



A multimarker approach to assess the influence of inflammation on the incidence of atrial fibrillation in women

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Aims

To assess the joint influence of inflammatory biomarkers on the risk of incident atrial fibrillation (AF) in women.

Methods and results

We performed a prospective cohort study among women participating in the Women's Health Study. All women were free of AF at study entry and provided a baseline blood sample assayed for high-sensitivity C-reactive protein, soluble intercellular adhesion molecule-1, and fibrinogen. To evaluate the joint effect of these three biomarkers, an inflammation score was created that ranged from 0 to 3 and reflected the number of biomarkers in the highest tertile per individual. During a median follow-up of 14.4 years, 747 of 24 734 women (3.0%) experienced a first AF event. Assessed individually, all three biomarkers were associated with incident AF, even after adjustment for traditional risk factors. When combined into an inflammation score, a strong and independent relationship between inflammation and incident AF emerged. Across increasing inflammation score categories, there were 1.66, 2.22, 2.73, and 3.25 AF events per 1000 person-years of follow-up. The corresponding hazard ratios (95% confidence intervals) across inflammation score categories were 1.0, 1.22 (1.00–1.49), 1.32 (1.06–1.65), and 1.59 (1.22–2.06) (*P* for linear trend 0.0006) after multivariable adjustment.

Conclusion

In this large-scale prospective study among women without a history of cardiovascular disease, markers of systemic inflammation were significantly related to AF even after controlling for traditional risk factors.

Keywords

Atrial fibrillation • Inflammation • C-reactive protein • Intercellular adhesion molecule-1 • Fibrinogen

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and its prevalence in the general population is increasing rapidly.^{1–3} The importance of AF is further underscored through its association with death, stroke, heart failure, cognitive dysfunction, and a reduced quality of life.^{4–8} As treatment of established AF is of limited long-term success and carries significant risks,^{9,10} characterizing potentially modifiable risk factors for AF has substantial clinical relevance.

Although several small, mainly cross-sectional studies found increased levels of high-sensitivity C-reactive protein in patients with prevalent AF,^{11,12} it remains unclear whether inflammation

has a causal role in the development of AF. In one of the first prospective studies, high-sensitivity C-reactive protein levels in the highest quartile were associated with a 31% increased risk of incident AF among elderly individuals.¹³ This relationship was recently confirmed in an analysis from the Framingham Heart Study.¹⁴ Both of these studies included participants with prevalent cardiovascular disease at baseline; and therefore, associations could be due in part to well-established associations between inflammation and prevalent cardiovascular conditions that predispose to AF.¹⁵ Currently, prospective data on the association between inflammation and AF in apparently healthy populations is limited,¹⁶ as is data on inflammatory biomarkers other than high-sensitivity C-reactive protein.^{17,18}

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The ongoing Women's Health Study (WHS) presents a unique opportunity to prospectively examine the joint relationships between three markers of inflammation (high-sensitivity C-reactive protein, soluble intercellular adhesion molecule 1 (sICAM-1), and fibrinogen) and incident AF among 24 734 women free of cardiovascular disease and AF at baseline.

Methods

Participants

All study subjects were participants of the WHS, a completed randomized trial evaluating the risks and benefits of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. Details of the study design have been described previously.¹⁹ Briefly, beginning in 1993, 39 876 female health professionals in the United States who were 45 years or older and free of cardiovascular disease, cancer or other major illnesses were randomized to receive 100 mg aspirin every other day, 600 IU vitamin E every other day, both agents or placebo. Randomized treatment ended on March 31, 2004, and women were invited to participate in continued observational follow-up.

Women participating in the observational follow-up represented the target population for this study. Blood samples drawn at randomization were available for 25 883 of these women. Of these, 565 and 3 women were found to have AF and cardiovascular disease at study entry, respectively, and 581 women had incomplete data for high-sensitivity C-reactive protein, sICAM-1 or fibrinogen. Excluding these participants left 24 734 for the present analysis. Follow-up for all women started at randomization and was truncated on 2 March 2009. The study was approved by the institutional review board of Brigham and Women's Hospital, Boston, and was monitored by an external data and safety monitoring board.

Laboratory measurements

Three inflammatory markers were selected based on prior evidence of association with cardiovascular events and availability in the WHS.^{20,21} Plasma high-sensitivity C-reactive protein was measured with a validated high-sensitivity immunoturbidimetric method (Denka Seiken, Niigata, Japan). sICAM-1 was assayed by quantitative sandwich ELISA (R&D Systems, Minneapolis, MN) with a reproducibility of 8.9 and 6.4% at concentrations of 171.8 and 289.1 ng/mL, respectively. Fibrinogen levels were measured using an immunoturbidimetric assay, which is a mass-based assay with international standards (Kamiya Biomedical, Seattle, WA).²²

Study variables

Information on baseline variables was collected using mailed questionnaires. Follow-up questionnaires asking participants about study outcomes and other information were sent every six months during the first year and every 12 months thereafter. Covariates of interest that were assessed at study entry included age, blood pressure, smoking, diabetes, race/ethnicity, body mass index, exercise, and alcohol consumption.

Ascertainment of incident atrial fibrillation

Women were asked to report diagnoses of incident AF at baseline, 48 months, and then annually thereafter.^{23,24} Beginning on 19 September 2006, women enrolled in the continued observational follow-up who reported an incident AF event on at least one yearly questionnaire were sent an additional questionnaire to confirm the episode and

collect additional information. They were also asked for permission to review their medical records, particularly available electrocardiograms, rhythm strips, 24 h electrocardiograms and information on cardiac structure and function. For all deceased participants who reported AF during the trial and extended follow-up period, we contacted family members to obtain consent and additional relevant information. An endpoint committee of physicians reviewed medical records for reported events according to pre-defined criteria. An incident AF event was confirmed if there was electrocardiographic evidence of AF or if a medical report clearly indicated a personal history of AF. The earliest date in the medical records when documentation was believed to have occurred was set as the date of onset of AF. Only confirmed events are included in the present report.

Inflammation score

Simultaneous assessment of multiple inflammatory biomarkers may provide further insights in the relationship between inflammation and incident AF. To evaluate whether a multimarker approach using high-sensitivity C-reactive protein, sICAM-1, and fibrinogen provided additive information on the risk of incident AF, two separate analyses were performed. First, an inflammation score was created, where we *a priori* specified that one point would be added to the score of an individual woman for every biomarker in the highest tertile. We used tertiles instead of quartiles in order to have enough events in the highest inflammation score category. In a sensitivity analysis, biomarker-specific medians were used to create the score. As inflammatory markers are known to be interrelated, we used the first component of a principal component analysis of logarithmically transformed biomarker levels as a second method to capture common variation between different biomarkers.²⁵ The first principal component is the linear combination of markers, similar to a weighted average that explains the most total variance in the inflammatory markers and thus represents a summary measure of inflammation.

Statistical analysis

Baseline characteristics across inflammation score categories were compared using Kruskal–Wallis tests for continuous variables and χ^2 tests for categorical variables. Spearman correlation coefficients were used to assess the correlation between biomarkers. To determine whether there was a gradient of risk between individual biomarkers and incident AF, the study population was categorized into approximate tertiles according to plasma levels of high-sensitivity C-reactive protein, sICAM-1, and fibrinogen. We constructed Cox proportional hazards models to compare hazard ratios (HRs) and 95% confidence intervals (CIs) across biomarker tertiles. We also examined biomarkers as continuous variables. All biomarkers were log-transformed for analysis to improve the normality of their distributions as well as the linearity of the association with AF. We tested for deviation from linearity by including a quadratic term in the multivariable adjusted models.

For each woman, person-years of follow-up were calculated from the date of return of the baseline questionnaire to the date of first endpoint, death, loss to follow-up, or to 2 March 2009, whichever came first. Age-adjusted models were further adjusted for smoking, systolic blood pressure, body mass index, history of diabetes mellitus, HDL-C, LDL-C, exercise, alcohol consumption, and race/ethnicity. Cumulative probabilities of incident AF across inflammation score categories were estimated using the Kaplan–Meier method. Event rates across categories were compared using the log-rank test. Cox proportional hazards models were constructed to evaluate the association between incident AF and inflammation using inflammation score

categories or principal component parameters either as continuous variables or categorized into quartiles, respectively.

Even though the population was free of cardiovascular disease at baseline, an association between inflammation and incident AF may be caused by intercurrent cardiovascular events, given the strong relationship between inflammation and cardiovascular disease.^{15,20,21,26} We therefore refitted all Cox proportional hazards models after censoring women at the date of their first confirmed myocardial infarction, stroke, or coronary revascularization.¹⁹

Categorical variables were entered in the Cox models using binary indicator variables. Tests for linear trend were performed by assigning all women the tertile-specific median value for each biomarker. Effect modification was assessed using multiplicative interaction terms and likelihood ratio tests. The proportional hazards assumption was examined for all models by including a biomarker by logarithm of time interaction into the model.²⁷ No violation of this assumption was detected. All analyses were carried out using SAS version 9 (SAS Institute, Inc., Cary, NC). A two-tailed *P*-value <0.05 was considered to indicate statistical significance.

Results

The median (interquartile range) age of the 24 734 women was 53 (49–59) years. During a median follow-up (interquartile range) of 14.4 (13.8–14.8) years, 747 women experienced a first incident AF event. Median plasma levels of high-sensitivity C-reactive protein, sICAM-1, and fibrinogen were 2.0 (0.8–4.3) mg/L, 342 (300–393) ng/mL, and 350 (307–402) mg/dL. Spearman correlation coefficient was 0.29 for the association between high-sensitivity C-reactive protein and sICAM-1, 0.41 for the association between high-sensitivity C-reactive protein and fibrinogen, and 0.27 for the association between sICAM-1 and fibrinogen, suggesting weak to moderate correlations between the three biomarkers. When the study population was divided into tertiles of the inflammatory parameters, the cut-off values for the highest tertiles were 3.4 mg/L for high-sensitivity C-reactive protein, 373 ng/mL for sICAM-1, and 382 mg/dL for fibrinogen. After summing the number of inflammatory parameters in the highest tertile, 9640 women (39.0%) had a score of zero, 7876 (31.8%) a score of 1, 4909 (19.9%) a score of 2, and 2309 (9.3%) a score of 3. Baseline characteristics of the study population stratified by inflammation score categories are shown in *Table 1*.

Results for the individual biomarkers are shown in *Table 2*. When we assessed high-sensitivity C-reactive protein, sICAM-1, and fibrinogen as log-transformed continuous variables, all biomarkers were significantly associated with AF in the fully adjusted model (*Table 2*). HRs (95% CIs) per increase in 1 standard deviation were 1.11 (1.02–1.21), *P* = 0.02, 1.11 (1.02–1.20), *P* = 0.02, and 1.10 (1.02–1.20), *P* = 0.02 for high-sensitivity C-reactive protein, sICAM-1, and fibrinogen, respectively. Models including a quadratic term provided no evidence of a curvilinear relationship between any of the three biomarkers and incident AF. Tertile-specific analyses showed a gradual increase of incidence rates from 1.62 to 2.77 events per 1000 person-years for high-sensitivity C-reactive protein, from 1.84 to 2.67 events for sICAM-1, and from 1.95 to 2.68 events for fibrinogen. After multivariable adjustment, HRs (95% CIs) of incident AF among women in the highest tertile compared with those in the lowest tertile were

1.32 (1.07–1.63) for high-sensitivity C-reactive protein, 1.31 (1.08–1.60) for sICAM-1, and 1.18 (0.97–1.44) for fibrinogen.

Table 3 displays the results using the combined inflammation score. This score partitioned women into four groups with a gradually increasing risk of incident AF, as shown in *Figure 1*. Differences in event rates across inflammation score categories were statistically highly significant (*P* < 0.0001). Similarly, age-adjusted incidences gradually increased from 1.66 to 3.25 events per 1000 person-years from the lowest to the highest inflammation score category (*Table 3*). This trend was attenuated after controlling for cardiovascular risk factors, but remained statistically significant (*P* = 0.0006). The multivariable adjusted HR (95% CI) for women with an inflammation score of 3 was 1.59 (1.22–2.06). Among established risk factors, adjustment for body mass index resulted in the greatest attenuation in the association between the inflammation score and AF [HR (95% CI) 1.0, 1.23 (1.01–1.50), 1.31 (1.06–1.63), and 1.57 (1.22–2.03); *P*-trend 0.0005]. Again, there was no evidence of a curvilinear relationship (*Table 3*). Similar results were obtained when the inflammation score was based on biomarker-specific median values (2 mg/L for high-sensitivity C-reactive protein, 342 ng/mL for sICAM-1, and 350 mg/dL for fibrinogen). The multivariable adjusted HRs (95% CIs) for women with a score of 0, 1, 2, and 3 were 1.0, 1.37 (1.04–1.79), 1.49 (1.14–1.95), and 1.68 (1.26–2.23), respectively (*P* for linear trend across categories = 0.0006). Our findings were not significantly altered when 45 women who had a cardiovascular event prior to the occurrence of AF were censored from the analysis [multivariable adjusted HR (95% CI) 1.0, 1.24 (1.01–1.51), 1.30 (1.04–1.63), and 1.52 (1.16–2.01) for women with a score of zero, one, two and three; *p* linear trend 0.003].

Similar findings were also obtained, when we used the first component of a principal components analysis as a summary measure of inflammation. The first principal component explained 55% of the total common variation between the three biomarkers. Similar to the inflammation score, there was a significant relationship between the extent of inflammation as measured by the first principal component and incident AF. The HR (95% CI) per 1 standard deviation increase of the first principal component was 1.29 (1.19–1.39), *P* < 0.0001 and 1.17 (1.07–1.28), *P* = 0.0005 after age and multivariable adjustment, respectively. Fully adjusted HRs (95% CIs) across increasing quartiles of the first principal component were 1.0, 1.54 (1.20–1.98), 1.49 (1.15–1.94), and 1.57 (1.20–2.06). Again, we did not find evidence for a curvilinear relationship.

Subgroup analyses revealed consistent results across strata of age, body mass index, systolic blood pressure, diabetes, LDL-C, and HDL-C. Accordingly, none of the inflammation score by subgroup interaction terms was statistically significant (all *P* for interaction >0.05).

Discussion

This study indicates that inflammation, as jointly measured by plasma levels of high-sensitivity C-reactive protein, sICAM-1, and fibrinogen, is significantly associated with the risk of incident AF in a female population free of cardiovascular disease at baseline, suggesting that inflammation may confer an increased risk of

Table 1 Baseline characteristics according to inflammation score categories

Characteristic	Inflammation score				P-value
	0 (n = 9640)	1 (n = 7876)	2 (n = 4909)	3 (n = 2309)	
Age (years)	51 (48–56)	54 (49–59)	55 (50–61)	55 (50–61)	<0.0001
Body mass index (kg/m ²)	23.3 (21.6–25.7)	25.0 (22.6–28.2)	27.1 (24.0–31.1)	29.3 (25.7–33.7)	<0.0001
Current smoking	4.9	12.2	15.9	23.5	<0.0001
History of diabetes	0.8	2.1	4.2	8.5	<0.0001
History of hypercholesterolemia	22.3	31.1	36.4	38.3	<0.0001
Alcohol consumption					<0.0001
Rarely/never	36.5	43.6	51.3	55.6	
1–3 drinks per month	12.7	13.6	14	13.4	
1–6 drinks per week	37.6	32.8	27.3	24.7	
≥1 drink per day	13.2	10	7.5	6.3	
Systolic blood pressure					<0.0001
<120 mmHg	56.9	44.7	34.1	26.2	
120–139 mmHg	36.3	43.5	48.3	48.7	
≥140 mmHg	6.7	11.8	17.6	25.1	
Highest education level					<0.0001
Less than a bachelor's degree	47.9	55.8	60.6	63.8	
Bachelor's degree	27	23.5	21.3	21	
Master's degree or doctorate	25.1	20.7	18.1	15.2	
Exercise (times/week)					<0.0001
Rarely/never	30	37	43.2	50.8	
<1	18.6	19.5	21.1	20.4	
1–3	36.5	32.4	27.7	22.9	
>3	15	11.1	8	5.9	
High-sensitivity C-reactive protein (mg/L)	0.9 (0.4–1.7)	2.1 (1.0–3.8)	4.6 (2.9–7.0)	7.0 (4.9–14.4)	
sICAM-1 (ng/mL)	307 (277–336)	351 (310–396)	386 (342–433)	433 (401–489)	
Fibrinogen (mg/dL)	314 (281–343)	354 (315–395)	405 (368–445)	446 (412–497)	

Data are median (interquartile range) or percentages. sICAM-1, soluble intercellular adhesion molecule-1.

Table 2 Tertiles of inflammatory parameters and risk of incident atrial fibrillation

	Tertile 1	Tertile 2	Tertile 3	<i>P</i> _{linear trend}	Continuous ^a	<i>P</i>
High-sensitivity C-reactive protein (mg/L)	≤1.1	1.1–3.4	>3.4			
Number of events	162	258	327			
Age-adjusted incidence rate ^b	1.62	2.19	2.77			
Age-adjusted HR (95% CI)	Referent	1.38 (1.13–1.68)	1.76 (1.45–2.12)	<0.0001		
Multivariable adjusted HR (95% CI) ^c	Referent	1.20 (0.98–1.47)	1.32 (1.07–1.63)	0.02	1.11 (1.02–1.21)	0.02
sICAM-1 (ng/mL)	≤315	315–373	>373			
Number of events	179	247	321			
Age-adjusted incidence rate ^b	1.84	2.14	2.67			
Age-adjusted HR (95% CI)	Referent	1.19 (0.98–1.44)	1.48 (1.23–1.78)	<0.0001		
Multivariable adjusted HR (95% CI) ^c	Referent	1.10 (0.90–1.31)	1.31 (1.08–1.60)	0.005	1.11 (1.02–1.20)	0.02
Fibrinogen (mg/dL)	≤322	322–382	>382			
Number of events	192	224	331			
Age-adjusted incidence rate ^b	1.95	1.99	2.68			
Age-adjusted HR (95% CI)	Referent	1.02 (0.84–1.24)	1.33 (1.11–1.60)	0.0007		
Multivariable adjusted HR (95% CI) ^c	Referent	1.01 (0.83–1.23)	1.18 (0.97–1.44)	0.07	1.10 (1.02–1.20)	0.02

HR, hazard ratio; CI, confidence interval; sICAM-1, soluble intercellular adhesion molecule-1.

^aPer increase in one biomarker-specific standard deviation (log-transformed).

^bPer 1000 person-years of follow-up.

^cAdjusted for age, smoking, systolic blood pressure, body mass index, history of diabetes mellitus, HDL-C, LDL-C, exercise, alcohol consumption, and race/ethnicity. Due to missing covariates, the multivariable model was based on 722 events in 23 781 women.

Table 3 Inflammation score and risk of incident atrial fibrillation

	Inflammation score				<i>P</i> _{linear trend}	<i>P</i> _{nonlinear trend}
	0	1	2	3		
Number of events	190	248	196	113		
Age-adjusted incidence rate ^a	1.66	2.22	2.73	3.25		
Age-adjusted HR (95% CI)	Referent	1.34 (1.11–1.63)	1.58 (1.29–1.93)	2.04 (1.62–2.59)	<0.0001	0.74
Multivariable adjusted HR (95% CI) ^b	Referent	1.22 (1.00–1.49)	1.32 (1.06–1.65)	1.59 (1.22–2.06)	0.0006	0.84

HR, hazard ratio; CI, confidence interval.

^aPer 1000 person-years of follow-up.

^bAdjusted for age, smoking, systolic blood pressure, body mass index, history of diabetes mellitus, HDL-C, LDL-C, exercise, alcohol consumption, and race/ethnicity. Due to missing covariates, the multivariable model was based on 722 events in 23 781 women.

incident AF that is independent of clinically manifest cardiovascular disease. In this large cohort of women free of cardiovascular disease at baseline, a high inflammation score was a significant predictor of incident AF after adjustment for other cardiovascular risk factors. These results were consistent when other measures were used to define inflammation, suggesting that our findings were not dependent on the cut-off chosen to create the score.

Although it has long been recognized that inflammation post-cardiac surgery may lead to post-operative AF,^{28,29} whether inflammation plays a causal role in AF development in other settings as well is more controversial. Inflammatory infiltrates, myocyte necrosis, and fibrosis have been found in atrial biopsies of patients with both lone and non-valvular AF,^{30,31} and chronic inflammation may induce electrophysiological and structural changes in the atrial

myocardium that may predispose patients with triggering atrial foci to both the development and persistence of AF.¹³ In agreement with these pathologic findings, high-sensitivity C-reactive protein levels and other markers of inflammation have been found to be higher in patients with AF when compared with those without in retrospective studies.^{11,12,32} However, as inflammatory markers were measured at the time of or after the diagnosis of AF in these studies, the temporal relationship is unclear, and thus inflammatory marker elevations may be a consequence rather than a cause of AF.

Several prospective cohort studies, which reduce the potential for this type of bias, have reported associations between individual markers of inflammation and AF. Together with our own, three prospective cohort studies involving different populations have

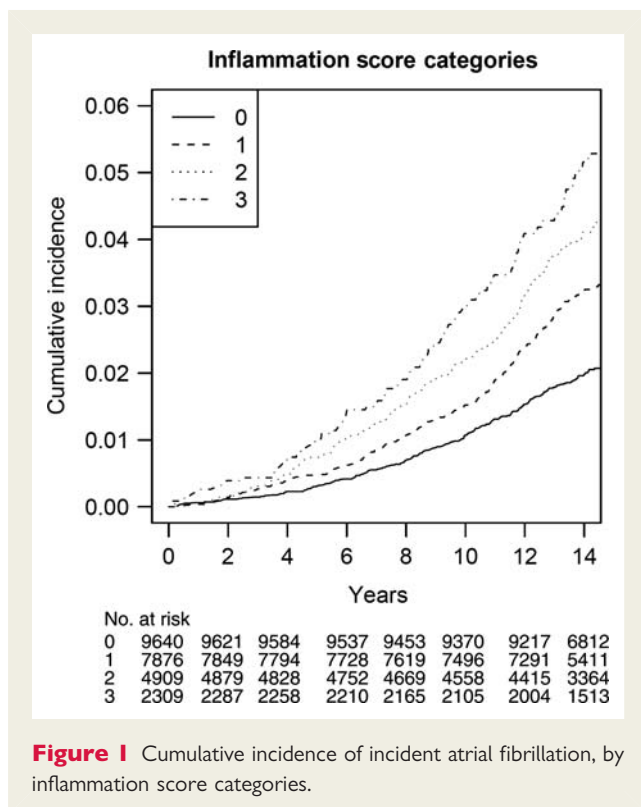


Figure 1 Cumulative incidence of incident atrial fibrillation, by inflammation score categories.

found that high-sensitivity C-reactive protein levels were directly associated with AF incidence. The risk estimates observed for high-sensitivity C-reactive protein in our apparently healthy population are similar to those previously reported in the Cardiovascular Health Study [HR (95% CI) 1.31 (1.08–1.58)]¹³ and the Framingham Study [HR (95% CI) 1.25 (1.07–1.45)],¹⁴ where a proportion of participants had prevalent cardiovascular disease. With regard to fibrinogen levels, we found a much more modest association than that previously reported in a Danish study¹⁸ using hospitalized AF as the endpoint, which likely included more severe cases of AF. Finally, to our knowledge, our study is the first to have found a significant association between sICAM-1 and AF. In one prior prospective study utilizing a smaller number of AF events, an HR of 1.08 (95% CI 0.91–1.28) was observed,¹⁷ which would be consistent with the HR of 1.11 (1.02–1.20) observed in the present analysis with a larger number of events. These findings may suggest that endothelial dysfunction could have a role in the pathogenesis of AF.³³

The simultaneous examination of multiple inflammatory biomarkers may provide a more comprehensive picture of the complex inflammatory process³⁴ and allow for more complete estimates of the association between inflammation and AF. Previously, a panel of 12 inflammatory biomarkers was found to be significantly associated with incident AF in another analysis from the Framingham Heart Study utilizing 148 incident AF events.¹⁷ However, these relationships were markedly attenuated and became non-significant after adjusting for interim myocardial infarction or heart failure.¹⁷ Another prospective study performed exclusively among apparently healthy men and women¹⁶ found a strong association with only 99 AF events when a combination

of high C-reactive protein and complement levels was examined.¹⁶ We now confirm these latter results utilizing a combination of three inflammatory biomarkers in a much larger population of women free of cardiovascular disease at baseline, where the association persists even when women with interim cardiovascular events were censored from the analysis. Taken together, these prospective studies suggest that chronic inflammation may have a pro-arrhythmic effect and lead to the development of AF in susceptible individuals.

Strengths of the present study include its prospective design, sample size, and long-term follow-up with a large number of confirmed events. Potential study limitations that require discussion are the following: First, we included initially healthy, middle-aged female health professionals, most of whom are Caucasian, and generalizability to other populations may be limited. Second, screening electrocardiograms were not performed in this cohort. Therefore, it is possible that asymptomatic AF cases may have gone undetected. However, the number of asymptomatic AF cases in this cohort of health professionals ($n = 74$, 9.9%) was very similar to the number of asymptomatic cases detected by screening electrocardiograms in other population-based cohort studies.³⁵ Third, our analysis was based on a single baseline determination of each plasma marker, and events occurred over an extended follow-up up to 15.8 years. Our inability to account for changes in these markers over time may have limited our power to detect small-to-moderate relative risks. Fourth, only three inflammatory biomarkers were available for analysis in this study. Although they are among the best evaluated markers in association with cardiovascular disease,^{15,20,21,26} we might have obtained different results if other or more inflammation markers had been assessed. Fifth, as with any observational study, the significant association between inflammation and AF could be due to residual confounding by other factors, such as undetected subclinical cardiac disease, and may not imply causality.³⁶ Sixth, the 4324 women from the original cohort who opted out of the observational follow-up were excluded from this analysis because their AF could not be reliably confirmed. However, very similar results were obtained when we repeated our analyses using self-reported AF events among all women as the main outcome variable (data not shown). Finally, given that medical records on AF were not obtained until 2006, some of the medical records were obtained retrospectively. However, information on potential endpoints and all exposure variables were collected prospectively, and medical record review was performed without knowledge of exposure status.

Conclusion

In this prospective study, markers of inflammation were independently associated with incident AF in initially healthy, middle-aged women, even after controlling for traditional risk factors. These findings suggest that inflammation may be involved in the pathogenesis of AF.

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Conflict of interest: Paul M. Ridker is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease.

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