

# Self-reported childhood maltreatment, lifelong traumatic events and mental disorders in American and Israeli rheumatoid arthritis patients

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## Abstract Objective

Psychological stress is thought to play a major role in the development and exacerbation of autoimmune diseases in general, as well as in rheumatoid arthritis (RA) in particular. The aims of the current study are to compare retrospective self-reports of childhood maltreatment and lifetime major life/traumatic experiences of American and Israeli RA patients, using standardised instruments, while adjusting for concomitant mental disorders and psychological distress, in order to rule out their part in the subjective reports, thus addressing the trans-cultural robustness of the association between childhood maltreatment, traumatic experiences and RA.

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## Methods

RA patients at the participating study centres were recruited by their physicians, both in Israel and the USA. Patients filled out questionnaires regarding demographic data, disease activity, psychological distress, potential anxiety and potential depression. In addition, patients answered questions regarding pain and childhood maltreatment.

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## Results

83 RA patients were recruited in the US and 23 patients in Israel. The comparison of CTQ-subcales between the US and Israeli cohorts showed significant differences between the groups only in the subscales of emotional neglect (US  $10.30 \pm 5.05$ , Israeli  $22.67 \pm 3.68$ ,  $p < 0.05$ ) and emotional abuse (US  $10.46 \pm 5.77$ , Israeli  $7.13 \pm 4.84$ ,  $p < 0.05$ ). 87% of Israeli patients had severe emotional neglect. Severe emotional abuse was associated with probable depression (OR 7.778, CI [1.907-31.716]). Using Pain Disability Index (PDI) score, Americans reported more pain during sexual activity than Israelis (US PDI Score  $5.64 \pm 3.70$ , Israeli  $3.16 \pm 3.86$ ,  $p < 0.05$ ). PDI score was also associated with a previous traumatic event ( $36.89 \pm 18.57$  vs.  $16.82 \pm 14.85$ ,  $p < 0.05$ ).

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## Conclusion

A high degree of similarity was demonstrated between American and Israeli populations of RA patients, regarding psychological stressors and previous traumatic events. As expected, the results indicated a link between emotional abuse and depression in these patients. In addition, a previous traumatic event was associated with more significant pain. Physicians caring for RA patients should be vigilant regarding the possible association with childhood adversity and should consider appropriate consultations when indicated. In addition, while dealing with pain management in RA patients, physicians should keep in mind the possible contribution of distant childhood adversity.

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## Key words

rheumatoid arthritis, Israeli, American, mental disorders, traumatic events, pain

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## Introduction

The aetiology of rheumatoid arthritis RA, similarly to other autoimmune diseases, remains incompletely understood, and is considered to be a combination of pre-determined genetic factors and environmental triggers. Psychological stress is thought to play a major role in the development and exacerbation of autoimmune diseases in general (1), as well as in RA in particular (2).

Psychological stressors have been demonstrated to have an effect on the short term symptoms of RA (3), while psychological interventions have been found to be beneficial in the treatment of RA (4-8). Moreover, RA patients have been documented to demonstrate a differential immune response to stress and pain, compared to controls (3, 9). Psychological stressors are also considered to play a role in RA onset, although such a link is difficult to establish, since stressors may occur years before the diagnosis, and are thus inevitably based on retrospective recall, a method fraught with inaccuracy and bias. Moreover, quantifying the stressors objectively is challenging. Only a few studies have investigated the association of preceding psychological distress and the development of RA, and the trans-cultural robustness of this association has yet to be demonstrated. In a study conducted in Sweden, 4.4% of RA patients reported psychological trauma preceding disease onset (10). In a Guatemalan study, the prevalence of abuse was higher among patients with rheumatic disorders compared to controls (11), while O'Donovan *et al.* (12) showed that trauma-exposure and post-traumatic stress disorder (PTSD) in veterans may increase the risk of autoimmune disorders, including RA (13).

It has long been postulated that stress plays an important role in various forms of arthritis, including RA (14) and has been correlated with disease activity (15, 16). In addition, symptoms of PTSD have recently been shown to increase the risk of developing RA in a large prospective cohort study (17). Moreover, PTSD has been shown to be associated with worse patient-reported RA outcomes and tender joint counts,

but not with other clinical or laboratory-based measures of disease activity (18).

The aims of the current study are to compare retrospective self-reports of childhood maltreatment and lifetime major life/traumatic experiences of American and Israeli RA patients, using standardised instruments, while adjusting for concomitant mental disorders and psychological distress, in order to rule out their part in the subjective reports, thus addressing the trans-cultural robustness of the association between childhood maltreatment, traumatic experiences and RA.

## Methods

### Participants and settings

Consecutive RA patients at the participating study centres were recruited by their physicians. Data collection took place in the USA from July 1, 2013 to December 31, 2013. Patients were recruited by four private rheumatology offices. Patients under continuous care were included. Only newly referred patients were approached for participation. In Israel, data collection took place from June 2015 to April 2016. Patients were consecutively recruited among attendants of the Tel Aviv medical centre rheumatology clinic, which is a tertiary referral centre. Patients were included if the diagnosis of RA had been established in the past or recently by one of the study physicians and the diagnosis of RA was verified according to ACR criteria (19). All physicians were experienced in the management of RA. Only persons aged 18 years and above with adequate written comprehension of their native tongue were included. Patients that had a fibromyalgia diagnosis by at least one physician were excluded from the study. There were no other inclusion or exclusion criteria. The questionnaires were handed out by the physicians at each centre with a standardised letter explaining the study and providing directions on proper questionnaires completion. No identifying information was written on the study materials or questionnaires. Completed questionnaires were sealed in an envelope and returned anonymously to the investigators.

Competing interests: none declared.

Measures and questionnaires

• Demographic data

Age, sex, family status, educational level, and current professional status were assessed by a demographic questionnaire.

• Rheumatoid Arthritis Disease Activity

The Rheumatoid Arthritis Disease Activity Index (RADAI) is a validated instrument for measuring self-reported disease activity attributable to rheumatoid arthritis (20).

• Psychological distress, potential anxiety and potential depression

The 4-item Patient Health Questionnaire-4 (PHQ-4) (21, 22) was used to determine mental distress and illness. Two PHQ-4 items measure two of the DSM-IV criteria for major depression over a four-point scale (0: "not at all" - 3: "nearly every day"). A score  $\geq 3$  has a sensitivity of 82.9% and a specificity of 90% for the diagnosis of major depression and sensitivity of 62.3% and a specificity of 94% for the diagnosis of any depressive disorder and was used as the cut-point for depression in this study (22). However, we must mention that this Questionnaire is used in general as a screening method. Two PHQ-4 items measure two DSM-IV criteria for general anxiety disorder. A score  $\geq 3$  has sensitivities of 0.86, 0.76, 0.70, 0.59 and 0.65, as well as specificities of 0.83, 0.81, 0.81, 0.81 and 0.88 for the criterion standards of generalised anxiety disorder, panic disorder, social anxiety disorder, posttraumatic stress disorder and any anxiety disorder respectively and was used as the cut-point for anxiety in this study (23). The total score of the PHQ-4 (Minimum 0, Maximum 12) is a measure of psychological distress (22).

• Pain-related disability

The Pain Disability Index (PDI) rates the degree to which pain interferes with the patient's functioning in 7 broad areas: family/home responsibilities, recreation, social activity, occupation, sexual behaviour, self-care, and life-support activity (24, 25). Each domain is rated using an 11-point scale ranging from 0 (no disability) to 10 (total disability). The total score ranges from 0 to 70.

Table I. Comparison of demographic data of American and Israeli patients.

	American group n=83	Israeli group n=23	p-value
Mean age mean $\pm$ SD	52.5 $\pm$ 12.86	59.13 $\pm$ 11.99	$p < 0.05$
Female gender n (%)	76 (91.6%)	20 (87%)	$p = 0.391$
Race			
Caucasian n (%)	58 (69.8%)	23 (100%)	-
Living with family/partner n (%)	56 (67.5%)	16 (69.6%)	$p = 0.334$
Highest educational level			
High-school n (%)	9 (10.8%)	16 (69.6%)	$p < 0.05$
University n (%)	74 (89.2%)	6 (26.1%)	
Professional status			
Unemployed n (%)	8 (9.6%)	3 (13%)	$p < 0.05$
Part time work n (%)	35 (42.2%)	3 (13%)	
Full time work n (%)	6 (7.2%)	5 (21.7%)	
Pension n (%)	27 (32.5%)	6 (26.1%)	
Housewife n (%)	7 (8.4%)	5 (21.7%)	

• Childhood maltreatment:

The short form of the standardised self-report Childhood Trauma Questionnaire (CTQ) is a well-validated and highly reliable instrument that measures the severity of different types of childhood and adolescence maltreatment (emotional, physical and sexual abuse, emotional and physical neglect). The scores of each subscale range between 5 (no abuse or neglect) and 25 (maximum abuse or neglect). We used the validated CTQ cut-off scores to detect any type of maltreatment and to grade the severity of maltreatment (26).

Ethics

The US study was approved by the MedStar Health, protocol number 2012-391. The Israeli study was approved by the institutional ethics review board of the Tel-Aviv Sourasky Medical Centre (protocol number 0507-13-TLV). There was no external funding for the study and the participating patients were not paid for their participation.

Statistical analysis

The data were analysed by SPSS v. 18.0. Categorical descriptive data were presented as absolute values with percentages and continuous data as mean (standard deviation). Group comparisons of categorical data were performed by  $\chi^2$  tests and of continuous data by the Mann-Whitney U-test. A p-value of  $\leq 0.05$  was assumed to be significant. We compared the CTQ-subscale scores of both groups by ANOVA (27).

Results

83 RA patients were recruited in the US and 23 patients were recruited in Israel. Patients with a concomitant diagnosis of fibromyalgia were excluded. This exclusion was in order to prevent a biased result. 69.8% of patients in the US cohort were Caucasians. All of the Israeli patients were of Caucasian Jewish origin; 8 patients (34.8%) were of Ashkenazi origin, while the other patients were of other non-Ashkenazi Jewish decent, including a variety of ethnic origins (North African, Yemenite, Iranian, Turkish, etc.). Additional demographic data of the American and Israeli patients is presented in Table I. Table II displays the comparison of the CTQ-subscores between the US and Israeli cohorts. Significant differences between the groups were only seen in the subscales of emotional neglect and emotional abuse. We have no data regarding emotional neglect and abuse in the general Israeli population, so we cannot compare the data regarding non-RA patients. Regarding the frequency of self-reported severe and very severe abuse/neglect in childhood/adolescence, the US and Israeli cohorts differed only in the emotional neglect subscale (Table III). Table IV displays the association between depression and severe abuse. By combining the American and the Israeli groups, we showed that only severe and very severe emotional abuse was significantly more frequently reported by RA patients with depressive disorder

**Table II.** Comparison of retrospective reports of childhood maltreatment of American and Israeli patients with rheumatoid arthritis.

Variable	USA (n=83)	Israel (n=23)	p-value
Emotional neglect CTQ (5-25) mean ± SD	10.30 ± 5.05	22.67 ± 3.68	0.009
Physical abuse CTQ (5-25) mean ± SD	7.16 ± 4.03	5.91 ± 2.66	0.165
Sexual abuse CTQ (5-25) mean ± SD	7.41 ± 4.44	6.22 ± 3.10	0.228
Emotional abuse CTQ (5-25) mean ± SD	10.46 ± 5.77	7.13 ± 4.84	<0.001
Physical neglect CTQ (5-25) mean ± SD	6.63 ± 2.81	6.01 ± 2.12	0.335

**Table III.** Comparison of retrospective reports on childhood adversities (assessed by Childhood Trauma Questionnaire) of American and Israeli patients with rheumatoid arthritis.

	USA (n=83)	Israel (n=23)	p-value
Severe and very severe emotional neglect n (%)	7 (8.4%)	20 (87.0%)	0.01
Severe and very severe physical abuse n (%)	2 (2.4%)	0	-
Severe and very severe sexual abuse n (%)	4 (4.8%)	0	-
Severe and very severe emotional abuse n (%)	9 (10.8%)	2 (8.7%)	0.18
Severe and very severe physical neglect n (%)	0	0	-

than without. In this aspect we did not attempt to compare the groups, but rather tried to examine the association of abuse/neglect and depressive disorder. This was done in order to show minimum association and by thus exclude a possible bias. We must also mention that PHQ-4 is a screening method for depression and not a method of definitive diagnosis.

In Table V we show that there was no statistically significant difference between RA-patients with and without anxiety disorder in the frequency of self-reported severe and very severe forms of childhood maltreatment.

Table VI displays the degree to which pain interferes with functioning regarding different broad areas of life, comparing between the US and Israeli cohorts, as reflected by the PDI questionnaire. Significant differences were found only in the sexual behaviour cat-

egory. We checked the PDI subscales in different areas of life.

Further analysis of the American group demonstrated that RA patients with previous traumatic events had significantly higher PDI scores compared with RA patients who had no report of traumatic event in their past (Table VII). Some correlation between past traumatic events and higher RADAI score was shown; however this was not statistically significant.

When analysing medical treatments received by the Israeli RA patients, revealed that 60% were being treated with biological medications, 39% were being treated with steroids, 39% were on anti-metabolite treatment (e.g. methotrexate), 13% were treated with hydroxychloroquine and 8% were on analgesics. Most patients were receiving more than one medication concomitantly.

**Discussion**

In the present cross-sectional study, the frequency of retrospectively reported childhood adversities and of lifetime traumatic events was compared between American and Israeli RA patients, in order to examine the transcultural validity of this association in RA patients.

Our results demonstrated in general a great deal of similarity between the two cohorts, except in the subscales of emotional abuse and emotional neglect, which were more frequently reported by US patients. Probable mental disorders, such as depressive disorder and anxiety, did not change significantly the frequency of severe and very-severe self-reported adversities.

Comparing the cohorts demographically demonstrated considerable similarity regarding female predominance and household partnerships, although differences were noted in educational and occupation subcategories. Also, the cohorts did not differ significantly in the degree to which pain interferes with functioning, except in the area of sexual behaviour among Americans. Such variance may partially reflect cultural differences regarding sexual openness, although such an explanation remains speculative.

A notable finding in the current study regards the finding of significantly higher PDAI scores among RA patients with a reported previous traumatic event when compared with patients without such a report (Table VII). As traumatic childhood events have previously often been associated with the subsequent development of chronic pain conditions such as fibromyalgia (28), this finding highlights the fact that pain as well as pain-related disability may also be as-

**Table IV.** Comparison of self-reported severe and very severe childhood adversities in American and Israeli rheumatoid arthritis patients (combined) with and without potential depressive disorder.

	With probable depressive disorder (n=32)	Without probable depressive disorder (n=73)	OR [95% CI]	p-value
Severe and very severe emotional neglect n (%)	10 (31.25%)	17 (23.28%)	1.497 [0.594- 3.771]	0.468
Severe and very severe physical abuse n (%)	1 (3.13%)	1 (1.37%)	2.323 [0.141-38.332]	0.519
Severe and very severe sexual abuse n (%)	2 (6.25%)	2 (2.74%)	2.367 [0.318-17.591]	0.584
Severe and very severe emotional abuse n (%)	8 (25%)	3 (4.11%)	7.778 [1.907-31.716]	<0.05
Severe and very severe physical neglect n (%)	-	-		

**Table V.** Comparison of self-reported severe and very severe childhood adversities in American and Israeli rheumatoid arthritis patients with and without potential anxiety disorder.

	With probable anxiety disorder (n=43)	Without probable anxiety disorder (n=62)	OR [95% CI]	p-value
Severe and very severe emotional neglect n (%)	13 (30.23%)	14 (22.58%)	1.486 [0.615-3.589]	0.496
Severe and very severe physical abuse n (%)	0	2 (3.23%)	-	0.512
Severe and very severe sexual abuse n (%)	2 (4.65%)	2 (3.23%)	1.463[0.198-10.811]	1
Severe and very severe emotional abuse n (%)	7 (16.28%)	4 (6.45%)	2.819 [0.771-10.314]	0.12
Severe and very severe physical neglect n (%)	-	-		

**Table VI.** Comparison of retrospective reports of the effect of pain in American and Israeli patients with rheumatoid arthritis.

	American score (n=83)	Israeli score (n=23)	p-value
Family mean ± SD	5.15 ± 3.10	4.70 ± 3.84	0.56
Recreation mean ± SD	6.12 ± 3.16	6.13 ± 3.72	0.98
Social activity mean ± SD	4.71 ± 3.22	3.22 ± 4.08	0.12
Occupation mean ± SD	5.28 ± 3.45	5.61 ± 4.15	0.33
Sexual behaviour mean ± SD	5.64 ± 3.70	3.16 ± 3.86	<0.05
Self-care mean ± SD	3.15 ± 2.87	3.26 ± 3.74	0.89
Little support activities mean ± SD	2.45 ± 2.70	2.91 ± 3.29	0.54

**Table VII.** comparison of PDI score and RADAI score between American RA patients with and without previous trauma.

	With previous trauma (n=19)	Without previous trauma (n=22)	p-value
PDI mean ± SD	36.89 ± 18.57	16.82 ± 14.85	<0.05
RADAI mean ± SD	31.53 ± 17.85	23.55 ± 16.65	0.147

sociated with trauma in patients suffering from inflammatory joint disease such as RA. This association has clinical relevance for physicians treating RA patients who are charged with addressing musculoskeletal pain which may appear to be not in direct correlations with clinical and laboratory markers of disease activity.

In a previous study conducted by Häuser *et al.* (16), adult fibromyalgia syndrome (FMS) was associated with childhood maltreatment and lifelong traumatic experiences, as was proven by investigating self-reported questionnaires of American and German FMS patients. In the current study, we used the same questionnaires among American and Israeli RA patients. Similar to the results of the FMS study, psychological stressors were also found to be linked to RA. The comparison of two heterogeneous populations from two vastly different countries thus emphasises the transcultural robustness of the findings.

Interestingly, we showed that RA patients who reported previous traumatic events had higher PDI score, compared to RA patients with no such a report, and also tended to have higher RADAI index. Hence, previous psychological stressors in RA patients are highly related to current disease severity, response to treatment and quality of life. Various theories have been suggested regarding the possible mechanisms underlying the association between psychological stressors and autoimmune disorders. Psychological stressors dysregulate the hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adreno-medullary system, resulting in dysregulation of different components of the immune system, which may lead to the development of autoimmunity. Previous studies have investigated the effect of psychological stressors, including sexual abuse and PTSD, on the immune system, and have shown that those stressors dysregulate specific components of the innate

immunity, as well as of the adaptive immunity (29-32). Recently intriguing evidence is accumulating regarding the role of epigenetic changes such as DNA methylation in the pathogenesis of stress-related disorders (33). Thus, in the case of RA, reduced methylation of the IL-6 promoter was demonstrated to be related to increased exposure to childhood trauma (34), providing an elegant mechanistic model for this association.

Notwithstanding these breakthroughs, the aetiology of autoimmune diseases remains a mystery. Our findings strengthen the hypothesis that psychological stressors are highly related to rheumatic diseases, including RA, emphasising the need for further research into the mechanisms underlying this association, in the hope of both achieving possible prevention as well as precise medical therapeutic strategies.

Our study had several limitations. It was carried out in the context of routine outpatient clinics, not by a professional psychiatric team. Data on childhood maltreatment in the past were based on self-reports, which are inherently subject to recall-bias. Furthermore, RA was proven to have a serious impact on mental health and may impose psychological stress owing to a greater disease burden (35), which hypothetically may influence the subjective answers of the patients in the present. However, inconsistencies in reporting traumatic events are also inherent in standardised psychiatric clinical interviews (36). Physical history of the patients did not include information regarding physical disorders other than RA. In addition the number of Israeli subjects is smaller than the number of the American subjects, which affected the statistical significance of our database.

The population examined consisted of an American group and an Israeli group, which are considered to be genetically and culturally different. We did not test the transcultural robustness of our findings on other populations. The two cohorts tested were different in size, thus some comparisons could not be completed.

Some practical clinical insights may be implemented in view of our results. Thus, clinicians treating RA patients may find it useful to keep in mind that some patients may demonstrate unexpectedly high levels of disability despite what appears to be a good clinical and laboratory response to treatment. Screening such patients for co-morbid mental disorders may be useful, and cases which screen positive for such disorders may benefit from referral to appropriate mental health professional, who might further explore the possibility of previous childhood adversity and trauma, as well as offering therapeutic interventions.

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