# Correspondence on 'Factors associated with progression to inflammatory arthritis in first-degree relatives of individuals with RA following autoantibody positive screening in a non-clinical setting'

We have read with great interest the work of Bemis *et al* studying the factors associated with the progression to inflammatory arthritis (IA) in high-risk immune-positive individuals.[1] In their work, the authors longitudinally followed patients at very high risk of developing IA since they cumulated a first-degree relative with rheumatoid arthritis (RA) and the presence of at least one autoantibody associated with RA: rheumatoid factor and/or anticyclic-citrullinated peptide antibodies (ACPA). They confirmed earlier studies showing that high titres of ACPA may predict the development to IA.[2] Unexpectedly and in opposition to similar studies,[3 4] the authors did not find any association between patient genetic factors (presence of shared epitope), clinical examination (tender joints) and inflammatory biomarkers (C reactive proteins (CRP)) with the subsequent development of IA. While the absence of shared epitope as a predictive factor of IA development in ACPA-positive individuals is unsurprising since shared-epitope predispose to ACPA development but not inflammation, we believe that at least three points should be discussed to integrate these new results and help guiding further development of predictive models.

First, considering the prevalence of musculoskeletal diseases in the general population,[5] a report of joint pain or the presence of one tender joint on examination (as used in this study) lacks specificity to predict an inflammatory disorder. To address this caveat, the concept of clinically suspect arthralgia (CSA) has recently emerged. The definition of CSA takes into account anamnestic factors (pain localisation, morning stiffness) and clinical examination (squeeze test) and positively predicts the development IA in at-risk individuals.[6] Therefore, we believe CSA definition would be valuable in predictive model of IA.

Second, to better capture the complexity of patients with inflammatory rheumatic diseases, predictive models should aim at integrating more complex data. In this study, biological inflammation (as assessed by CRP) was used as a qualitative variable (present if CRP ≥3 mg/L) instead of a continuous variable. Arbitrary simplification might dramatically alter the predictive impact of inflammatory markers, since a CRP level of 4 mg/L is of different significance to one measured at 10–15 mg/L. A similar comment may be applied to other studied factors such as tender joints, body mass index, smoking burden and genetic factors (eg, number of shared epitope allele). To reach the goal of precision medicine in such complex disease, modern rheumatology will need to tackle a wide range of data sources. These data sources may include joint imaging,[4] genomic data, subtle immunological alterations such as oligoclonal B-cell expansion[7] or the emergence in the blood of preinflammatory mesenchymal cell prior to disease flare-up (or onset).[8]

Finally, modifiable factors should be studied and evaluated, since they are the cheapest and most acceptable therapeutic intervention in asymptomatic patients.[9] These factors include environmental exposures such as smoking, presence of gingivitis, weight and nutritional factors.

To conclude, we believe that this century will witness the precision and predictive medicine, particularly in inflammatory rheumatic diseases. Since proof-of-concept studies have shown the potential to delay RA disease onset in at-risk individual,[10] one can only dream as to how we will practice rheumatology years from now. Yet, the development of accurate prediction models will likely necessitate the integration of complex data from multiple origins to account for the complexity of these diseases. However, increasing the number of studied factors is only feasible when large cohort are available, and further studies might need to form national or even international cohorts of at-risk individuals to allow robust predictions.

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