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Concise report

Clinically suspect arthralgia patients with a low educational attainment have an increased risk of developing inflammatory arthritis

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Abstract

Objectives. Cross-sectional studies have shown that rheumatoid arthritis is more prevalent among people with a lower educational attainment. No longitudinal data are present on educational attainment in the at-risk phase of clinically suspect arthralgia (CSA). We therefore analysed the association between educational attainment and progression from CSA to inflammatory arthritis (IA), and performed mediation analysis with subclinical joint inflammation to elucidate pathways of this association.

Methods. A total of 521 consecutive patients presenting with CSA were followed for IA development during median 25 months. Educational attainment was defined as low (lower secondary vocational education), intermediate or high (college/university education). Subclinical inflammation in hand and foot joints was measured at presentation with contrast enhanced 1.5 T-MRI. Cox-regression was used to analyse IA development per educational attainment. A three-step mediation analysis evaluated whether subclinical joint inflammation was intermediary in the path between educational attainment and IA development, before and after age correction. Association between educational attainment and IA development was verified in an independent CSA cohort.

Results. Low educational attainment was associated with increased IA development (HR = 2.35, 95% CI = 1.27, 4.33, $P = 0.006$), independent of BMI and current smoking status (yes/no). Moreover, patients with a low educational attainment had higher levels of subclinical inflammation, which also was associated with IA development. Partial mediation effect of subclinical inflammation was observed in the relationship between education and IA development. Low educational attainment was also associated with increased IA development in the validation cohort (HR = 5.72, 95% CI = 1.36, 24.08, $P = 0.017$).

Conclusion. This is the first study providing evidence that lower educational attainment is associated with a higher risk of progressing from arthralgia to IA. This effect was partially mediated by subclinical joint inflammation.

Key words: Educational attainment, clinically suspect arthralgia, rheumatoid arthritis, socio-economic status

Rheumatology key messages

- Lower educational attainment is associated with higher risk of progressing from arthralgia to inflammatory arthritis.
- This association is partially mediated by more subclinical inflammation in patients with lower educational attainment.
- These results emphasize the relevance of socio-economic status during the development of rheumatoid arthritis.

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CLINICAL SCIENCE

Introduction

RA is a highly prevalent disease and is a major cause of reduced disability adjusted life years worldwide [1]. Although the exact developmental pathway of this systemic auto-immune disease remains largely unknown, genetic and environmental factors both contribute to RA development [2]. Previous studies on demographic factors have shown that RA is not equally distributed throughout the population and that RA is more prevalent among individuals with a lower educational attainment. This association has been observed in studies comparing RA prevalence between different countries, but also within the same country; thus, when national health care services are similar [3, 4]. Educational attainment is described as the highest completed educational grade and is an established proxy for an individual's socioeconomic status (SES) [5].

Low education has not only been associated with an increased RA prevalence, but also with increased disease activity within RA patients [6–8]. This association was partially mediated by less uptake of costly bDMARDs in patients with a lower educational attainment [7]. These findings suggest that a more severe disease course may be explained by environmental factors that are associated with lower SES and RA-related inflammation, but also by factors that are related to the health system such as patients' health literacy, access to early referral strategies and implementation of tight disease control [6].

Although it is known that low educational attainment is associated with a higher prevalence of RA, the timing of the effects of socioeconomic factors on disease development is completely unidentified. RA development can be differentiated in an asymptomatic phase in which auto-immune responses can develop and increased inflammatory markers can be found [9]. This is followed by a symptomatic period in which patients have symptoms and impairments while clinical arthritis is absent. Patients in this latter phase are described as having clinically suspect arthralgia (CSA) [10]. Longitudinal studies on educational attainment in these individuals at risk for RA could shed light on the disease phase in which socioeconomic factors have an impact on RA development. Because no studies on educational attainment in the pre-RA phase have been performed to date, we aimed to determine the association between educational attainment and progression from CSA to inflammatory arthritis (IA), and to perform mediation analysis with subclinical joint inflammation to elucidate pathways of this association.

Patients and methods

Patients

We longitudinally studied CSA patients who were consecutively included in the Leiden CSA cohort and had at least one year follow-up. The CSA cohort is an inception cohort including patients with arthralgia of the small joints for less than one year that is considered suspicious for progression to RA and in whom the arthralgia cannot be explained by another disease (Supplementary Data S1, available at *Rheumatology* online). Patients were followed up for two years for development of clinical arthritis, confirmed with joint swelling at physical examination by the rheumatologist. During total follow-up until clinical arthritis development, CSA patients were not treated with DMARDs (including corticosteroids). All patients provided written informed consent.

Educational attainment and inflammation

Patient-reported educational attainment was defined as low (lower secondary vocational education), intermediate or high (college or university education) based on the Dutch education system. Furthermore, all patients underwent a unilateral contrast-enhanced 1.5 T MRI of hand and foot at baseline on the side with the most symptoms, or the dominant side when symptom severity was symmetrical. The MRI was evaluated for subclinical joint inflammation. Subclinical joint inflammation was defined as the sum of synovitis, tenosynovitis and osteitis, and was scored according to the method of rheumatoid arthritis MRI scoring system (RAMRIS) and Haavardsholm (Supplementary Data S2 and S3, available at *Rheumatology* online).

External validation in an independent CSA cohort

In order to externally validate our results, we analysed the association between educational attainment and IA development in an independent CSA cohort from Rotterdam, the Netherlands. The inclusion criteria, follow-up scheme and further protocol was completely similar to that of the Leiden CSA cohort (Supplementary Data S1, available at *Rheumatology* online), with the only difference that no MRI was made in the Rotterdam cohort. Patients with at least one year follow-up were included. All patients provided written informed consent.

Statistical analyses

The association between educational attainment and IA development was studied with Cox regression analysis. Additionally, ACPA stratification was performed. To evaluate if subclinical joint inflammation is intermediary in the path between educational attainment and IA development, a three-step mediation analysis was performed according to Baron and Kenny [11]. Thereafter, we performed mediation analyses between educational attainment and subclinical joint inflammation through BMI, current smoking status (yes/no) and patient delay. Current smoking status (yes/no) was assessed at baseline and did not include former smoking status. The association between educational attainment and subclinical joint inflammation was studied with linear regression analyses in which inflammation scores were transformed (ln(inflammation-score + 1)) to approximate a normal

Table 1 Patient characteristics

CSA cohort Leiden	Low education ($n = 66$)	Intermediate education ($n = 258$)	High education ($n = 197$)	*P*-value low *vs* high
Female	47 (71)	202 (78)	159 (81)	0.11
Age (years)	51 (12)	43 (14)	44 (11)	<0.001
ACPA-positive	9 (14)	35 (14)	21 (11)	0.51
RF-positive	9 (14)	46 (18)	41 (21)	0.19
MRI-detected inflammation	4.5 (2.5–9.25)	3.0 (1.5-6.0)	2.5 (1.5-4.5)	<0.001
Positive MRI	37 (57)	97 (40)	65 (36)	0.003
CRP increased (≥5 mg/L)	23 (35)	60 (23)	30 (16)	0.001
BMI	28.6 (5.0)	27.0 (5.4)	25.2 (3.9)	<0.001
Current smoking status, yes	20 (31)	67 (26)	26 (13)	0.001
Symptom duration (days)[a]	170 (64–331)	154 (89–365)	120 (61–308)	0.28
Patient delay (days)[b]	123 (32–214)	96 (31–244)	69 (30–158)	0.041
Referral delay (days)[c]	23 (11–42)	23 (14–62)	25 (11–52)	0.71
CSA cohort Rotterdam (validation)	**Low education ($n = 9$)**	**Intermediate education ($n = 28$)**	**High education ($n = 22$)**	***P*-value low *vs* high**
Female	4 (44)	23 (82)	16 (73)	0.066
Age (years)	55 (16)	44 (14)	47 (8)	0.032
ACPA-positive	5 (56)	6 (21)	3 (14)	0.032
RF-positive	3 (38)	8 (29)	5 (25)	0.57
CRP increased (≥5 mg/L)	3 (38)	4 (16)	3 (14)	0.26
BMI	29.1 (8.3)	29.6 (6.6)	25.6 (3.5)	0.29
Current smoking status, yes	3 (33)	4 (14)	3 (14)	0.089
Symptom duration (days)[a]	91 (81–179)	138 (62–266)	181 (115–335)	0.35
Patient delay (days)[b]	45 (1–103)	45 (14–131)	103 (34–199)	0.13
Referral delay (days)[c]	57 (34–77)	61 (34–120)	62 (37–97)	0.90

Legend: data are *n* (%), mean (S.D.) or median (IQR). [a]'Symptom duration' is the total duration of symptoms during the first visit to the rheumatologist. [b]'Patient delay' is the time between symptom onset and visiting the general practitioner. [c]'Referral delay' is the time between the first visit to the general practitioner and the rheumatologist.

distribution. SPSS v.25 was used and *P*-values < 0.05 were considered statistically significant.

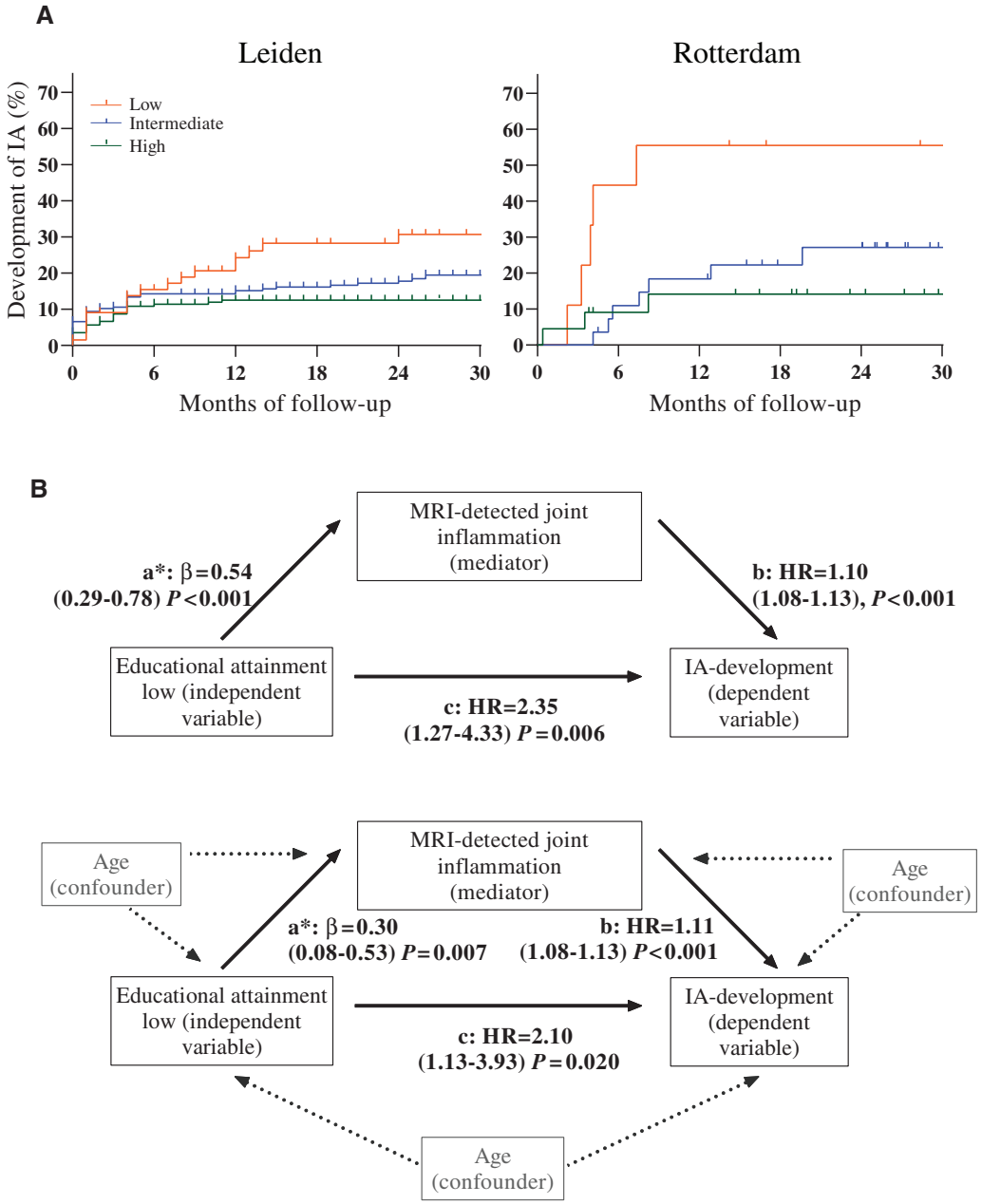
Results

For the current study, 109 CSA patients were excluded from analyses because of participation in the TREAT-EARLIER Trial [12]. Additionally, 79 patients were excluded because data on educational attainment was missing. Baseline characteristics and IA development during follow-up were comparable in patients with and without data on educational attainment. Patient characteristics at first presentation ($n = 521$) are shown in Table 1. Sixty-six patients (13%) had a low educational attainment, compared with 258 (50%) with an intermediate and 197 (38%) with a high educational attainment. Patients with a low educational attainment were on average older [51 (12) *vs* 44 (11) years, $P < 0.001$], had a higher BMI [28.6 (5.0) *vs* 25.2 (3.9), $P < 0.001$], and were more often current smokers (31% *vs* 13%, $P = 0.001$) compared with patients with a high educational attainment (Table 1). In addition, patients with a low educational attainment waited longer before visiting the general practitioner ('patient delay'), were more likely to have an elevated CRP (35% *vs* 16%, $P = 0.001$) and had higher levels of subclinical joint inflammation [4.5(2.5–9.25) *vs* 2.5 (1.5–4.5), $P < 0.001$].

Educational attainment and IA development

Median follow-up duration was 25.0 months (IQR 18.0–26.0). Low educational attainment was associated with increased IA development (HR = 2.35, 95% CI = 1.27, 4.33, $P = 0.006$; Fig.1A), compared with high educational attainment. This association was present, independent of lifestyle factors such as BMI and current smoking status (yes/no) (HR = 2.68, 95% CI = 1.40, 5.14, $P = 0.003$). An ACPA-stratified analysis suggested that low educational attainment was associated with increased IA development in both ACPA-positive and ACPA-negative CSA

FIG. 1 (**A**) IA development according to level of educational attainment, (**B**) mediation analyses between educational attainment and IA development



(**A**) development of inflammatory arthritis (IA) in patients with clinically suspect arthralgia (CSA) is shown according to level of educational attainment, defined as low (lower general secondary education), intermediate or high (college or university education). In the Leiden CSA cohort (n = 521), low educational attainment was associated with increased IA development (HR = 2.35, 95% CI = 1.27, 4.33, $P = 0.006$), compared to high educational attainment. In the Rotterdam CSA cohort ($n = 59$), this association was: HR = 5.72, 95% CI = 1.36, 24.08, $P = 0.017$. (**B**) mediation analyses were performed in the Leiden CSA cohort according to Baron and Kenny. In the model above, the association between educational attainment and IA development (c) decreased after adding subclinical joint inflammation (HR = 1.70, 95% CI = 0.89, 3.25, $P = 0.108$). In the model below, correction for age was performed and a comparable decrease occurred in (c): HR = 1.82, 95% CI = 0.93, 3.57, $P = 0.080$. This suggests that the association between educational attainment and IA development is partially mediated by subclinical joint inflammation. *a=effect sizes are estimated on a natural logarithmic scale.

(Supplementary Fig. S1, available at *Rheumatology* online).

Mediation analysis with subclinical joint inflammation

Low educational attainment could potentially be associated with increased IA development through a mediating effect of subclinical joint inflammation. To study this assumption, a mediation analysis was performed according to Baron and Kenny, who described three requirements (Fig. 1B) [11]. First, the independent variable (educational attainment) should be associated with the dependent variable (IA-development) (c), which was the case (HR = 2.35, 95% CI = 1.27, 4.33, $P = 0.006$). Second, the independent variable is associated with the mediator (a): low educational attainment was associated with more subclinical joint inflammation ($\beta = 0.54$, 95% CI = 0.29, 0.78, $P < 0.001$, on a natural logarithmic scale). A β of 0.54 on a natural logarithmic scale can be interpreted as an increase of 54% in MRI-detected subclinical inflammation in patients with a low educational attainment, compared with those with a high educational level. And third, the mediator should be associated with the dependent variable (b): subclinical joint inflammation was associated with IA development (HR = 1.10, 95% CI = 1.08, 1.13, $P < 0.001$). The association between educational attainment and IA development (c) decreased after adding subclinical joint inflammation to the model (HR = 1.70, 95% CI = 0.89, 3.25, $P = 0.11$), suggesting that the association between low educational attainment and IA development is partially mediated by higher levels of subclinical joint inflammation. Because CSA patients with a low educational attainment were older, the mediation analysis was repeated with correction for age. This showed a comparable mediating effect of subclinical joint inflammation (Fig.1B).

Mediation analyses with smoking and BMI

Patients with a low educational attainment had a higher BMI and smoked more often (Table 1). Smoking and BMI did not mediate the association between education with IA development as both factors were not associated with progression from CSA to IA (HR = 1.51, 95% CI = 0.95, 2.40, $P = 0.084$ for smoking and HR = 0.99, 95% CI = 0.95, 1.04, $P = 0.76$ for BMI). Next, we wondered if smoking and/or BMI had mediated the development of more severe subclinical joint inflammation. Therefore, we performed a mediation analysis between educational attainment and subclinical MRI-detected joint inflammation. This showed that neither smoking, nor BMI mediated the presence of subclinical joint inflammation in this group (Supplementary Fig. S2A and B, available at *Rheumatology* online).

Mediation analysis with patient delay

In addition to differences in BMI and smoking status, patients with a low educational attainment had a longer 'patient delay' in the Leiden CSA cohort, indicating that they waited longer with going to the general practitioner, while there was no difference in the time between the first visit to the general practitioner and the rheumatologist ('referral delay'). Patient delay did not mediate the effect of education with IA development as it was not associated with progression from CSA to IA (HR = 1.00, 95% CI = 0.999, 1.00, $P = 0.43$). Furthermore, patient delay did not mediate the association between educational attainment and subclinical MRI-detected joint inflammation (Supplementary Fig. S2C, available at *Rheumatology* online).

External validation in an independent CSA cohort

Finally, we analysed the association of lower educational attainment with IA development in an independent CSA cohort to validate the findings. The sample size of the Rotterdam CSA cohort was smaller ($n = 59$), but also in this cohort, patients with a lower educational attainment were on average older and smoked more often. The stepwise increasing risk of IA development according to level of educational attainment in this CSA cohort was comparable to the Leiden CSA cohort (Fig.1A) and patients with a low educational attainment had an increased hazard to develop IA compared with patients with a high educational attainment: HR = 5.72, 95% CI = 1.36, 24.08, $P = 0.017$. This association remained, independent of BMI and current smoking status (HR = 5.81, 95% CI = 1.26, 26.83, $P = 0.024$).

Discussion

Although it has been described that lower educational attainment, or lower socio-economic status, is associated with an increased prevalence of RA, it was unknown in which RA period SES-related factors exert their effect. We studied the symptomatic pre-RA phase, during which some patients progressed to RA and others did not, and demonstrated that patients with a lower educational attainment had a twofold increased hazard to develop IA. Moreover, we observed that this was partially mediated by more subclinical joint inflammation in patients with a low educational attainment. The fact that our finding of increased risk was validated in an independent CSA cohort reinforces the robustness of the results.

From this, the important question arises why patients with lower educational attainment had an increased risk for IA development. Educational attainment is a proxy for SES [5]. Multiple environmental factors for RA are more prevalent in persons with a lower SES; for instance a higher BMI, more smoking and air pollution, and a lower dietary intake of fatty acids [13–15]. In addition, physical workload has been associated with increased RA prevalence and this association may be mediated by joint inflammation [16]. A limitation of our study is that we could analyse the risk and lifestyle factors BMI and smoking, but had no information on air pollution, diet or physical workload. Interestingly, difference in smoking and BMI did not underly the association of educational attainment/SES with IA development in our data.

Deductively, the increased hazard for IA development was either mediated by environmental factors that we did not study, less easily measured lifestyle choices and circumstances, overall health and well-being, and/or a potential interplay between these factors.

In line with an increased IA development in patients with lower educational attainment, we also showed more local subclinical joint inflammation in these patients, which was not mediated by BMI or current smoking status. This finding is also suggestive for unmeasured risk factors and mediating factors that are related to SES and promote joint inflammation processes during RA development.

Apart from biological factors that are related to SES and joint inflammation, evaluating potential differences in health literacy is also important when interpreting our results. As such, we observed that the time between symptom onset and the first visit to the general practitioner is longer in persons with a low educational attainment in one of the cohorts. Although this finding did not mediate the association with IA development and thus does not explain the increased risk for progression from arthralgia to clinical arthritis, it underlines the relevance of health literacy when focusing on early (referral) strategies in rheumatology.

A limitation in our study is that we could not study health literacy more directly and used educational attainment as a proxy for health literacy. The concept of health literacy covers multiple aspect including personal competencies and situational resources needed for people to access, understand, appraise and use information and services to make decisions about health [17]. Although educational attainment covers more than only health literacy, these two factors are highly correlated [18].

In conclusion, this is the first study demonstrating that a lower educational attainment confers an increased risk for development of inflammatory arthritis in patients with clinically suspect arthralgia. This association was partially mediated by more subclinical joint inflammation in patients with lower educational attainment, but was not explained by smoking, BMI or a delay in seeking medical care. These results emphasize the role of SES during the symptomatic pre-RA phase in RA development. In addition, these results promote further studies on the effects of SES on RA development, as increased comprehension may provide clues for interventions targeting the underlying processes or factors during RA development. Finally, the current data show evident risks related to health disparities, and support putting societal health inequalities on the public health agenda.

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Disclosure statement: The authors have declared no conflicts of interest.

Ethics: The study was conducted in compliance with the Helsinki Declaration. Written informed consent was obtained from all patients. Research protocol for the Leiden CSA cohort (P11.210) was approved by the local Medical Ethical Committee of the Leiden University Medical Center (LUMC). Research protocol for the Rotterdam CSA cohort (MEC-2017–028) was approved by the local Medical Ethical Committee of the Erasmus Medical Center (EMC).

Data availability statement

The data underlying this article are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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