Letter to the editor

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Letter to the editor: Prevalence of connective tissue disease autoantibodies in a large longitudinal population-based cohort from the Netherlands

Dear editor,

Connective tissue disorders (CTD) are systemic autoimmune diseases in which autoantibodies, especially anti-nuclear antibodies (ANA), can often be detected. The majority of patients with primary Sjögren's syndrome (pSS), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), mixed connective tissue disease (MCTD), polymyositis (PM) and dermatomyositis (DM) express ANA. However, presence of ANA in serum is not specific. ANA can also be partly characterized into antibodies directed against extractable nuclear antigens (anti-ENA), and against double stranded DNA (anti-dsDNA), which are more specific for diagnosis of the different CTDs. [1] Interestingly, some autoantibodies can be detected in serum many years before the clinical onset of CTDs. [2–4]

In contrast to the presence of ANA in the general population, less is known concerning prevalence of specific CTD autoantibodies and of characteristics of individuals who express these autoantibodies, as well as their predictive value for development of CTDs.

Therefore, prevalence of CTD autoantibodies was determined in the population-based Lifelines cohort. Data regarding demographics, general laboratory analyses and self-reported symptoms were gathered and were linked to follow-up data.

Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics". [5] Participants <18 years of age were excluded from this study.

CTD-autoantibody-screen (CTD-screen) was determined at baseline, using the EliA CTD-screen (ThermoFisher Scientific, Freiburg, Germany) on a Phadia-250 analyzer, in which total reactivity to a mixture of the following antigens is measured: human recombinant U1RNP (RNP70, A, C), SS-A/Ro (60 kDa, 52 kDa), SS-B/La, Centromere B, Scl-70, Jo-1, fibrillarin, RNA Polymerase III, Ribosomal-P protein, PM-Scl, PCNA, Mi-2 proteins, Sm proteins, and native purified DNA.

Participants were defined as having CTD by self-reported CTD (pSS, SLE, SSc, PM, DM, or MCTD), in combination with use of prescription drugs, or visit to a medical specialist. At follow-up after median 41 months (IQR 31–48), questionnaires were again screened for self-reported CTD. Statistical analysis was performed using IBM SPSS Statistics V.23 (SPSS, Chicago, Illinois, USA). *P*-values ≤0.05 were considered statistically significant.

A total of 40,135 participants were included, of which 23,255 were female (58%) and median age was 44 years (range 18–92). The participants were mostly of Caucasian descent (>96%). In total, 49 participants had a CTD at baseline (14 pSS, 23 SLE, 6 SSc, 4 PM/DM, 2 MCTD), of which 25 (51%) had a positive CTD-screen. After excluding all 49 CTD patients, 40,086 individuals remained, of which 1084 (2.7%) had a positive CTD-screen.

Notably, proportion of CTD-screen positive individuals increased gradually with age, from 1.6% in age group 20–29 years, to 6.1% in age group 70–79 years.

Baseline characteristics of CTD-screen negative versus CTD-screen positive participants are shown in Table 1. CTD-screen positive participants were significantly older, more frequently female, more often reported joint stiffness, and had significantly lower levels of haemoglobin, leukocytes, lymphocytes and creatinine than CTD-screen negative individuals. In multivariate logistic regression analyses, correcting for age and gender, only lower lymphocyte counts (OR 0.80, 95% CI 0.72–0.90) remained significantly associated with CTD-screen positivity.

After a median follow-up time of 41 months, 29,191 participants (73%) completed the follow-up questionnaire. Of these, 14 participants (0.05%) had developed a CTD (6 pSS, 2 SLE, 5 SSc, 1 DM/PM). In 6 of these 14 participants (43%), CTD-screen was positive at baseline. Compared to participants who did not develop a CTD, these CTD patients were more frequently women ($p = 0.03$), more often reported fatigue ($p = 0.006$) and joint stiffness at baseline ($p = 0.001$), and more often had a positive CTD-screen at baseline ($p < 0.0001$). Also, these patients had lower haemoglobin levels ($p = 0.005$), and higher thrombocyte counts ($p = 0.03$). Looking at all CTD-screen positive individuals at baseline with available follow-up data ($n = 816$), the vast majority ($n = 810$) did not develop a CTD during follow-up.

Limitations to this study are the fact that the data does not contain linkage with medical records of the participants, and CTD diagnoses were obtained from self-reported data. Also presence of overall ANA was not available.

In conclusion, in this large, mostly Caucasian, population-based cohort, the prevalence of CTD-screen positivity was 2.7%. Among the individuals who developed a CTD at follow-up, 43% had a positive CTD-screen at baseline. Based on these data, detection of specific autoantibodies could play a role in prediction of development of CTD, but is not enough. Other variables, for example levels of lymphocytes, in combination with specific symptoms such as joint stiffness, are needed for a more precise prediction of CTD in the general population. Moreover, longer follow-up of the Lifelines population to confirm current data and gather more power to investigate which of the CTD-screen positive participants are prone to develop CTD on a longer term.

Sincerely,

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Table 1
Baseline characteristics of CTD-screen negative versus CTD-screen positive participants excluding patients with defined CTD.

	CTD-screen negative (n = 39,009)	CTD-screen positive (n = 1084)	p-value
Age (years)	44 (34–51)	46 (39–54)	**<0.001**
Gender (females)	58%	70%	**<0.001**
BMI (kg/m^2)	25.3 (22.9–28.1)	25.4 (23.1–8.3)	0.23
Alcohol intake (g/day)	3.6 (0.7–10.7)	4.3 (0.8–10.7)	0.26
Smoking status			
Current (yes)	21%	19%	**0.05**
Former (yes)	30%	32%	0.18
Never (yes)	49%	49%	0.75
Selfreported symptoms			
Fatigue (yes)	23%	25%	0.30
Joint pain (yes)	17%	19%	0.10
Joint stiffness (yes)	16%	20%	**<0.001**
Hormonal status			
Nulliparity (yes)	8%	7%	0.11
Menopausal (yes)	28%	36%	**<0.001**
Miscarriage (yes)	20%	18%	0.35
OAC use			
Ever (yes)	92%	93%	0.84
Current (yes)	39%	34%	**0.003**
Hormone use other than OAC (yes)	15%	17%	0.27
Haemoglobin (mmol/L)	8.8 (8.3–9.4)	8.6 (8.2–9.2)	**<0.001**
Leukocytes (10^9/L)	5.9 (5.0–7.0)	5.7 (4.8–6.9)	**<0.001**
Lymphocytes (10^9/L)	2.0 (1.7–2.4)	1.9 (1.6–2.4)	**<0.001**
Neutrophils (10^9/L)	3.1 (2.5–3.9)	3.1 (2.4–3.8)	0.12
Monocytes (10^9/L)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.59
Thrombocytes (10^9/L)	243 (210–280)	246 (210–284)	0.21
Creatinine (μmol/L)	72 (64–81)	70 (63–79)	**<0.001**

Data are presented as median (IQR) for continuous variables and as percentages for categorical variables. P-values ≤0.05 are considered significant.
CTD = connective tissue disease, BMI = Body Mass Index, OAC = Oral Anti Conception.

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Authorship statement

All authors made substantial contributions to either the conception of the word, or the acquisition, analysis or interpretation of data. All authors have drafted or revised the work critically, and have approved the final version. Also all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data sharing statement

Data may be obtained from a third party and are not publicly available, but are available upon reasonable request in the Lifelines database https://www.lifelines.nl/.

Patient consent and ethical approval

All participants provided written informed consent. The LifeLines cohort study was conducted according to the principles of the Declaration of Helsinki, approved by the local ethics committee of the Universal Medical Centre Groningen (UMCG).

Declaration of Competing Interest

None of the authors have competing interests that ae relevant to the submitted manuscript.

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