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Functional Disability to Evaluate the Risk of Arthritis in First-degree Relatives of Patients With Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** The events that occur prior to the onset of rheumatoid arthritis (RA) continue to be delineated. We examined the relationship between self-reported joint symptoms, functional disability, and anticitrullinated protein antibody (ACPA) status in a cohort of first-degree relatives (FDR) of patients with RA who are at risk of future disease development.

Methods. We studied a cohort of 279 FDR of First Nations (FN) patients with RA who are at increased risk for future RA development, and analyzed data collected at their enrollment study visit. In parallel, we analyzed data from 279 FN subjects with no family history of RA. A subset of FDR developed inflammatory arthritis and we analyzed longitudinal data in this group.

Results. The prevalence of joint symptoms and functional disability was higher in FDR compared to non-FDR (all $P < 0.001$). Difficulty walking (37.3% vs 18.0%) and modified Health Assessment Questionnaire (HAQ) results were higher in ACPA-positive FDR compared to ACPA-negative FDR, and HAQ was independently associated with ACPA seropositivity (OR 2.79, 95% CI 1.56–5.00). Longitudinally, in individuals who developed ACPA-positive RA, ACPA level and HAQ score were significantly associated ($R = 0.45$, $P < 0.001$) in the preclinical period.

Conclusion. Compared to population-based controls, FDR have a high burden of joint symptoms and functional disability. Functional disability was most closely associated with ACPA seropositivity in the FDR, suggesting a direct role for ACPA outside of the context of clinically detectable synovitis. HAQ appears to be particularly valuable in the assessment of individuals at risk for future RA development.

Key Indexing Terms: anticitrullinated protein antibodies, modified Health Assessment Questionnaire, preclinical rheumatoid arthritis, rheumatoid arthritis, risk

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease that primarily targets the synovial joints and which, if not treated effectively early in the disease course, causes irreversible articular damage leading to disability and functional decline.[1] It is now well established that prior to the onset of clinically detectable RA (preclinical RA), most individuals develop anticitrullinated protein antibodies (ACPA), along with a spectrum of other autoantibodies.[2] Individuals with RA-associated autoantibodies may exhibit symptoms that are typical of established disease, such as joint pain (arthralgia), tenderness, and stiffness. Thus, a key clinical research strategy has emerged where individuals with RA-associated autoantibodies and suggestive symptoms such as arthralgia are recruited into structured cohorts and followed longitudinally for onset of clinically detectable synovitis. Much has been learned about the preclinical stages of RA from cohort studies of at-risk individuals who present with clinically suspect arthralgia (CSA), with or without detectable RA autoantibodies.[1,3,4,5,6] While these 2 key clinical domains are often the basis of referral to specialized centers, the relationship between the 2 domains remains poorly understood. Whether symptom onset is representative of a key biological event that stratifies individuals at the highest risk to develop inflammatory arthritis (IA) remains unknown. Further, exactly how to evaluate individuals with preclinical RA symptoms has not been clearly defined.[7]

Based on a model where human ACPA are introduced into a mouse, it has been suggested that the ACPA may have a direct role in generating pain.[8] It is proposed that ACPA activate cellular mechanisms that drive chemokines to modulate nociception.[9] Moreover, other models have shown that immune complex-mediated activation of neurons facilitates mechanical hypersensitivity.[10] Indeed, it was recently shown in an at-risk first-degree relative (FDR) cohort that individuals with ACPA displayed enhanced symmetrical joint pain.[11] Therefore, if pathogenic ACPA leads to enhanced pain, it might provide a biological explanation for preclinical symptomatology in individuals who develop IA.

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To better understand the interplay between symptomatology and autoantibody development in preclinical RA, we undertook a prospective longitudinal study of unaffected First Nations (FN) FDR of patients with RA, a population with a strong predilection to develop RA due, in part, to high prevalence of HLA-DRB1 risk alleles. This genetic risk variant has been shown to closely associate with the development of ACPA.[12,13] Given this, we sought to understand the interaction between self-reported symptomatology, functional disability, and ACPA seropositivity, and our hypothesis was that these variables would be associative in individuals at high risk for RA development.

METHODS

Cohort recruitment. Methods and protocols for patient recruitment into this study were described in our group's previously published work[14] for the cohort of FDR. In brief, First Nations probands with RA who met the 2010 American College of Rheumatology/European League Against Rheumatism criteria[15] were asked to help recruit their eligible FDR for longitudinal follow-up. Patients with RA (probands) and FDR were required to have at least 3 grandparents with FN ethnicity by self-report and be aged ≥ 18 years. The cohort has been described in previous publications, and participants were followed for an average of approximately 5 years.[5] Non-FDR were recruited from a separate study investigating environmental risk factors associated with RA autoantibodies.

Ethics. All study participants provided informed consent in accordance with the Declaration of Helsinki. The Biomedical Research Ethics Board of the University of Manitoba approved all aspects of the study (board approval number HS14453). Specific community research agreements were put in place with the study communities, and we established an arthritis advisory board to provide FN peoples' oversight for the study.

Participants entered the longitudinal study and underwent annual examination for the presence of clinical synovitis. At inception, all FDR were examined by a rheumatologist to confirm the absence of IA and 44 tender and swollen joint counts were recorded using a homunculus. Clinical assessments for new symptoms that were triggered by participants occurred as soon as possible. If synovitis was detected in ≥ 1 joints, the participant was deemed to have progressed into IA. ACPA were detected using cyclic citrullinated peptide-2 or cyclic citrullinated peptide-3 ELISA using the manufacturer's cutoff. A second cohort recruited for an alternate but related study was used as a non-FDR comparator group. Of note, all non-FDR included in this study were recruited from rural locations. An overview of the cohorts can be found in Supplementary Figure 1 (available with the online version of this article).

Survey. Demographics, BMI, and smoking history were recorded at the inception visit. A survey was completed by each participant that included a modified Health Assessment Questionnaire (herein referred to as HAQ), along with other questions on daily function (Supplementary Figure 2, available with the online version of this article). Three visual analog scales were completed on fatigue, patient global health, and pain. An arthritis symptom survey was also used to identify participant experiences with symptoms that are commonly observed in RA, including joint pain, stiffness, and swelling (Section E, Questions 4–9).

Statistical Analysis. Data from each participant's inception survey were extracted and loaded into R (R Foundation for Statistical Computing) for the statistical analysis. Missing data were imputed using multiple imputation by chained equations.[16] We observed very few responses to the ordinal scale that were > 1; therefore, we converted to answers to binary,[17] using a logical cutoff of yes (some difficulty, much difficulty, or unable to do) and no (performed without any difficulty). Inception data analyses are presented as either continuous (median with IQR) or as a proportion (percentage). Chi-square test was used to analyze binary outcomes, while Wilcoxon signed-rank test was used for continuous outcomes, and within each survey we corrected for multiple comparisons using the Benjamini-Hochberg method. Relationships between continuous variables were analyzed using Spearman correlation. A correlation matrix was constructed to analyze the relationship within patient-reported symptoms using Spearman correlation corrected by Bonferroni. Logistic regression models were constructed to identify independent variables that associated with ACPA seropositivity. HAQ, the variable of interest, and its association with ACPA was controlled for sex, age, and location (rural/urban). Our results suggested that functional disability, specifically difficulty walking on flat ground, was enriched in ACPA-seropositive FDR. To better understand why some FDR report difficulty walking on flat ground, we extracted clinical joint exams from all individuals who reported difficulty with walking (n = 118) and a cohort of FDR without difficulty walking, matched by propensity score derived from age, sex, BMI, and location (rural/urban).

Although ACPA seropositivity is the best predictor for the development of future RA, we have previously shown in our prospective cohort of at-risk FDR that individuals who are ACPA positive commonly seroconvert to ACPA negative when followed over time.[5] For our longitudinal analysis, we filtered out participants who had only a single visit or a single ACPA measurement (missing ACPA levels were excluded from the analysis and not imputed). We then surveyed longitudinal serological data and classified each participant as follows: (1) persistently ACPA negative or ACPA seroconverted, where the participant was ACPA positive, but on subsequent visits became ACPA negative and remained so until their last visit; (2) persistently ACPA positive; or (3) developed ACPA-positive RA. All graphs were generated in R using the package ggplot2. For all statistical tests, an adjusted P value of < 0.05 was considered statistically significant.

RESULTS

Self-reported joint symptoms and functional disability are more prevalent in FDR of patients with RA compared to non-FDR. We used survey data generated from 2 distinct FN cohorts, 1 cohort of RA proband FDR (n = 607), and another non-FDR cohort (n = 279) to identify specific symptoms enriched in those at future risk of RA development. There were no significant differences in sex between the 2 cohorts, but the FDR cohort was slightly older (35.1 vs 31.8 yrs, $P = 0.003$; Table 1). We found that all self-reported joint symptoms were significantly increased in FDR (Figure 1A). A wide range of functional disability based on the HAQ questionnaire also revealed clear differences between the 2 cohorts (Figure 1B). Overall, the mean HAQ score was higher in the FDR cohort (0.22 vs 0.09, $P < 0.0001$; Figure 1C), suggesting higher global functional disability. Given the inherent sex bias of RA, we stratified our analysis based on sex, to better determine if our observations were consistent across both male and female sexes. Indeed, we observed

Table 1. Inception demographics of 2 recruited cohorts.

	FN FDR, n = 607	FN Non-FDR, n = 279
Sex, female	60.1	52.4
Age, yrs[a]	35.1 (20.9)	31.8 (17.6)
Smoker	85.8	88.5
Pack-yrs	3.5 (11.8)	5 (11.8)
BMI	28.7 (9.1)	30.4 (9.8)

Continuous variables are reported as median (IQR), and proportional variables are reported as percentages. [a] Age was significantly higher in the FDR cohort ($P = 0.003$). FDR: first-degree relative; FN: First Nations.

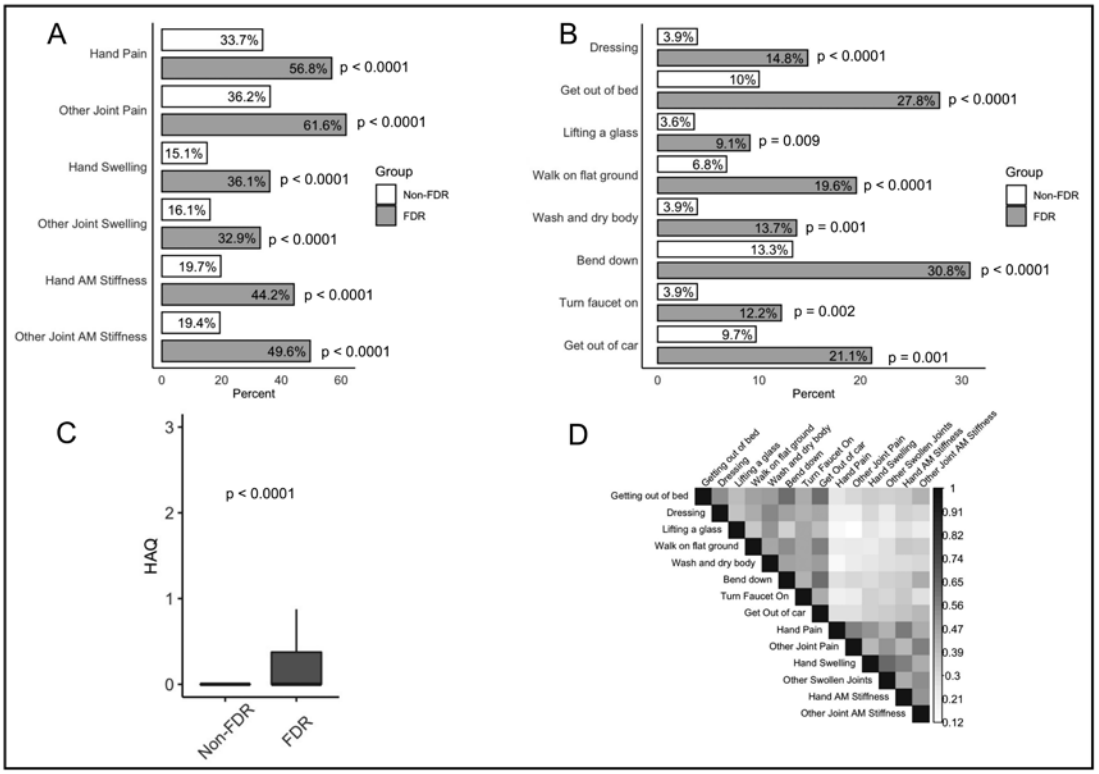

Figure 1. Differences in survey responses between FDR and non-FDR cohorts. (A) Joint symptom survey affirmative responses by self-report. Questions focused primarily on hand or non-hand (Other) symptomatology. (B) Functional survey responses by self-report; % represents prevalence of difficulty with tasks listed above. (C) HAQ scores. (D) Correlation matrix of questions from all responses in joint symptom and functional surveys (FDR and non-FDR cohort), shaded by Spearman correlation coefficient. FDR: first-degree relative; HAQ: Health Assessment Questionnaire.

substantial differences in functional disability in FDR compared to non-FDR when we restricted the analysis to either males or females alone (Supplementary Table 1, available with the online version of this article). Using a correlation matrix (Figure 1D), we found that the self-reported joint symptoms correlated only modestly with the measures of functional disability, despite a high degree of correlation internally within each of these types of measures.

ACPA-positive FDR report increased functional disability compared to ACPA-negative FDR. ACPA seropositivity remains the most important predictor of imminent IA[5,18] and based on animal models and in vitro studies, may itself lead to pain.[9,10] Given that our at-risk cohort of FDR reported a high prevalence of joint symptoms and functional disability as a group, we next sought to determine if ACPA seropositivity, a marker of enhanced risk for imminent RA, was associated with any specific participant-reported experience. In total, 51 (8.4%) participants in our cohort were ACPA seropositive at their inception visit (Supplementary Table 2, available with the online version of this article) and characteristics were similar between the 2 groups. Interestingly, we found that self-reported joint symptoms were not more prevalent in ACPA-seropositive FDR compared to seronegative FDR (Supplementary Figure 3). In contrast to joint symptoms, we observed clear differences in functional disability in the ACPA-seropositive FDRs. Indeed, all the responses to the HAQ questions were higher in seropositive individuals, with difficulty walking on flat ground (37.3% vs 18.0%, $P = 0.01$) reaching statistical significance (Figure 2A and Supplementary Table 3). Mean HAQ score was also higher in ACPA-seropositive individuals (0.38 vs 0.21, $P = 0.03$; Figure 2B). We used logistic regression to assess if HAQ score was associated with ACPA seropositivity, and found that after controlling for baseline variables, HAQ was independently associated with ACPA seropositivity (OR 2.79, 95% CI 1.56–5.00, Supplementary Table 4; AUC = 0.65, Supplementary Figure 4).

Given that difficulty walking on flat ground is more prevalent in ACPA-seropositive FDR, we next sought to understand clinical factors that associate with functional disability. Based on clinical exam, FDR who reported difficulty walking had increased joint tenderness to the lower extremity (42.4% vs 21.2%, $P = 0.002$; Figures 3A,B). Analysis of the remaining joint locations suggested diffuse joint tenderness elicited on clinical exam, including in the upper extremity, among those who endorsed difficulty walking (Figure 3C; Supplementary Table 5, available with the online version of this article). There was a strong association between total tender joints and HAQ score ($R = 0.47$, Figure 3D), indicating that joint pain may be one of many variables that leads to reduced functional capacity.

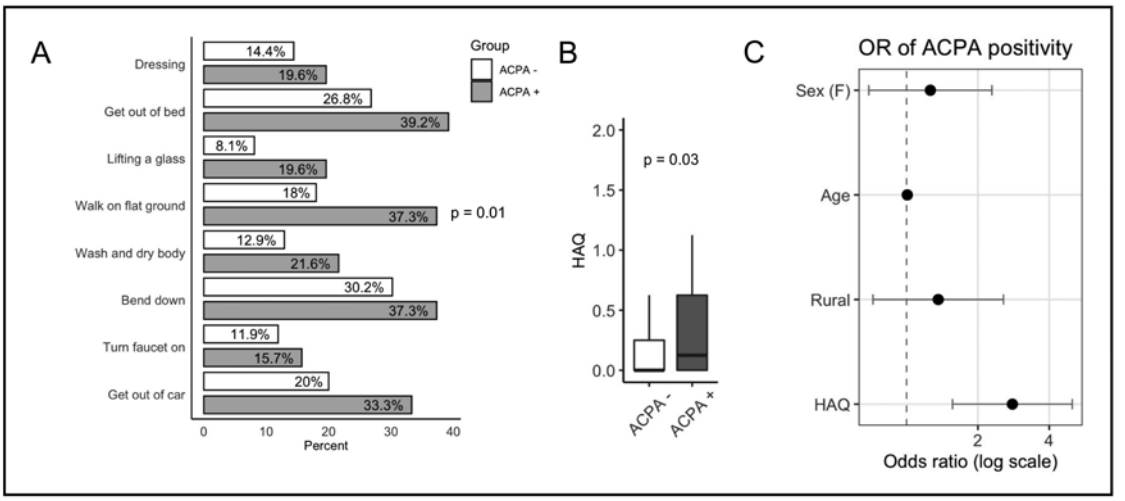

Figure 2. Functional differences between ACPA-positive FDR and ACPA-negative FDR. (A) Functional survey responses by self-report; % represents prevalence of difficulty with tasks listed above. (B) HAQ scores and total number of tender joints on clinical exam. (C) Forest plot of OR for HAQ (OR 2.70, 95% CI 1.56–5.00) after controlling for age, sex and community (rural vs urban). X-axis scale is logarithmic. ACPA: anticitrullinated protein antibody; FDR: first-degree relative; HAQ: Health Assessment Questionnaire.

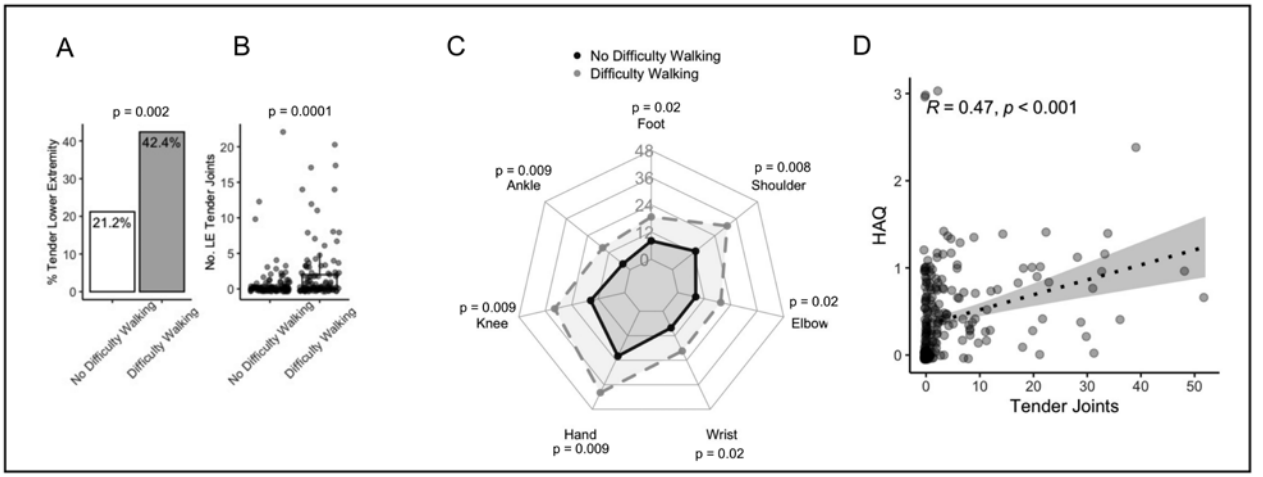

Figure 3. Individuals with self-reported difficulty walking display diffuse joint tenderness on clinical exam. (A) Presence of LE tender joints on clinical exam expressed by percentage (%). (B) Number of LE tender joints on clinical exam. (C) Radar plot of prevalence of joint tenderness split by anatomical location. Percentage is annotated on graph. (D) Spearman correlation between tender joints and HAQ in FDR. FDR: first-degree relative; LE: lower extremity; HAQ: Health Assessment Questionnaire.

Functional disability at inception is associated with longitudinal risk of arthritis in FDR. In order to gain further insight into the relevance of functional disability in assessing those at risk to develop RA, we next explored longitudinal outcomes in our FDR cohort. In total, we were able to classify 325 individuals based on their serological and clinical status with sufficient longitudinal follow-up (Table 2). Median follow-up time was 61 (IQR 54) months. Nineteen (5.8%) individuals developed ACPA-positive RA, 22 (6.8%) were persistently ACPA seropositive, 59 (18.2%) had transient ACPA that seroconverted after follow-up, and 225 (69%) were persistently ACPA negative (Table 2), totaling 284 FDR (87.4%) who were longitudinally classified as ACPA negative. Inception HAQ trended higher in FDR who were persistently ACPA positive (0.22) and had ACPA-positive RA (0.26) compared to ACPA-negative subjects (0.19). There were also trends toward increased difficulty with several specific activities of daily living in individuals who were ACPA positive or developed ACPA-positive RA. For example, the prevalence of difficulty lifting a glass increased in a stepwise manner across our outcomes: 6.3% in ACPA-negative subjects, 13.6% in ACPA-positive subjects, and 15.8% in subjects with ACPA-positive RA (Figure 4A, $P = 0.06$). A similar trend was observed in those with difficulty walking on flat ground, which was more prevalent in persistent ACPA-positive individuals compared to ACPA-negative individuals (36.4% vs 15.5%, $P = 0.02$; Supplementary Table 6, available with the online

Table 2. Inception demographics of FDR cohort with longitudinal follow-up.

	ACPA Negative, n = 284	Persistent ACPA Positive, n = 22	ACPA-positive RA, n = 19
Age	34.4 (20.8)	33.3 (20.2)	27.5 (11.2)
Sex, female	66.2	68.2	73.7
Rural	65.1	59.1	63.2
Follow-up, months	61 (57)	52.5 (31.4)	87 (63.5)
Smoker	83.5	86.4	94.7
Pack-yrs	3.5 (10.8)	3.0 (6.6)	3.0 (10.9)
BMI	29.6 (9.3)	28.5 (9.4)	25.6 (11.3)
ACPA positive	6.0	31.8	57.9
HAQ	0.19 (0.36)	0.22 (0.35)	0.26 (0.37)

Continuous variables are reported as median (IQR), while proportional variables are reported as percentages. ACPA: anticitrullinated protein antibody; FDR: first-degree relative; HAQ: Health Assessment Questionnaire; RA: rheumatoid arthritis.

version of this article). Consistent with our previous analysis, self-reported joint symptoms were not associated with longitudinal outcomes (Supplementary Table 7).

Next, we isolated longitudinal data from 19 ACPA-positive individuals who were followed into arthritis onset (progressor). We plotted HAQ scores over sequential visits as individuals progressed and found that HAQ was stable longitudinally, up until the point of progression into IA (Figure 4B). Interestingly, we found that this pattern was symmetrical with longitudinal ACPA levels. Indeed, in our 19 progressors, there was a positive correlation ($R = 0.45$, $P < 0.001$; Figure 4C) between HAQ and ACPA as individuals were followed into disease onset.

DISCUSSION

Accumulating evidence from both prospective and retrospective cohort studies of individuals who ultimately developed RA has provided important insights into the biological and immunological events that precede RA onset.[1,2,3,5,19–21] It is now unequivocal that specific autoantibodies directed toward posttranslationally modified proteins are detectable during the preclinical phase for most patients who develop seropositive RA.[2,3] These autoantibodies, particularly ACPA, remain the single most important predictor of future RA development in otherwise unaffected individuals.[5,22,23] It is also well established that a spectrum of newly developed and evolving symptoms that include arthralgia, muscle weakness, paresthesia, and fatigue is often reported in the months immediately preceding the onset of clinically detectable joint inflammation.[24] The best described of these is what has been termed *CSA*, a poorly defined symptom complex that incorporates elements of pain, stiffness, and subjective swelling in specific joints and joint areas.[25,26] To date, the relationship between ACPA and self-reported symptoms such as CSA is incompletely understood, particularly since most published data have been from cohorts of individuals who were included based on exhibiting either RA autoantibodies, CSA, or both. In the current study, we prospectively evaluated this relationship in cohorts of individuals who had varying degrees of risk for future RA development based on family history, patterns of ACPA evolution over time, and ultimately the development of IA. Our results indicate that the symptoms of joint pain, stiffness, and

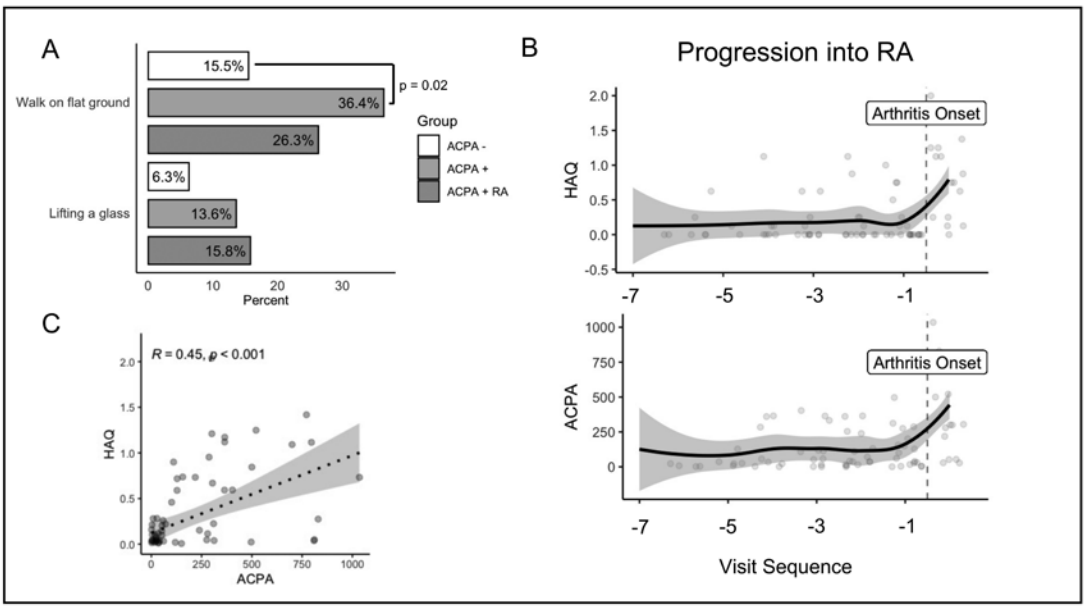

Figure 4. Longitudinal associations between functional disability and persistent ACPA seropositivity for the development of ACPA-positive RA. (A) Functional survey responses by self-report; % represents prevalence of difficulty with tasks listed above at inception. (B) Longitudinal HAQ or ACPA level (AU/mL) over sequential visits for individuals who progressed into inflammatory arthritis (n = 19). (C) Spearman correlation between ACPA level and HAQ in progressors into the development of ACPA-positive RA. ACPA: anticitrullinated protein antibody; HAQ: Health Assessment Questionnaire; RA: rheumatoid arthritis.

subjective joint swelling were common and nonspecific, but that self-reported measures of functional limitations, such as those identified using the HAQ questionnaire, were more specific and predictive of ACPA persistence and future RA. These results have implications for the design of future studies of the preclinical phase of RA.

A direct association between ACPA and joint pain, outside the known context of seropositive IA, is supported by animal models demonstrating that human ACPA uniquely induce pain behavior in mice. This process is proposed to be mediated by the nociceptive effects of CXCL1, which is produced by osteoclasts that are directly activated by ACPA. Thus, aspects of preclinical joint symptomatology[26,27,28] may be directly mediated by the ACPA, despite the absence of detectable synovial inflammation. In the current study, we attempted to address this hypothesis in a longitudinal cohort of at-risk FDR of patients with RA that was not selected on the basis of either the detection of ACPA or the presence of joint symptoms. We showed that ACPA positivity, rather than being associated with a higher prevalence of joint symptoms, is more closely related to specific functional limitations such as difficulty walking on flat ground. These self-reported functional parameters performed better as prognostic indicators of future IA and ACPA persistence than did direct questioning of the presence of joint symptoms. These findings are also consistent with an emerging hypothesis that synovitis in RA may be detectable earliest in the feet[29] and is strongly associated with progression to RA in ACPA-positive individuals. Our data also suggest that self-reported functional disability may be indicative of subclinical joint inflammation, which is detectable as joint tenderness on clinical exam. Given the well-recognized risk of RA associated with ACPA seropositivity, our data promote the use of functional questionnaires to assess RA risk, above other tools such as self-reported joint symptoms.

We observed large differences in self-reported symptoms, both joint-specific and functional, between FDR and non-FDR. We also found that there was only a modest correlation between joint symptoms and functional disability, suggesting that these domains may capture unique aspects of preclinical symptomatology. Indeed, others have reported high rates of regional pain in FDR of patients with RA .[7,30] FDR may have heightened self-awareness of RA symptoms due to their exposure to family members with arthritis. Further, the FDR cohort was slightly older than the non-FDR cohort, and may explain increased self-reported pain. The psychological effect of the perceived increased risk of RA development in FDR,[31] and how this modulates the pain experience, requires further study. Recently, results from an at-risk cohort of FDR suggested that ACPA is associated with heightened symmetrical joint pain using the Symptoms in Persons At Risk of Rheumatoid Arthritis (SPARRA) questionnaire.[11] Notably, we did not find an association between ACPA and joint pain by self-report in our present study. It is important to note the differences between this cohort study and our own. The prevalence of joint pain among FDR in our cohort is > 50%, whereas in the SPARRA study, only 17.9% of FDR reported joint pain. Our cohort is entirely First Nations, compared to the SPARRA cohort, which is > 90% White. Further, most of our cohort are active cigarette smokers, and this has a complex interaction with chronic pain.[32] Unfortunately, the CARRA study[11] did not report associations between functional status and seropositivity. Contrasting our results with this recent, highly relevant study is of great importance to improving our understanding of preclinical symptomatology across different at-risk populations.

While our patient-reported survey provided a robust dataset of preclinical RA symptoms, there are important limitations to consider. Most of the studied variables collected are by self-report, which introduces recall bias.[33] Joint tenderness, though more prevalent in those with difficulty walking, is a nonspecific measure of subclinical joint activity. Though firm conclusions cannot be drawn from this association, there are clearly individuals who experience difficulty walking without objective joint tenderness on examination. This suggests that there are other potential unmeasured variables that lead to difficulty walking, including nonjoint-related pain and muscle weakness. Imputation of data can lead to misleading results and bias, particularly if data are not missing at random.[34] It is important to note that individuals without any survey data were excluded from our analysis. Finally, the relatively low number of progressors in our cohort (n = 19) reduces the statistical power and generalizability of our observations.

In conclusion, we present evidence that functional disability is associated with inception and longitudinal outcomes in an at-risk FDR cohort. Further, we provide the first human evidence that ACPA is associated with symptomatology in the absence of IA. Joint symptoms and tenderness on clinical exam, despite being highly prevalent in FDR, were not associated with ACPA seropositivity or the development of IA. Overall, these data provide clear evidence that functional disability, specifically difficulty walking, is representative of preclinical RA symptomatology and may provide important insights into individuals at the highest risk to develop clinical synovitis.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Deane KD, El-Gabalawy H. Pathogenesis and prevention of rheumatic disease: focus on preclinical RA and SLE. Nat Rev Rheumatol 2014;10:212-28.
2. Sokolove J, Bromberg R, Deane KD, et al. Autoantibody epitope spreading in the pre-clinical phase predicts progression to rheumatoid arthritis. PLoS One 2012;7:e35296.
3. Koppejan H, Trouw LA, Sokolove J, et al. Role of anti-carbamylated protein antibodies compared to anti-citrullinated protein antibodies in Indigenous North Americans with rheumatoid arthritis, their first-degree relatives, and healthy controls. Arthritis Rheumatol 2016;68:2090-8.
4. El-Gabalawy HS, Robinson DB, Smolik I, et al. Familial clustering of the serum cytokine profile in the relatives of rheumatoid arthritis patients. Arthritis Rheum 2012;64:1720-9.

5. Tanner S, Dufault B, Smolik I, et al. A prospective study of the development of inflammatory arthritis in the family members of Indigenous North American people with rheumatoid arthritis. Arthritis Rheumatol 2019;71:1494-1503.
6. O'Neil LJ, Spicer V, Smolik I, et al. Association of a serum protein signature with rheumatoid arthritis development. Arthritis Rheumatol 2021;73:78-88.
7. van Beers-Tas MH, Ter Wee MM, van Tuyl LH, et al. Initial validation and results of the Symptoms in Persons At Risk of Rheumatoid Arthritis (SPARRA) questionnaire: a EULAR project. RMD Open 2018;4:e000641.
8. Totsch SK, Sorge RE. Immune system involvement in specific pain conditions. Mol Pain 2017;13:1744806917724559.
9. Wigerblad G, Bas DB, Fernades-Cerqueira C, et al. Autoantibodies to citrullinated proteins induce joint pain independent of inflammation via a chemokine-dependent mechanism. Ann Rheum Dis 2016;75:730-8.
10. Bersellini Farinotti A, Wigerblad G, Nascimento D, et al. Cartilage-binding antibodies induce pain through immune complex-mediated activation of neurons. J Exp Med 2019;216:1904-24.
11. Costello RE, Humphreys JH, Sergeant JC, et al. Symptoms in first-degree relatives of patients with rheumatoid arthritis: evaluation of cross-sectional data from the Symptoms in Persons At Risk of Rheumatoid Arthritis (SPARRA) questionnaire in the PRe-clinical EValuation of Novel Targets in RA (PREVeNT-RA) cohort. Arthritis Res Ther 2021;23:210.
12. Hitchon CA, Khan S, Elias B, Lix LM, Peschken CA. Prevalence and incidence of rheumatoid arthritis in Canadian First Nations and non-First Nations people: a population-based study. J Clin Rheumatol 2020;26:169-75.
13. Raychaudhuri S, Sandor C, Stahl EA, et al. Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. Nat Genet 2012;44:291-6.
14. Smolik I, Robinson DB, Bernstein CN, El-Gabalawy HS. First-degree relatives of patients with rheumatoid arthritis exhibit high prevalence of joint symptoms. J Rheumatol 2013;40:818-24.
15. Cader MZ, Filer A, Hazlehurst J, de Pablo P, Buckley CD, Raza K. Performance of the 2010 ACR/EULAR criteria for rheumatoid arthritis: comparison with 1987 ACR criteria in a very early synovitis cohort. Ann Rheum Dis 2011;70:949-55.
16. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res 2011;20:40-9.
17. Ragland DR. Dichotomizing continuous outcome variables: dependence of the magnitude of association and statistical power on the cutpoint. Epidemiology 1992;3:434-40.
18. Di Matteo A, Mankia K, Duquenne L, et al. Third-generation anti-cyclic citrullinated peptide antibodies improve prediction of clinical arthritis in individuals at risk of rheumatoid arthritis. Arthritis Rheumatol 2020;72:1820-8.
19. Deane KD, Cheung TT. Rheumatoid arthritis prevention: challenges and opportunities to change the paradigm of disease management. Clin Ther 2019;41:1235-9.
20. Deane KD, O'Donnell CI, Hueber W, et al. The number of elevated cytokines and chemokines in preclinical seropositive rheumatoid arthritis predicts time to diagnosis in an age-dependent manner. Arthritis Rheum 2010;62:3161-72.
21. Ercan A, Cui J, Chatterton DE, et al. Aberrant IgG galactosylation precedes disease onset, correlates with disease activity, and is prevalent in autoantibodies in rheumatoid arthritis. Arthritis Rheum 2010;62:2239-48.
22. Bemis EA, Demoruelle MK, Seifert JA, et al. Factors associated with progression to inflammatory arthritis in first-degree relatives of individuals with RA following autoantibody positive screening in a non-clinical setting. Ann Rheum Dis 2021;80:154-61.
23. Ford JA, Liu X, Marshall AA, et al. Impact of cyclic citrullinated peptide antibody level on progression to rheumatoid arthritis in clinically tested cyclic citrullinated peptide antibody-positive patients without rheumatoid arthritis. Arthritis Care Res 2019;71:1583-92.
24. van de Stadt LA, Witte BI, Bos WH, van Schaardenburg D. A prediction rule for the development of arthritis in seropositive arthralgia patients. Ann Rheum Dis 2013;72:1920-6.
25. van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJ, et al. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. Ann Rheum Dis 2017;76:491-6.
26. Burgers LE, Siljehult F, Ten Brinck RM, et al. Validation of the EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. Rheumatology 2017;56:2123-8.
27. Ruta S, Prado ES, Chichande JT, et al. EULAR definition of "arthralgia suspicious for progression to rheumatoid arthritis" in a large cohort of patients included in a program for rapid diagnosis: role of auto-antibodies and ultrasound. Clin Rheumatol 2020;39:1493-9.
28. Ten Brinck RM, Boeters DM, van Steenbergen HW, van der Helm-van Mil AH. Improvement of symptoms in clinically suspect arthralgia and resolution of subclinical joint inflammation: a longitudinal study in patients that did not progress to clinical arthritis. Arthritis Res Ther 2020;22:11.
29. Di Matteo A, Mankia K, Duquenne L, et al. Ultrasound erosions in the feet best predict progression to inflammatory arthritis in anti-CCP positive at-risk individuals without clinical synovitis. Ann Rheum Dis 2020;79:901-7.
30. Pérez-Barbosa L, Garza-Elizondo MA, Vega-Morales D, et al. High frequency of rheumatic regional pain syndromes in first-degree relatives of patients with rheumatoid arthritis. Clin Rheumatol 2020;39:3303-7.
31. Stack RJ, Stoffer M, Englbrecht M, et al. Perceptions of risk and predictive testing held by the first-degree relatives of patients with rheumatoid arthritis in England, Austria and Germany: a qualitative study. BMJ Open 2016;6:e010555.
32. LaRowe LR, Ditre JW. Pain, nicotine, and tobacco smoking: current state of the science. Pain 2020;161:1688-93.
33. Fransson E, Knutsson A, Westerholm P, Alfredsson L. Indications of recall bias found in a retrospective study of physical activity and myocardial infarction. J Clin Epidemiol 2008;61:840-7.
34. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393.