and current depression, and (ii) to analyze whether the hypothesized association differs between women and men.

Methods

Procedure and participants

The RA sample was recruited at the Department of Rheumatology and Clinical Immunology, Schön Klinik, Hamburg Eilbek (Germany). Because we intended to obtain a broad sample of adult RA patients, we only chose three inclusion criteria: (i) definite RA according to the 1987 revised criteria for the classification of rheumatoid arthritis by the American Rheumatism Association [33], (ii) age at 1st RA diagnosis older than 16 years, and (iii) ability to engage in self-report measures, i.e. lack of cognitive impairment and/or fluent in German language. 570 patients attending the clinic in 2009 and 2010 met these criteria. All of them were approached by letter including an invitation to participate, a consent form and the self-report measures for the assessment of childhood trauma and current depression (see below for details). 66 of these eligible subjects refused participation, and 159 patients did not respond to repeated efforts of contact. Of the 345 participants returning the questionnaires, 14 (4.1%) had to be excluded due to incomplete data on childhood adversities. Thus, 331 adult RA patients were considered for the present study.

The control subjects from the general population participated in the "**L**ife-**E**vents and **G**ene-**En**vironment Interaction in **D**epression" (LEGEND) study [25,26,34] representing a cross-sectional investigation nested in a community-based cohort study, the Study of Health in Pomerania (SHIP) in North East Germany [35]. For the purpose of the present study that was approved by the local Institutional Review Board and conforms to the principles of the Declaration of Helsinki we only included individuals without cognitive impairment (assessed by clinical psychologists). Control subjects were randomly selected in a 2:1 ratio, matched for age, gender, marital status and educational level to the case subjects. All participants gave written informed consent.

Measures

The Childhood Trauma Questionnaire (CTQ) was used for the self-report of child maltreatment [36]. It is a brief, reliable and valid screening device for histories of childhood trauma including *emotional*, *sexual* and *physical abuse* as well as *emotional* and *physical neglect*. Each of these dimensions is captured by five items each which are endorsed on a 5-point Likert scale with higher scores indicating a higher degree of childhood maltreatment. In addition to a dimensional scoring procedure, the manual provides threshold scores to determine the severity of abuse and neglect (none = 0, low = 1, moderate = 2 and severe to extreme = 3). Dichotomized variables (0 and 1 as absent versus 2 and 3 as present) were created for each trauma type. In independent studies the CTQ was reported to show good reliability and validity. Additionally, the five-factor model (i.e. the 5 subscales reflecting the different types of childhood trauma) was empirically confirmed [36,37]. The psychometric properties of the German version of the CTQ were found to be similar to the original [38]. Current depression (i.e. in the last two weeks) was measured by the Beck Depression Inventory (BDI-II), which is a 21-item self-report questionnaire with high reliability and validity [39].

Statistical analysis

The data analyses were computed using the 'Statistical Package for the Social Sciences' (SPSS, version 18.0). RA patients and participants of the control group were compared by analyses of variance (ANOVA) for continuous variables and χ^2 test for categorical variables. Because there were differences in gender distribution and current depression, these variables were taken into account as potential confounders in subsequent analyses. We also calculated effect sizes (Cohen's d) when possible. To determine the relationship between childhood trauma and RA, we performed logistic regression analyses with the different types of childhood trauma as dependent variable and health status (RA vs. control group) as independent variables. These analyses were re-run for women and men separately. We report odds ratios (OR) with the corresponding 95% confidence interval (95% CI). Significance level was set at $p<.05$.

Results

The sociodemographic and clinical data of the RA patients and the control group from the general population are presented in Table 1. As intended there were no differences between the samples with respect to gender distribution, age, marital status, and educational level. Patients with RA reported more current depression as measured with the BDI-II than the control group. Among RA patients, the mean age at 1st diagnosis of RA was 49.8 years (SD = 14.4).

As depicted in Table 2, most dimensional CTQ scores were significantly higher in the RA sample compared to the general population, even when gender and depression were accounted for (apart from the subscales *sexual abuse* and *physical neglect*). Effect

Table 1
Sociodemographic and clinical characteristics of the two samples: patients with RA and controls from the general population

	RA patients (n = 331)	Control group (n = 662)	χ^2/F	p ≤
Women, %	81.6	81.6	0.0	1.0
Age, mean years (SD; range)	61.0 (13.6; 20–90)	61.0 (12.9; 29–89)	0.04	.947
Marital status, %			1.38	.502
Never married	10.6	8.5		
Married	61.8	64.5		
Separated, divorced, widowed	27.6	27.0		
Educational level, %			1.01	.604
<10 years	46.2	45.3		
10–11 years	34.1	37.0		
>11 years	19.6	17.7		
BDI-II, mean (SD)	14.3 (9.0)	6.7 (6.8)	219.66	.001

sizes for these comparisons ranged between d = 0.28 (*sexual abuse/physical neglect*) to d = 0.51 (*emotional abuse*). Among women, RA patients scored significantly higher on the subscales emotional and physical abuse as well as on the total score. There were no differences between men with RA and male control subjects; however, the scores for *emotional neglect* differed to a moderate degree as indicated by the effect size.

Using the categorical scoring method of the CTQ yielded basically the same finding: Adjusting for gender and current depression, RA patients had higher likelihoods to report *emotional* and *physical abuse* as well as *emotional neglect* with increases in this likelihood ranging between the factor 2.0 for *emotional neglect* and 2.6 for *emotional abuse* (cf. Table 3). Gender-specific analyses revealed the same pattern for women. Among men, there were no significant differences.

The mean age at 1st RA diagnosis did not significantly correlate with any childhood trauma type captured by the CTQ (data not presented).

Discussion

In this case–control study we found that RA patients reported significantly more childhood maltreatment than adults from the general population except sexual abuse and physical neglect. This pattern emerged using both the dimensional and the categorical scoring method of the CTQ, and remained significant when gender and current depression were accounted for. Our findings are in line with previous studies indicating that traumatic experiences in childhood negatively affect physical health in adulthood [13,15,32]. This seems to be particularly true for conditions involving inflammatory processes such as asthma, cardiovascular and autoimmune diseases [18,19]. Gender-specific analyses revealed that RA and self-reported childhood trauma were selectively associated in women. Among men, only emotional neglect was more prominent in RA patients than in adults from the general population. This result is in good keeping with prior research suggesting sex-differentiated risk factors for RA [40,41].

Table 3
Frequencies of self-reported childhood maltreatment in patients with RA and controls from the general population

	RA (n = 331)	Control group (n = 662)	Logistic regression	
	%	%	AOR	95% CI
Emotional abuse	13.6	3.1	2.6**	1.4–4.7
Physical abuse	11.2	2.4	2.5**	1.3–4.8
Sexual abuse	10.0	4.3	1.7	0.9–3.0
Emotional neglect	29.3	11.0	2.0***	1.4–3.0
Physical neglect	27.4	17.0	1.1	0.8–1.6
Women only	RA (n = 270)	Control group (n = 540)	Logistic regression	
	%	%	AOR[a]	95% CI
Emotional abuse	15.2	3.6	2.6**	1.4–4.8
Physical abuse	12.6	2.2	3.2**	1.5–6.6
Sexual abuse	11.9	5.1	1.7	1.0–3.1
Emotional neglect	30.0	11.8	1.9**	1.3–2.9
Physical neglect	28.8	18.9	1.1	0.7–1.6
Men only	RA (n = 61)	Control group (n = 122)	Logistic regression	
	%	%	AOR[a]	95% CI
Emotional abuse	6.6	0.8	2.2	0.2–27.3
Physical abuse	4.9	3.3	0.6	0.1–4.0
Sexual abuse	1.6	0.8	0.3	0.0–10.7
Emotional neglect	26.2	7.5	2.7*	1.0–7.4
Physical neglect	21.3	9.0	1.2	0.4–3.3

AOR = odds ratio, adjusted for gender and depression (BDI-II score); 95% CI = 95% confidence interval.
[a] Odds ratio, adjusted for depression (BDI-II score).
* p ≤ .05.
** p ≤ .01.
*** p ≤ .001.

Table 2
Comparison of self-reported childhood maltreatment between patients with RA and controls from the general population

Dimensional CTQ scores	RA (n = 331)		Control group (n = 662)		Statistics		
	M	SD	M	SD	F[a]	p ≤	d
Emotional abuse	7.9	4.5	6.1	2.2	12.8	.001	0.51
Physical abuse	6.5	3.2	5.5	1.3	6.3	.012	0.41
Sexual abuse	6.0	3.2	5.3	1.5	2.9	.091	0.28
Emotional neglect	11.3	5.7	9.2	4.3	4.0	.045	0.42
Physical neglect	8.1	3.2	7.3	2.5	0.0	.866	0.28
CTQ total score	39.7	15.8	33.6	8.5	7.0	.008	0.48
Women only	RA (n = 270)		Control group (n = 540)		Statistics		
	M	SD	M	SD	F[b]	p ≤	d
Emotional abuse	8.2	4.7	6.2	2.3	14.4	.001	0.54
Physical abuse	6.6	3.4	5.5	1.2	7.1	.008	0.43
Sexual abuse	6.2	3.6	5.4	1.7	3.5	.061	0.28
Emotional neglect	11.3	5.8	9.3	4.5	2.5	.114	0.39
Physical neglect	8.2	3.3	7.5	2.6	0.1	.735	0.24
CTQ total score	40.5	16.7	33.9	9.0	6.8	.009	0.49
Men only	RA (n = 61)		Control group (n = 122)		Statistics		
	M	SD	M	SD	F[b]	p ≤	d
Emotional abuse	6.6	3.4	5.8	1.5	0.0	.844	0.30
Physical abuse	6.1	2.1	5.7	1.6	0.3	.592	0.21
Sexual abuse	5.1	0.7	5.0	0.4	0.2	.677	0.18
Emotional neglect	11.2	5.3	9.0	3.3	2.2	.140	0.50
Physical neglect	7.3	2.2	6.7	2.2	0.3	.602	0.27
CTQ total score	36.3	10.0	32.1	6.2	0.6	.423	0.50

[a] ANOVA adjusted for gender and depression (BDI-II score).
[b] ANOVA adjusted depression (BDI-II score).

Emotional maltreatment was more closely associated with RA than the other types of childhood trauma, particularly in women. For example, the effect sizes for emotional abuse (d = 0.51) and neglect (d = 0.42) were higher than those for other types of maltreatment (d < 0.3). Moreover, in males emotional neglect was more prominent in RA patients compared to men from the general population. The significance of emotional maltreatment as possible risk factor for autoimmune diseases was reported for MS patients, too [19]. Correspondingly, recent studies have suggested that different types of childhood trauma may predict different outcomes [42,43]. Particularly, emotional abuse was found to have a substantial and independent effect on adult health, and there is evidence that emotional maltreatment additionally accentuates the adverse effects of other forms of abuse and neglect, which are closely interrelated and often co-occur [42,43].

Although beyond the scope of our study, it might be worthwhile to speculate on potential pathways by which childhood trauma might be linked to RA. Although these mediating mechanisms have not yet been studied, an effect of trauma on neuro-endocrine-immune networks is a likely candidate. The nervous, endocrine and immune systems are functionally inter-connected and disturbances in the communication between these systems play a role in RA pathogenesis [44,45]. Mounting data indicates that childhood trauma produces long-lasting alterations in the hypothalamic–pituitary–adrenal (HPA) axis and the autonomic nervous system, which are possibly more prominent in women [46,47]. A persistent sensitization of these stress systems mainly due to a long-lived dysregulation of the HPA axis as a result of childhood adversities may impact the balance between pro- and anti-inflammatory factors, and prior research indicated that traumatic stress in general and early life stress in particular are independently related to a pro-inflammatory state in later life [20,21]. A dysregulated stress system in combination with abnormalities of the systemic anti-inflammatory feedback and hyperactivity of local pro-inflammatory factors [48] may be the mediating mechanisms by which childhood trauma increases the risk for RA in genetically susceptible individuals, especially in

women. Moreover, these dysregulations possibly amplify the detrimental effects of other environmental factors involved in the complex pathogenesis of RA.

Our study has some major strengths, e.g. the assessment of childhood trauma with a psychometrically sound measure, the exclusion of individuals with cognitive impairment, and the use of a gender- and age-matched control group from the general population. Moreover, we controlled for depression which is a frequent condition in RA and may bias recall of adverse experiences in childhood [29–31]. However, some limitations merit discussion, too. First, because our investigation was cross-sectional, the reported associations do not allow any definite causal inferences. However, considering that the CTQ inquires about adverse events in childhood, and given that the mean age at RA onset was 49.8 years (SD = 14.4), it is very likely that the traumatic childhood experiences antedated RA onset in almost all cases. Nevertheless, we cannot rule out reverse causation, i.e. RA patients are more likely to endorse items of childhood trauma. Because humans seek explanations, a phenomenon called "effort after meaning", it may be that RA patients misattribute their illness to childhood maltreatment, particularly since effort after meaning was shown to distort memory [49]. Additionally, considering the response rate of 58% in our study, we cannot rule out the possibility of response bias. However, traumatic stress research indicates that those with severe trauma histories tend to avoid participating in trauma-focused studies as they are afraid of being confronted with negative memories and aversive affective states [34]. If this was true, survivors of extreme child abuse might be under-represented in our study, thus reducing the risk of response bias. Second, disregard of smoking as an important environmental risk factor for RA [41] may have biased our findings, particularly since adult survivors of child maltreatment are known to have poor health behavior including smoking [13,17]. Finally, because we included RA patients referred to a tertiary care setting, it remains unknown if our results can be generalized to other RA samples, e.g. in primary care settings. Additionally, we did not differentiate between serologic subtypes of RA defined by the presence or absence of rheumatoid factor or auto-antibodies to cyclic citrullinated peptides which were shown to differ in their non-genetic risk factor profiles [50].

Despite these caveats possibly limiting the generalizability of our results, we suggest that childhood trauma may play a role in the complex pathogenesis of RA, particularly in women. Although the potential mechanisms underlying the association of RA and traumatic stress have not yet been adequately tested among patients with RA, research in this area is likely to contribute to and expand on the theory of developmental origins of adult disease and health. Because adverse experiences in childhood are common and RA is a chronic and often debilitating condition, future studies are warranted that focus on the impact of traumatic stress on adult chronic diseases such as RA.

Conflict of interest statement

None of the authors has any conflict of interest.

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