We examined: 1. the total effect of latitude on age at diagnosis at hospital and country level (Main model); 2. the amount of the total effect that is mediated by patient factors at the patient and hospital level (Model A); and 3. the amount of the total effect that is mediated by country factors at the country level (Model B). In each model we disentangled the effect in different measurement levels. For example, a patient level variable can vary at the patient, hospital, and country level.

Results: We included 39,782 patients nested in 94 hospitals nested in 17 countries. The mean age at diagnosis per country ranged from 39 to 55 years. The study spanned a range of latitude between 9.9 and 55.8 degrees (i.e. from Nige- ria to the United Kingdom). In the main model, we confirmed the association between latitude and age at diagnosis and found that it only occurred at the county level (not at the hospital level). Per degree increase in country latitude, the average age at diagnosis per country increased by 0.23 years (95% credibility interval 0.07; 0.40). At the hospital level however, this effect was negligible: β=0.040 [0.16; 0.00] which means associations between latitude and several patient factors were not found at the country level, but these patient factors only associated with age at diagnosis at the patient level, not at the country (or hospital) level (Model A).

This means patient-factors did not explain the association between latitude and age at diagnosis at the country level (main effect changed from 0.23 before to 0.37 after inclusion of patient factors). In model B latitude associated with most country factors (except GDP per capita). Even though none of these variables separately were significantly associated with age at diagnosis, inclusion of the set of country level factors reduced the country level effect of latitude on age at diagnosis from 0.23 to almost zero: β=0.033 [-0.51; 0.37]. Sensitivity analyses with age at symptom onset as outcome provided similar results.

Conclusion: Patients living close at the equator indeed get RA far earlier than those living closer to the poles. We here suggest that, rather than due to variations in patients characteristics, this latitude gradient is a country level phenomenon explained by indicators of countries’ socioeconomic status, and not by patient specific genetic or environmental factors. This big data analysis in a worldwide prevalence cohort provides a direct link between countries’ levels of welfare and the onset of RA.

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[Image 307x542 to 547x659]

Background: Cross-sectional studies on educational levels have shown that inflammatory arthritis (IA) and rheumatoid arthritis (RA) are more prevalent among people with a lower educational attainment. Studies on educational attainment in individuals at risk for RA could shed light on the influence of socioeconomic factors on RA development, which is divided in an asymptomatic and symptomatic pre-RA stage. To our knowledge, longitudinal studies on educational attainment and IA-development in symptomatic individuals at risk of RA are lacking.

Objectives: To determine the association between educational attainment and progression from clinically suspect arthralgia to IA and to perform mediation analysis to elucidate pathways.

Methods: 600 consecutive patients presenting with clinically suspect arthralgia were followed for the development of IA, identified at joint examination by rheumatologists during median follow-up of 25 months. Educational attainment was defined as low (lower general secondary education), medium, or high (college or university education). Contrast enhanced 1.5T MRI of hand and foot were made throughout the entire study period. To evaluate if subclinical joint inflammation is intermediary in the path of educational attainment and IA-development, a three-step mediation analysis was performed, before and after correction for age. Results: Patients with a low level of educational attainment were older, had a higher BMI, and smoked more often compared to patients with a high educational level. Low educational attainment was associated with increased IA-development (HR=2.5, 95%CI=1.4-4.7; p=0.003; see Figure 1), also after correction for age, BMI and smoking-status (HR=2.1, 95%CI=1.03-4.4; p=0.041). Moreover, patients with a lower educational level had higher levels of subclinical inflammation at presenta- tion, which associated with a higher risk of progression to IA. Mediation analyses revealed that the association between low educational attainment and IA-de- velopment reduced when adding the level of subclinical inflammation (HR=1.8, 95%CI=0.9-3.5, p=0.073), suggesting that the association between educational attainment and IA-development is partly mediated by higher levels of subclinical inflammation. Mediation analysis with age correction provided similar results.

Figure. Progression from clinically suspect arthralgia to inflammatory arthritis (IA), according to educational attainment

Conclusion: This is the first evidence that lower educational attainment of patients with arthritis is associated with a higher risk of developing arthritis. This is partly caused by more severe subclinical joint inflammation. Further research into the role of socioeconomic factors on the development of RA is warranted.

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OP0037

USE OF PRIMARY HEALTHCARE AND RADIOLOGICAL IMAGING PRECEDING A DIAGNOSIS OF RHEUMATOID ARTHRITIS: A DANISH NATIONWIDE COHORT STUDY

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Background: Focus on early diagnosis and treatment initiation is key in rheuma- toid arthritis (RA) to prevent permanent joint damage and systemic manifestations. Increased use of healthcare services before an RA diagnosis can be seen as a proxy for symptom presentation and the actions taken by healthcare profession- als, and thus indicate an opportunity for earlier diagnosis. However, little is known about where and when people use healthcare services before an RA diagnosis.

Objectives: To explore the pattern in use of healthcare services during the 12 months preceding a diagnosis of RA in Denmark.

Methods: We conducted a population-based cohort study using data from Danish national registries. For every patient diagnosed with RA in 2014-2018 we matched ten reference persons from the Danish general population without RA, listed in the same general practice and with same age and sex. Healthcare use was defined as: daytime visits, face to face contacts to general practice, contacts to private practice rheumatologists. We estimated the monthly healthcare use for patients with RA and reference persons in the 12 months preceding the diagnosis, and we compared their healthcare use by incidence rate ratios (IRR) for each month, adjusted for socio- demographic characteristics and comorbidity.

Results: 10,270 RA and 74,270 reference persons were included in the study. The median age was 62 years (interquartile interval IQR): 51-71, and 65% were women. Patients with RA had an average of 0.5 contacts per month in general practice from 12 months until six months prior to the diagnosis (Figure 1); this number increased from six months before the diagnosis to an average of one contact in the last month before the diagnosis. Reference persons had an average of 0.4 contacts per months throughout the entire study period. Compared to their references, patients with RA had statistically significantly more contacts during all 12 months before the diagnosis date. IRR increased from 1.25 (95% CI: 1.19-1.30) to 2.63 (2.55-2.71) during the study period. Patients with RA also had statistically significantly more contacts to physiotherapists compared to their references throughout the entire study period, and increasing contact rates from eight months before the diagnosis. This was pri- marily driven by more contacts in women with RA compared to their references. Conclusion: Patients with RA had more contacts to general practice and physio- therapists in all 12 months preceding the RA diagnosis compared to references and these contact rates increased further the last six to eight months in patients with RA. This indicates symptom presentation for several months before the RA
is diagnosed, and it indicates that a window of opportunity exists to expedite referral to specialist care and the diagnosis of RA.

Background: Strong biologic rationale supports both vitamin D and marine omega-3 (n-3) fatty acids for prevention of autoimmune disease (AD). Within the randomized, double-blind, placebo-controlled VITamin D and OmegaA-3 Trial (VITAL), we tested the effects of these supplements on AD incidence. We previously reported results after 5.3 years of randomized follow-up showing overall protective effects for vitamin D on AD incidence (HR 0.78, 95% CI 0.61-0.99) and suggestive results for n-3 fatty acids (HR 0.85, 95%CI 0.67-1.08)\(^1\).

Objectives: We aimed to test effects of these supplements with two more years of post-intervention follow-up in VITAL.

Methods: VITAL enrolled and randomized men and women (age ≥50 and ≥55 years, respectively) in a 2-by-2 factorial design to vitamin D\(_3\) (2000 IU/d) and/or n-3 fatty acids (1000 mg/d) or placebo and followed for median 5.3 years. Here, we followed participants for another 2 years of observation to assess for sustained effects. Incident AD diagnoses were reported by participants annually and confirmed by medical record review by expert physicians using existing classification criteria. The primary endpoint was total incident AD, including rheumatoid arthritis (RA), polymyalgia rheumatica (PMR), autoimmune thyroid disease (AITD), psoriasis, and all others. Pre-specified secondary endpoints included individual common AD; and probable AD. Cox models calculated hazard ratios (HR) for incident ADs.

Results: Of 25,871 participants randomized, 71% self-reported non-Hispanic Whites, 20% Black, 9% other racial/ethnic groups, 51% women, mean age was 67.1 years. During 7.5 years median follow-up, confirmed AD was diagnosed in 156 participants in vitamin D arm vs 198 in vitamin D placebo arm, HR 0.79 (0.64-0.97). Incident AD was confirmed in 167 participants in n-3 fatty acid arm and 187 in n-3 fatty acid placebo arm, HR 0.89 (0.72-1.01). For vitamin D, HRs trended toward reduction for RA 0.67 (0.37-1.21) and PMR 0.69 (0.46-1.03) and psoriasis 0.57 (0.33-0.99). For n-3 fatty acids, HRs trended toward reduction for RA 0.69 (0.37-1.21) and PMR 0.69 (0.46-1.03) and psoriasis 0.57 (0.33-0.99). For n-3 fatty acids, HRs trended toward reduction for RA 0.58 (0.30-1.10) and AITD 0.61 (0.33-1.12). Vitamin D’s effect on AD incidence was stronger in those with body mass index (BMI) < 25 (HR 0.65, 0.44-0.96) than ≥ 25 kg/m\(^2\) (p interaction 0.01).

Conclusion: Supplementation for 5.3 years with 2000 IU/day vitamin D (compared to placebo), followed by 2 years of observational follow-up, significantly reduced overall incident AD by 21% in older adults. HRs for RA, PMR and psoriasis trended toward reduction with vitamin D, with stronger effect in those with normal BMI. Supplementation with 1000 mg/day n-3 fatty acids did not significantly reduce total AD.

REFERENCES: