

Identification of Lifelines participants at high risk for development of rheumatoid arthritis

We would like to thank Michael Mahler¹ for his letter, 'Population-based screening for anticitrullinated protein antibodies (ACPA): A step in the pathway to the prevention of rheumatoid arthritis?' In his letter, Dr Mahler makes a plea to analyse and define reliable biomarkers to identify subjects who are on the trajectory to develop rheumatoid arthritis (RA). We agree with this notion of Dr Mahler as current efforts are increasingly focusing on the possibility to install early preclinical treatment to prevent progression to RA. For example, several randomised placebo-controlled trials (RCTs) have been initiated recently. These clinical trials will investigate the therapeutic potential of several immunomodulatory agents such as rituximab (PRAIRI study: NTR No. 1969), abatacept (APIPPRA study: ISRCTN No. 46017566 and ARIAA study: EudraCT No. 2014-000555-93), hydroxychloroquine (StopRA trial: NCT No. 02603146) and methotrexate (TREAT EARLIER: NTR No. 4853) in individuals at risk of RA. A study evaluating the immunomodulatory effect of atorvastatin in patients with seropositive arthralgia has also been initiated (STAPRA study: NTR No. 22389).

Our publication contributes to these and other efforts as it describes the presence of a prominent biomarker for RA, ACPAs, in a large population-based study and thereby aids to the development of predictive algorithms identifying individuals at risk for RA development. As outlined in this publication, we determined the prevalence of ACPA positivity and its association with known RA risk factors in 40 136 participants from the Lifelines cohort.² Lifelines is a large ongoing prospective population-based cohort study and biobank to investigate the interaction between environmental and genetic factors in the development of chronic diseases. The standardised protocol includes physical examination, extensive questionnaires, and biobanking of serum, plasma, urine and DNA. Participants will be followed up according to a fixed protocol for at least 30 years.³⁻⁴ Within the existing infrastructure, additional collection of data and additional studies in already biobanked and future samples can be performed. For example, the composition of the microbiome is currently being analysed in over 900 subjects participating in the Lifelines deep cohort,⁵ eventually facilitating the contribution of the microbiome composition to the risk to develop RA. Likewise, genetics such as whole genome sequencing including human leukocyte antigen (sub-) typing can be performed, thereby allowing the analyses of the contribution of the microbiome in the susceptible genetic background to the development of autoimmunity.⁶ Other described predictive markers like the acute-phase reactants erythrocyte sedimentation rate and C reactive protein and additional markers can be incorporated in the development of prediction models. Indeed, recent insight into the specificity of the combined presence of ACPA, rheumatoid factor and anticarbamylated protein antibodies provides interesting possibilities in further narrowing down persons at risk.⁷⁻⁸

Overall, Lifelines will give us the unique opportunity to gain follow-up information on our study population. With funding, it will be possible to measure additional biomarkers as indicated above. Therefore, this cohort is well suited for subsequent analyses on other biomarkers and risk factors, as also advocated by Dr Mahler.

Our future goal is to build a prediction model that can distinguish participants at high risk from those at low risk to develop

RA. Such a model is relevant because both animal data and clinical data suggest that prevention of RA may be possible and early treatment aiming at drug-free remission is possible.⁹⁻¹⁰

The performance of RCTs on preventive treatment strategies in individuals at risk for RA is challenging. The development of reliable assays and predictive algorithms to define a population with high enough at risk is crucial to allow the design of effective preventive therapy aiming to restore immune homeostasis with a great specificity, low toxicity and long-term effectiveness.

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