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Original research

# Inflammatory proteomics profiling for prediction of incident atrial fibrillation

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## ABSTRACT

**Objective** Atrial fibrillation (AF) has emerged as a common condition in older adults. Cardiovascular risk factors only explain about 50% of AF cases. Inflammatory biomarkers may help close this gap as inflammation can alter atrial electrophysiology and structure. This study aimed to determine a cytokine biomarker profile for this condition in the community using a proteomics approach.

**Methods** This study uses cytokine proteomics in participants of the Finnish population-based FINRISK cohort studies 1997/2002. Risk models for 46 cytokines were developed to predict incident AF using Cox regressions. Furthermore, the association of participants' C reactive protein (CRP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) concentrations with incident AF was examined.

**Results** In 10 744 participants (mean age of 50.9 years, 51.3% women), 1246 cases of incident AF were observed (40.5% women). The main analyses, adjusted for participants' sex and age, suggested that higher concentrations of macrophage inflammatory protein-1 $\beta$  (HR=1.11; 95% CI 1.04, 1.17), hepatocyte growth factor (HR=1.12; 95% CI 1.05, 1.19), CRP (HR=1.17; 95% CI 1.10, 1.24) and NT-proBNP (HR=1.58; 95% CI 1.45, 1.71) were associated with increased risk of incident AF. In further clinical variable-adjusted models, only NT-proBNP remained statistically significant.

**Conclusion** Our study confirmed NT-proBNP as a strong predictor for AF. Observed associations of circulating inflammatory cytokines were primarily explained by clinical risk factors and did not improve risk prediction. The potential mechanistic role of inflammatory cytokines measured in a proteomics approach remains to be further elucidated.

## INTRODUCTION

Atrial fibrillation (AF) and its fatal complications, such as stroke and heart failure, currently receive increasing clinical attention because of the epidemic nature of the disease in older adults. Since the underlying pathophysiology of the condition is complex and little understood, risk prediction has been hampered. Until now, clinical cardiovascular risk factors remain the most effective prediction tools. AF prevalence is strongly related to age and modestly increased among men and persons with elevated blood pressure.<sup>1</sup> However, a significant proportion of AF cases cannot be explained by the underlying burden of clinical risk factors.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Atrial fibrillation (AF) has emerged as a common condition in older adults, but its pathophysiology still is not entirely clear and there are not well-defined biomarkers for prevention, early detection and prognosis.

## WHAT THIS STUDY ADDS

⇒ This prospective, population-based study examined a cytokine biomarker profile for AF prediction in the community using a proteomics approach.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study confirmed N-terminal pro B-type natriuretic peptide as a strong predictor for AF in a large population-based cohort. The potential mechanistic role of inflammatory cytokines remains to be further elucidated as associations were primarily explained by clinical risk factors and did not improve AF risk prediction.

The constantly rising number of affected individuals<sup>2</sup> underlines the urgent need to develop other reliable risk markers for early identification and prevention strategies.

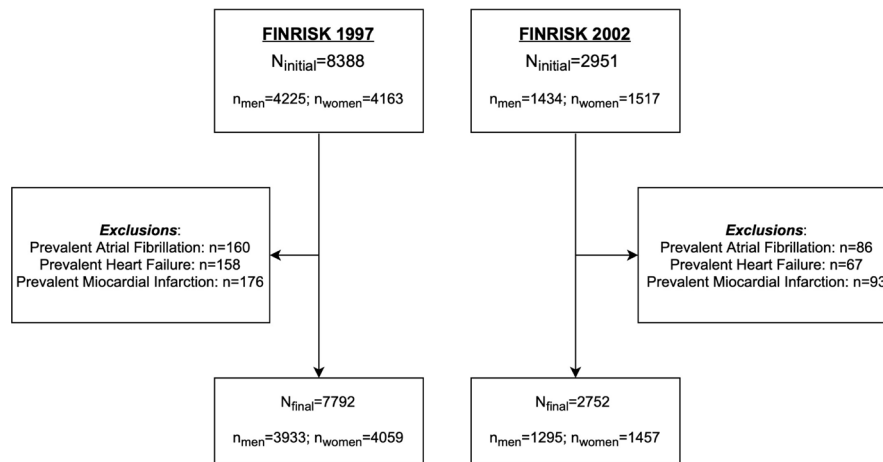
While AF is a heterogeneous disease with clinical and aetiological subtypes,<sup>3,4</sup> a uniform observation in AF patients is a consistent increase of subclinical inflammatory activity and oxidative stress.<sup>5</sup> Both processes are related to molecular and cellular changes in affected atrial tissue, leading to subsequent structural and electrical remodelling. In accordance, C reactive protein (CRP), a routinely available biomarker for inflammation, is commonly increased in AF patients. However, its predictive value for incident AF has remained limited.<sup>6</sup>

Current advances in high-throughput analysis of proteins allow a more holistic evaluation of biological pathways by simultaneous screening for large numbers of proteins involved. Correspondingly, several new biomarkers for AF could already be identified.<sup>7</sup> In heart failure, pathophysiologically closely tied to AF, proteomic profiling enabled the detection of novel prognostic inflammatory biomarkers.<sup>8</sup>



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**Figure 1** Study flow for each FINRISK cohort.

Unlike earlier studies, which evaluated either single or a few established cardiovascular biomarkers, this study utilised a multiplex cytokine panel to identify novel circulating inflammatory markers associated with AF later in life. For comparison, this investigation further incorporated the most thoroughly investigated biomarker for AF prediction: the N-terminal pro B-type natriuretic peptide (NT-proBNP).<sup>9</sup>

## METHODS

### FINRISK cohort description

This study uses data from two of the FINRISK cohorts of adult persons. A detailed description of the protocol for each of the FINRISK cohorts evaluated in this study can be found elsewhere.<sup>10</sup> In brief, the FINRISK are population-based cross-sectional surveys conducted every 5 years among the Finnish population since 1972. Their main aims are to monitor known risk factors for chronic and fatal non-communicable diseases,

such as cardiovascular disease or cancer, in the Finnish population. The study sample includes a stratified random sample of 25-year-old to 74-year-old adults in six geographical areas within the country: the provinces of (1) North Karelia, (2) Northern Savo, (3) Northern Ostrobothnia and Kainuu, (4) Lapland, (5) the Turku and Loimaa region of southwestern Finland and (6) the Helsinki and Vantaa metropolitan area. The sampling was stratified by area, sex and 10-year age group and the same numbers of men and women across 10-year age groups were finally sampled from each geographical area. Importantly, every FINRISK survey is independent of each other, and they comprise different sets of participants.

This study focused on analysing cytokine data obtained from the survey's participants in 1997 and 2002. In both cohorts, each participant underwent a clinical examination, during which a semi-fasting blood sampling was drawn to measure cytokines levels. Semi-fasting means a minimum of 4-hour fast. For FINRISK 1997, we obtained cytokine profiles from all participants where high-quality blood samples were available. However, for FINRISK 2002, budget constraints limited cytokine profiling to adults older than 50 years. The present study initially encompassed 8388 and 2951 persons from the FINRISK 1997 and the 2002 cohorts. Individuals with self-reported and physician-diagnosed history of AF as well as AF on the baseline ECG were defined as having prevalent AF and excluded from all analyses. Further, individuals with self-reported and physician-diagnosed history of myocardial infarction and/or heart failure were excluded. The number of participants declined to 7792 and 2752 for the 1997 and the 2002 cohorts, respectively (see detailed description in figure 1). The diagnosis of incident AF was based on study ECG tracings, questionnaire information, national hospital discharge registry data, ambulatory visits to specialised hospitals and screening of death registry data.

### Patient and public involvement

The FINRISK study is a well-established and broadly accepted population-based survey. Its results have been used widely in development and evaluation of health policy in Finland. Health examinations were conducted by trained personnel comprising public health nurses, laboratory technicians as well as nutritionists providing the opportunity of health education and active participation. As we used data from 1997 and 2002, study participants were not directly involved in the design of our current research.

**Table 1** Main characteristics of the overall FINRISK cohort

Characteristic	All (N=10 744)
Women No	5516 (51.34%)
BMI (kg/m <sup>2</sup> )	26.9 (SD 4.5)
Alcohol consumption(g/week)*†	28.4 (IQR 82.2)
Smoking No	2366 (22.0%)
Systolic blood pressure (mm Hg)	137.8 (SD 20.4)
Antihypertensive medication	5762 (53.6%)
Total cholesterol (mmol/L)	5.6 (SD 1.1)
HDL cholesterol (mmol/L)	1.4 (SD 0.4)
LDL cholesterol (mmol/L)	3.5 (SD 0.9)
Triglycerides (mmol/L)†	1.2 (IQR 0.9)
HbA1c (mmol/mol)‡	37 (IQR 5)
Age at baseline (years)	50.9 (SD 12.9)
Age at AF (years)	68.3 (SD 11.2)
Incident AF No	1246 (11.6%)
Incident myocardial infarction No	716 (6.7%)
Incident heart failure No	750 (7.0%)

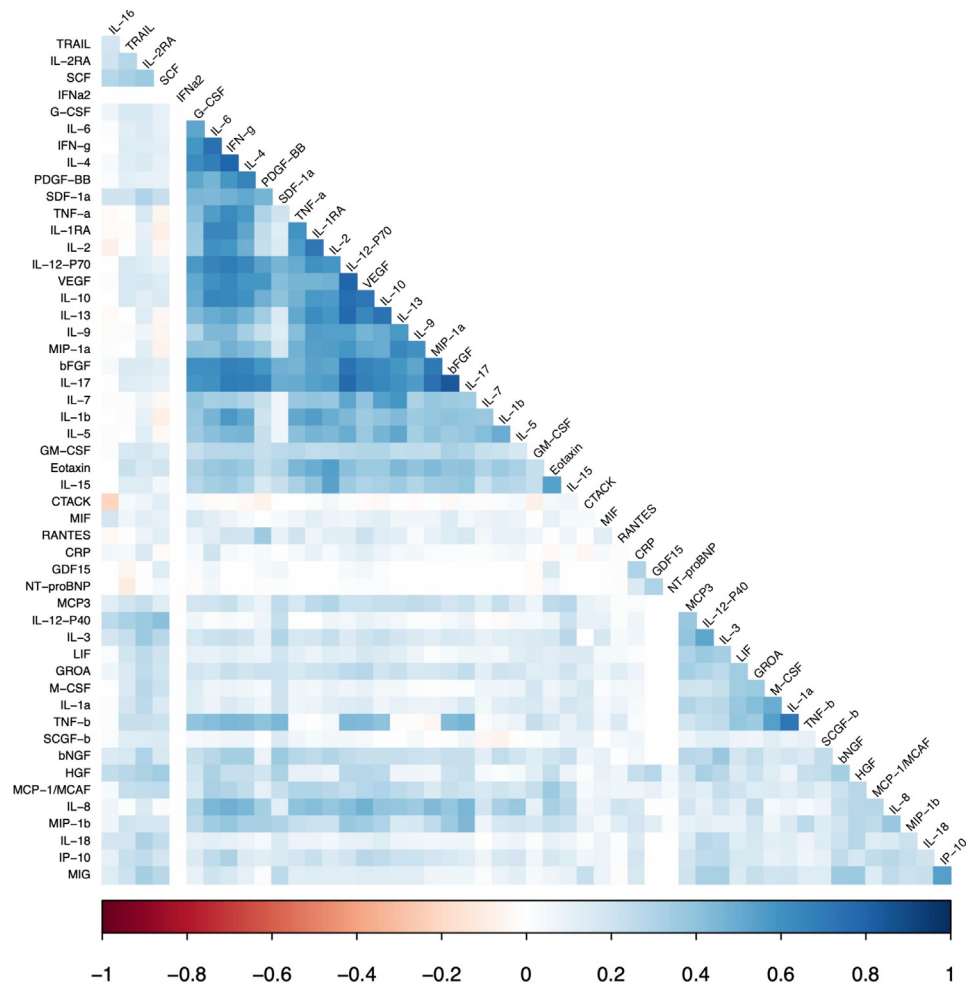
Quantitative measures are described as mean (SD), while sex and incidence measures are provided as the number of individuals (% respect the total).

\*Measurement only present in FINRISK 1997 cohort in 7706 individuals

†Measurement offered as median (IQR) due to its skewed distribution.

‡Measurement only present in FINRISK 2002 cohort in 1389 participants.

AF, atrial fibrillation; BMI, body mass index; HbA1c, glycated haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.



**Figure 2** Correlogram based on Pearson correlations of the measurements investigated (multiple imputed data). Measurements are ordered according to hierarchical clustering of their values; measurements with values in both cohorts are displayed as correlation meta-analyses, while those within a single cohort are shown as the value in that particular cohort. Abbreviations for cytokines are provided in the online supplemental materials.

### Cytokine, CRP and NT-pro-BNP measurements

The overall cytokine panel included 49 different cytokines measured using premixed Bio-Plex Pro Human Cytokine 27-plex Assay and 21-plex Assay, and Bio-Plex 200 reader with Bio-Plex 6.0 software, as described previously.<sup>11</sup> We followed the manufacturer's instructions to perform the assays, except that the number of beads, detection antibodies and streptavidin-phycoerythrin conjugate were used with 50% lower concentrations than recommended. The validity of this approach has been documented previously.<sup>12–14</sup> Cytokine measurements with values outside the detection range as well as more than 1/3 invalid measurements were excluded in the present study. After applying these exclusion criteria, 22 and 46 cytokines were available for examinations in the FINRISK 1997 and 2002 cohorts. These included 20 cytokines overlapping and present in both cohorts, and only one cytokine excluded in both cohorts (interferon alpha-2). CRP was determined by latex immunoassay (Abbott, Architect c8000) and NT-proBNP by an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics) using the ELECSYS 2010 platform.

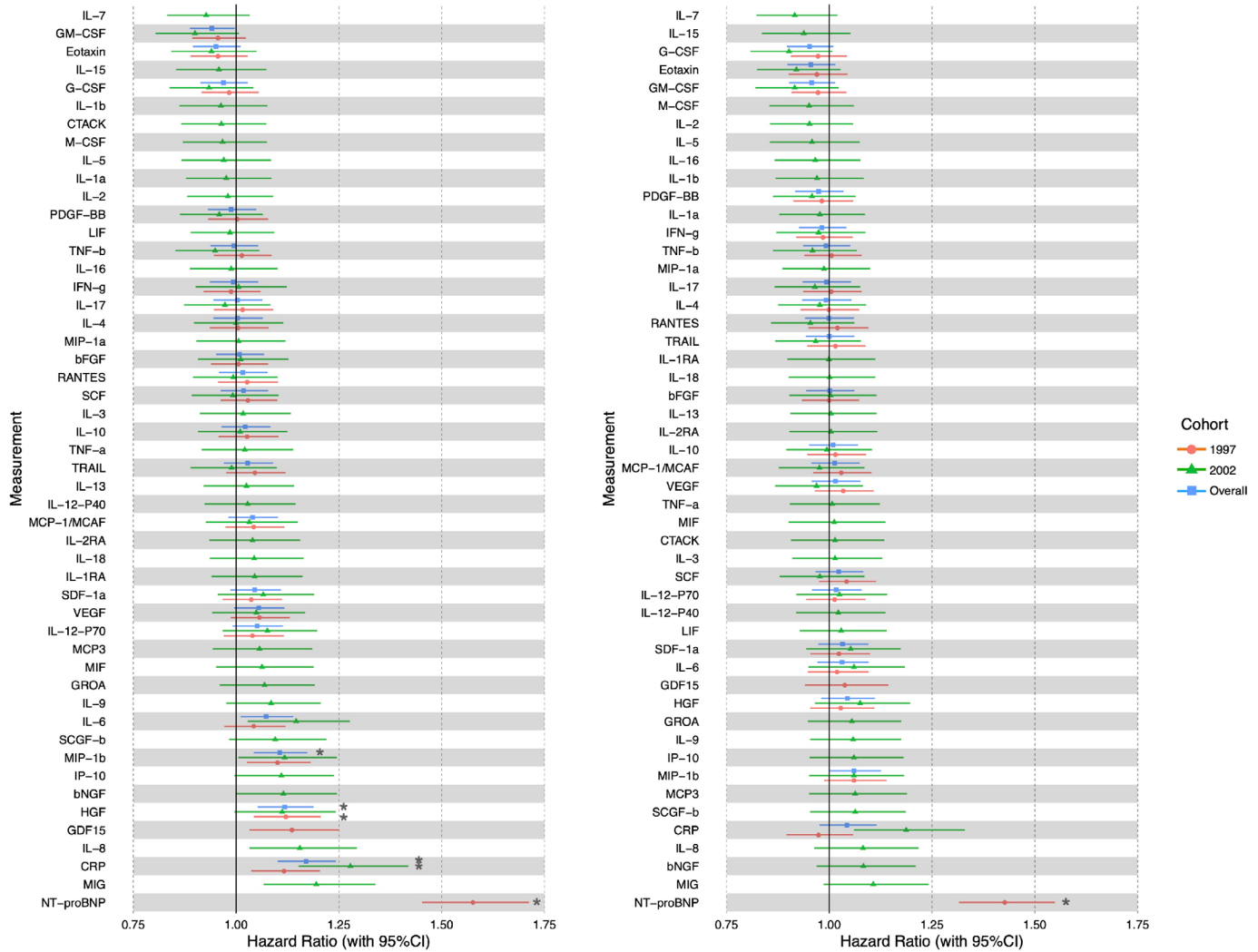
### Statistical analyses

Since cytokines showed highly skewed distributions and extreme values, we performed an inverse normal transformation and standardisation of cytokines levels to avoid further complications

within the primary analyses that may bias model estimates (see online supplemental figures 1 and 2).

The missing values in cytokine data usually derive from concentrations below the platform detection level or for technical reasons. However, as the cytokine panel evaluated also displayed a highly correlated internal structure with detectable clusters of cytokines, missingness in a given cytokine can be explained by the observed values in other cytokines and therefore, not dependent on the missing values themselves. Consequently, missing values can be deemed 'missing-at-random' in a sense proposed by Little and Rubin,<sup>15</sup> which allowed the development of multiple imputation procedures to overcome potential biases related to this missingness in later analyses.<sup>16</sup>

Accordingly, 100 multiple imputed datasets were obtained utilising the Amelia-II package<sup>17</sup> in R statistical software (V. 3.6.3),<sup>18</sup> which implements an expectation-maximisation with bootstrapping algorithm. This multiple imputed process was done through an imputation model that included all other cytokines together with sex, age at the study intake, body mass index (BMI), waist circumference, smoking at the baseline examination and self-reported alcohol drinking at the baseline examination (1997 cohort only), to help in the prediction. All subsequent statistical tests used the multiple imputed data, following the recommendations by Lynn and Rubin<sup>16</sup> to compute pooled test estimates.



**Figure 3** Forest plots of hazard ratios (with 95% CIs) for every cytokine measurement evaluated in each cohort and the overall meta-analysis; the left figure corresponds to the simpler, age-adjusted and sex-adjusted model, while the right figure corresponds to the multiple risk factor-adjusted model. Note: Multivariable adjustment comprised baseline age, sex, body mass index, smoking, total cholesterol, systolic blood pressure, antihypertensive medication, incident myocardial infarction and incident heart failure. Estimates with 95% CIs for each measurement were ordered from lower to higher; \*Statistically significant estimates ‘cohort-wise’ or overall (meta-analysis). Abbreviations for cytokines are provided in the online supplemental materials.

Subsequently, each multiple imputed cytokine was entered as a predictor of incident AF within Cox proportional hazards models within two steps. In the first step, the model (model 1) also included age and sex. In a second step, the model (model 2) also included age and sex, plus BMI, smoking at the study intake, total cholesterol, systolic blood pressure, antihypertensive medication and the time-dependent incident myocardial infarction and incident heart failure.

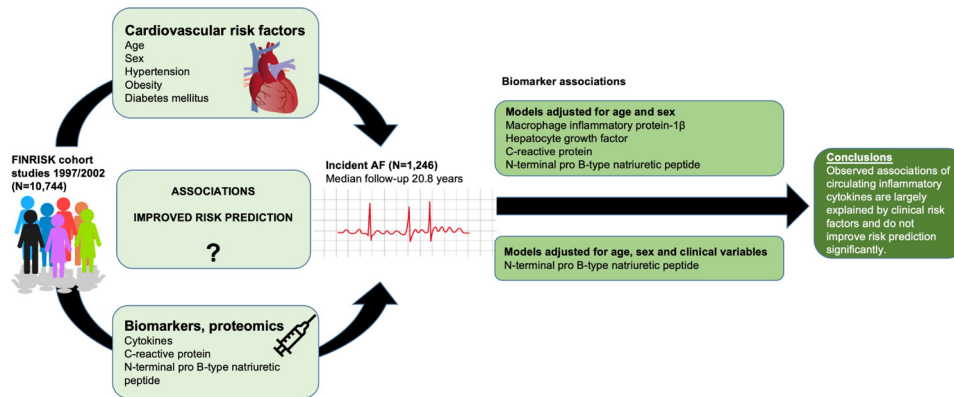
Due to these analyses’ complexity, we set a p value threshold for statistical significance both cohort-wise and for the meta-analysis that considered the family-wise error rate (Bonferroni method) and the expectedly high intrinsic correlation of the cytokine data. This procedure was done by dividing the traditional alpha level of significance (0.05) by the maximum number of independent tests, which was determined itself as the product of the minimum number of orthogonal linear (principal) components explaining >95% of the observed variance in the multiple imputed cytokine panel. Accordingly, there were 14 independent tests for FINRISK 1997 data and 37 independent tests for FINRISK 2002 data (see online supplemental figure 3), thus

setting the Bonferroni corrected p value threshold for statistical significance at  $p \leq 0.00357$  for the 1997 cohort and  $p \leq 0.00135$  in the 2002 cohort. For the meta-analysis of the 20 overlapping cytokines, we assumed 20 independent tests, thus setting this threshold at  $p \leq 0.00250$ .

**RESULTS**

The present study initially encompassed 8388 and 2951 persons from the FINRISK 1997 and the 2002 cohorts. After exclusion of individuals with history of AF, myocardial infarction and/or heart failure, the number of participants declined to 7792 and 2752 for the 1997 and the 2002 cohorts, respectively (figure 1). The mean age of the overall study cohort was 50.9 years; 51.3% were women (N=5516). Of the 10744 participants, N=1246 (11.6%) developed AF during a median follow-up time of 20.8 years, 40.5% in women. Table 1 describes the main characteristics of the participants. In online supplemental table 1, this information is provided by cohort for the FINRISK 1997 and the FINRISK 2002 cohorts.





**Figure 4** As cardiovascular risk factors only explain about 50% of AF cases, in this study risk models for 46 circulating cytokines, C reactive protein (CRP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) were calculated to predict incident AF in 10 744 participants of the population-based FINRISK cohort studies 1997/2002. Incident AF was observed in 1246 persons during a median follow-up of 20.8 years. The main analyses, adjusted for participants' age and sex, suggested that higher concentrations of macrophage inflammatory protein-1 $\beta$ , hepatocyte growth factor, CRP and NT-proBNP were associated with increased risk of incident AF. In further clinical variable-adjusted models, only NT-proBNP remained statistically significant. AF, Atrial fibrillation.

Correlations of the cytokine measurements investigated are shown in [figure 2](#). Proinflammatory cytokines, including tumour necrosis factor- $\alpha$ , interferon- $\gamma$  and interleukin-2, were strongly correlated. CRP, NT-proBNP and GDF-15 did not reveal any major correlations with any cytokine.

The primary analyses using a risk model adjusted for participants' sex and age pinpointed the following markers as associated with increased risk of incident AF (see [figure 3](#) and online supplemental table 2): macrophage inflammatory protein-1 $\beta$  (MIP-1 $\beta$ ) (HR per one SD=1.11; 95% CI 1.04, 1.17; FINRISK 1997), hepatocyte growth factor (HGF) (HR=1.12; 95% CI 1.05, 1.19; FINRISK 1997 and overall), CRP (HR=1.17; 95% CI 1.10, 1.24; FINRISK 2002 and overall) and NT-proBNP (HR=1.58; 95% CI 1.45, 1.71; FINRISK 1997). Only the finding for NT-proBNP (HR=1.43; 95% CI 1.32, 1.55; FINRISK 1997) remained still statistically significant (see [figure 3](#) and online supplemental table 3) after entering further covariates in the initial model (ie, BMI, baseline smoking, total cholesterol, systolic blood pressure, antihypertensive medication, incident myocardial infarction and incident heart failure).

The main findings of this study are graphically displayed in [figure 4](#).

## DISCUSSION

We evaluated the association of 46 circulating cytokines with incident AF using multiplex techniques in this proteomics approach. Elevated levels of MIP-1 $\beta$ , HGF, CRP and NT-proBNP initially were related to incident AF. However, more refined risk factor-adjusted analyses did not reveal any other biomarker to predict the development of AF besides NT-proBNP.

Early animal studies had shown electrical remodelling of the atrial myocardium causing and promoting inducibility and persistence of further AF episodes.<sup>19</sup> Systemic inflammation has been suggested as a central pathophysiological mechanism behind these changes and is a common finding in AF patients.<sup>5</sup>

Several smaller studies have suggested that individuals with permanent AF or ongoing AF have elevated levels of inflammatory markers, including tumour necrosis factor  $\alpha$ , interleukins 8 and 6, and CRP.<sup>5 20 21</sup> However, our multivariable-adjusted models failed to demonstrate that CRP, the most established biomarker of systemic inflammation, is substantially related to AF later in life. A Mendelian randomisation approach has

revealed that while elevated CRP levels were associated with an increased AF risk, genetically elevated CRP levels were not.<sup>22</sup> Therefore, a causal effect of plasma CRP on AF has become less likely, which is in line with the finding in the current study.

Before multivariable adjustment, our analyses suggested an association between MIP-1 $\beta$  as well as HGF and incident AF. MIP-1 $\beta$  mediates the recruitment of immune effector cells in the left atrial tissue of AF individuals.<sup>23</sup> HGF is involved in atrial fibrosis and decreases after successful cardioversion, indicating a role in the self-perpetuation of AF.<sup>24 25</sup> However, both associations lost statistical significance after adjustment for risk factors.

These findings indicate that systemic inflammation may reflect the underlying risk factor burden instead of triggering AF itself. In accordance, prominent risk factors for AF development, including age, sex, increased BMI, hypertension and heart failure, have been related to elevated cytokines.<sup>26</sup> Adjustment for these confounding conditions thus weakened the associations.

Another explanation why our analysis failed to identify strong associations of circulating cytokines with incident AF might be that localised but not systemic inflammatory processes play a more prominent role in AF development. Analyses of epicardial adipose tissue revealed that patients with atrial myocardial fibrosis, a substrate of AF, had increased levels of macrophages, myofibroblasts infiltration and proinflammatory and profibrotic cytokines.<sup>27</sup> Local inflammation may be so subtle that systemic measurement using multiplex techniques does not permit identifying small differences.

As confirmed by our results, NT-proBNP remains the most robust biomarker for predicting incident AF.<sup>28</sup> It reflects a different pathophysiological link between myocyte stretch and increased risk of AF, which appears to be stronger than for a broad range of inflammatory biomarkers.

## Strengths and limitations

The large number of individuals and the extended follow-up are key strengths of the current study, as both increased the predictive power. Nevertheless, our results may not be generalisable to other ethnicities as the FINRISK study is mainly composed of participants of European ancestry. Furthermore, if cytokines are expected to have a modest yet significant predictive capacity for incident AF, it would be necessary to study even larger sample sizes than those investigated here.

## CONCLUSIONS

This study systematically examined levels of a large number of inflammatory cytokines in a well-characterised, large cohort over a long follow-up period. It failed to identify any of them to predict the long-term incidence of AF independently. Initially observed associations lost statistical significance after adjustment and were thus explained mainly by cardiovascular risk factors. Our data suggest that more specific inflammatory cytokines may be required to predict this arrhythmia. Further, our results raise the question of whether localised cardiac inflammation may play a more prominent role in the pathophysiology of AF than chronic, subclinical systemic inflammatory processes.

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**Contributors** CSB was responsible for conception and design and drafted the manuscript. AO-A performed the analytic calculations. ASH verified the analytical methods. PJ, MS, SJ, SV and TN contributed to the design and implementation of the research and interpretation of data. TN and RBS were responsible for the overall content as the guarantors, supported conception and design and supervised the project. All authors discussed the results and contributed to the final manuscript.

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**Competing interests** RBS received consulting fees and speaker honoraria from BMS/Pfizer. SV reports personal fees from Sanofi and a grant from Bayer Ltd outside the submitted work.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and The Coordinating Ethical Committee of the Helsinki and Uusimaa hospital district (Finland) approved

the protocol for FINRISK. Approval ID number: 162/13/03/00/11. Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available upon reasonable request. FINRISK is a large Finnish population survey on risk factors on chronic, non-communicable diseases. The Department of Public Health Solutions coordinates the data analyses, reporting and access to data and samples.

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