Published in final edited form as:

Heart. 2017 December ; 103(24): 1954–1961. doi:10.1136/heartjnl-2016-311002.

Menopausal Age, Postmenopausal Hormone Therapy and Incident Atrial Fibrillation

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Abstract

Objective—Limited data exist on the association between menopause and atrial fibrillation (AF). We sought to examine the relationship between menopausal age, postmenopausal hormone therapy (PHT) use and incident AF.

Methods—The Women's Health Study (WHS) enrolled 39,876 female health professionals between 1992–1995. We prospectively examined 30,034 women in WHS using Cox proportional-hazard models. Participants were free of cardiovascular disease and AF at baseline and had not undergone hysterectomy without bilateral oophorectomy prior to menopause. Incident AF was confirmed by medical record review.

Results—At baseline, median age was 53 years [IQR 49–60], median menopausal age was 50 years [IQR 46–52], and 14,415 (48.0%) had prior PHT use. Over a median follow-up of 20.5 years, 1,350 AF events occurred. In multivariable analysis, relative hazards for AF were lower among women with younger age at menopause but did not differ significantly from women with the oldest menopausal age (<45: HR 0.82, 95%-CI 0.67–1.02; 45–49: HR 0.90, 95%-CI 0.74–1.08; 50–54: HR 0.89, 95%-CI 0.75–1.06; >54 years: referent). Use of estrogen-alone PHT, but not estrogen and progesterone, was independently associated with AF risk (HR 1.22; 95%-CI

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Contributorship Statement

Dr. Wong is the first and corresponding author. He was involved in study design and conception, data analysis and interpretation, drafting and revising of the manuscript, and final approval. He is the guarantor. Dr. Albert is the senior author and was involved in study design and conception, data analysis and interpretation, manuscript revision and final approval. Drs. Rexrode and Conen were involved in study design, data interpretation, manuscript revision and final approval. Dr. Sandhu was involved in data interpretation, manuscript revision and final approval. Dr. Moorthy was involved in data analysis, manuscript revision and final approval.

Disclosures

The authors have no conflicts of interest to disclose.

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1.02–1.45 vs. HR 1.04; 95%-CI 0.86–1.26). This relationship was not attenuated by intermediary cardiovascular events.

Conclusions—In this large prospective study, menopausal age was not significantly related to incident AF, while use of estrogen monotherapy was associated with increased AF risk. Our findings suggest a pathophysiological link between unopposed estrogen exposure and AF in women.

Keywords

Atrial fibrillation; Menopause; Menopausal Age; Post-menopausal Hormone Therapy; Epidemiology; Women

INTRODUCTION

Atrial fibrillation (AF) is a rapidly growing health care problem.¹ Although men are at higher risk of AF than women,² the prevalence of AF is greater in women after age 75.^{3, 4} Women with AF also have poorer outcomes. Female gender is associated with an increased risk of stroke,^{3, 5} including more disabling and fatal strokes, an increased risk of other AF-related complications,^{3, 5–8} and cardiovascular mortality.^{9–12} Given the significant burden and impact of AF in women, a greater understanding of gender-specific risk factors predisposing women to AF is important.

Early menopausal age has been associated with an increased risk of coronary heart disease, stroke and all-cause mortality.^{13–15} Previous studies have shown that younger menopausal age is associated with incident cardiovascular disease (CVD), and women with bilateral oophorectomy were at particularly high risk.^{13, 14, 16} These findings prompted large randomized trials on postmenopausal hormone therapy (PHT) use.^{17, 18} However, in these studies, PHT use was linked to increased CVD risk. In the Women's Health Initiative (WHI), women randomized to treatment with conjugated estrogen and progesterone had a greater risk of incident CVD compared to placebo.¹⁸

In contrast, the relationship between menopausal age, PHT use and incident AF remains poorly understood. To date, only three prior studies have examined these associations.^{19–21} In a modest-sized cohort from the Framingham Heart Study (FHS), no significant association was found between age of natural menopause and incident AF.¹⁹ In a sub-analysis from WHI, largely based on diagnostic codes for Medicare claims, estrogen-alone PHT was recently reported to be associated with an increased risk of incident AF.²⁰ A similar observation was reported in a retrospective study.²¹ Given the high prevalence and adverse impact of AF in women, and the incomplete understanding of the relationship between AF and this important aspect of women's health, we sought to characterize the relationship between menopausal age, PHT use and incident AF in a large cohort of women free of AF and CVD at baseline using data from the Women's Health Study (WHS). We hypothesized that early menopause and PHT would both be associated with an increased risk of incident AF, mediated by the development of interim CVD.

METHODS

Study Population: Women's Health Study

The detailed rationale and design of WHS have been described previously.^{12, 22, 23} Briefly, WHS was initiated as a randomized controlled trial of low-dose aspirin and/or vitamin E versus placebo for the primary prevention of CVD and cancer in women. Between 1992–1995, the study enrolled 39,876 female health professionals aged ≥45 who were free of CVD, cancer or any major illness. Upon completion of the randomized trial in March 2004, subjects were invited to participate in continued observational follow-up, which is ongoing. The present study consisted of 30,034 women from the WHS. We excluded subjects with a history of AF (N=876) or CVD (N=14) at baseline, and women who were either lost to follow-up during the randomized trial period or declined observational follow-up in 2004 (N=4210) since incident AF could not be adjudicated (Figure 1). Among those who declined follow-up, only 129 self-reported AF events occurred. Women who underwent hysterectomy without bilateral oophorectomy were excluded from analysis if their surgery occurred before AF onset (N=4742), because age of menopause could not be reliably determined. All participants completed questionnaires on demographics, medical history, CVD risk factors, and lifestyle habits at enrollment. Follow-up questionnaires were used to update demographic, lifestyle, and CVD risk factors (Supplemental Table 1), and to determine the development of relevant health outcomes. All participants provided written informed consent, and the study was approved by Brigham and Women's Hospital institutional review board.

Ascertainment of Incident Atrial Fibrillation

Ascertainment of incident AF in WHS has been described previously.¹² Briefly, at enrollment, 48-months, and annually thereafter, participants reported whether they had been newly diagnosed with AF. Participants who self-reported incident AF after randomization were contacted and asked for consent to review both inpatient and outpatient medical records. Confirmation of AF required the presence of electrocardiographic evidence or a medical report clearly indicating a history of AF. The earliest date on the medical record was used as the date of AF onset. Medical records could be obtained in approximately 80% of self-reported cases, and of these, 86% were ultimately confirmed to have AF by an endpoint committee of cardiologists. To maximize specificity, only AF cases validated by medical record review were used in this analysis. Person-time was calculated from the time of return of the baseline questionnaire to the date of incident AF, death, loss to follow-up, or December 31, 2014, whichever came first.

Assessment of Exposure: Menopausal Status and PHT

Women were asked to report their menopausal status and age at menopause at baseline and at 12, 36, 60, 96 and 126 months. Participants were also asked to indicate the cause of menopause (natural, surgical or radiation/chemotherapy-induced). Participants who reported surgical menopause were asked to indicate whether they had hysterectomy with or without oophorectomy. Data on the type and pattern of PHT use were collected at baseline and at 12, 36, 60, 96, 126, 150, 174 and 210 months. At each time point, women were asked to report their current status of PHT use (never, past use, or current use). Those reporting female

hormone use since the previous questionnaire were asked to indicate the regimen they had been on the longest from a list of PHT formulations, which included oral Premarin, oral Prempro, oral Estrace/Ogen, oral Premphase, and patch estrogen, as well as non-PHT formulations, which included vaginal estrogen and progesterone, or 'other' if none of the above applied. Based on these selections, subjects were classified as being on estrogen, estrogen and progesterone, or other PHT. Women who reported only using non-PHT regimens (i.e. vaginal estrogen) were considered unexposed. Actual PHT start and stop dates were not provided by participants.

Statistical Analysis

Age of menopause was determined based on women's responses on study questionnaires and was categorized into 4 groups [<45 , 45–49, 50–54, >54 years (referent)] based on studies of other CVD endpoints.¹⁴ PHT use was examined both in aggregate (never, past or current) and by hormone types (estrogen alone, estrogen and progesterone, or other). Cox proportional-hazard models using time-in-study as the time scale were used to estimate associations between menopausal age, PHT, and incident AF. Initial models were adjusted for multiple pre-specified covariates assessed at baseline as categorized in Table 1, and time-dependent covariates (including primary exposures) were updated at various time points during follow-up as outlined in Supplemental Table 1. Subsequent models were additionally adjusted for surgical/chemotherapy-induced menopause and CVD events during follow-up to assess their potential intermediary role. CVD events included myocardial infarction, stroke, percutaneous coronary intervention, and surgical revascularization. Similar to AF, CVD events were identified by self-report and confirmed by an independent committee of cardiologists through medical record review.

In the age of menopause analysis, baseline age was adjusted for in the final model given the expected collinearity with age of menopause and to be consistent with prior literature.¹⁹ For the PHT analyses, pattern of PHT use was modeled as three binary, time-dependent covariates (never, prior use and current use), and type of PHT was modeled as four binary, time-dependent covariates (none, estrogen, estrogen and progesterone, and other). If a woman reported a change in hormone therapy use, the date of questionnaire return was considered the date of change for analysis purposes. Tests of linear trends across categories of age at menopause were obtained by assigning the median value to each category and modeling this as an ordinal variable in separate Cox models. Since surgical menopause and PHT use may be important confounders or modifiers of the effect of menopausal age on AF, pre-specified stratified analyses were performed. Missing values corresponded to $<1\%$ for all baseline covariates (Table 1), and previous reported values were carried-forward to replace missing data during follow-up, which permitted $>99\%$ of the data to be analyzed as complete cases. The proportional hazards assumption was tested by assessing the interaction between age of menopause or PHT use and the logarithm of time, and no violation was identified. Two tailed p-values <0.05 were considered significant. SAS version 9.3 was used for all statistical analysis (SAS institute Inc., Cary, North Carolina).

RESULTS

Participant Characteristics

Patient characteristics according to baseline menopausal status and PHT use are summarized in Tables 1A and 1B, respectively. Median baseline age of the postmenopausal women was 53 [IQR 49–60] years, and median age at menopause was 50 [IQR 46–52] years. Age of menopause was significantly correlated with baseline age (Spearman correlation =0.27, $p<0.0001$), a relationship that was not significantly attenuated following adjustment for surgical/chemotherapy induced-menopause (adjusted correlation =0.25, $p<0.0001$). Participants with earlier menopause were younger, taller and had a lower prevalence of hypertension, but more frequently had history of hypercholesterolemia, surgical/chemotherapy-induced menopause, smoking and PHT use. Compared to never users, women on PHT at baseline were older, had earlier menopause, lower BMIs, higher prevalence of hypertension and hypercholesterolemia, and were more likely to exercise, consume alcohol and have surgical/chemotherapy-induced menopause.

Age at Menopause and Incident AF

During a median follow-up of 20.5 years (range: 1 day – 21.6 years), 1,350 incident AF cases occurred among 30,034 women. Multivariable adjusted hazard ratios (HR) and 95% confidence intervals (95%-CI) for incident AF according to age of menopause categories are summarized in Table 2. There was no significant trend across categories of age at menopause in any of the multivariable models. As compared to women who reported onset of menopause after age 54, women reporting an earlier age of menopause had marginally significant lower hazard ratios for incident AF after controlling for relevant covariates (Table 2, Model 3; <45: HR 0.80, 95%-CI 0.65–0.99; 45–49: HR 0.83, 95%-CI 0.69–1.00; 50–54 years: HR 0.83, 95%-CI 0.69–0.98). These relationships were significantly attenuated after adjustment for baseline age leaving only a trend toward a lower risk among the women with menopausal age <45 (Table 2, Model 4; HR 0.82, 95%-CI 0.67–1.02, $p=0.07$). The association between age of menopause and AF did not significantly differ according to type of menopause (Table 3; p -interaction=0.45) or by history of PHT use (Supplemental Table 2; p for interaction=0.77). However, fully adjusted stratified analyses did demonstrate a trend toward an inverse association between age of menopause and AF among women with surgical/chemotherapy induced menopause (Table 3, Model 4, p -trend=0.06); whereas no such association was observed in women with natural menopause.

PHT use and AF

Details on the use of conjugated estrogen and medroxyprogesterone during the study period are summarized in Supplemental Table 3. There was a sharp decline in their use around 120-months of follow-up, approximately when the results from the WHI hormone trials^{17, 18} were made available, after which a total of 856 (64%) incident AF cases occurred. The relationship between PHT use and incident AF is summarized in Table 4. In age-adjusted analyses, no significant relationship between PHT use and incident AF was identified. However, following full covariate adjustment, current PHT use was associated with a marginally increased hazard of AF (HR 1.18, 95%-CI 1.00–1.40, $p=0.046$). When type of PHT used was examined in multivariable adjusted models (Table 5), use of estrogen-alone,

but not combined estrogen and progesterone, was significantly associated with AF risk (HR 1.21, 95%-CI 1.02–1.45, $p=0.032$, and HR 1.04, 95%-CI 0.86–1.26, $p=0.7$, respectively). Further adjustment for CVD events during follow-up did not attenuate this relationship (estrogen-alone: HR 1.22, 95%-CI 1.02–1.45, $p=0.028$).

DISCUSSION

In this large, prospective study examining the relationship between menopausal age, PHT use and the risk of incident AF, we have identified several important findings. First, age of menopause was not significantly associated with incident AF after controlling for age in multivariable models; although a trend towards a modest decrease in risk remained among women with menopause at <45 years. There was also a weak trend toward an inverse association between age of menopause and AF among the subgroup of women with surgical and/or chemotherapy-induced menopause. Second, compared to never users, current PHT use was independently associated with increased risk of AF. Furthermore, estrogen monotherapy was associated with increased AF risk, while combined estrogen and progesterone use was not. Finally, cardiovascular events during follow-up were not important intermediaries in the relationship between PHT use and AF.

To our knowledge, only one other study has evaluated the relationship between menopausal age and AF. In a cohort of 1,809 postmenopausal women (mean age 71 years) in the Framingham Heart Study, age of natural menopause was not associated with incident AF events ($n=273$) over 10-years of follow-up.¹⁹ We add to this prior literature by examining the association between age of menopause and AF in a larger, younger, and broader cohort of postmenopausal women over a longer follow-up period during which a greater number of AF events accrued. We included women with surgical and/or chemotherapy-induced menopause and also controlled for PHT use and baseline age in the analysis. Despite these differences in study design and power, our results were similarly null, except for the possible modest decrease in AF risk noted in women who underwent menopause at a very early age, usually as the result of surgery or chemotherapy.

Our findings regarding the association between PHT and AF confirm and extend findings from WHI.²⁰ In a sub-study of the trial, Perez et al. linked participants to Medicare claims data and found that women randomized to estrogen-alone PHT were at increased risk for AF (HR 1.17, 95%-CI 1.00–1.36) compared to placebo. Despite significant methodological differences in exposure and outcome assessment, the findings between our two studies are remarkably similar lending strength to the validity of the finding. Interestingly, in both studies, AF risk did not extend to women on estrogen and progesterone, suggesting that the effect of estrogen may be mitigated by concurrent progesterone use. PHT regimens used by participants in the present study reflect the general practice patterns in the US over the past 20 years. While there have been substantial changes in the formulations and doses used, particularly after the release of the main results from the WHI hormone trials, the majority of AF cases in our study occurred after WHI, when study subjects were on more contemporary PHT regimens.

The mechanisms behind our observed associations are currently unknown. Adjustment for interim CVD events during follow-up did not significantly change the effect estimates, suggesting that CVD is not a significant intermediary in the causal pathway. This finding is also in keeping with prior literature as there was no apparent association between estrogen-alone PHT and CVD risk in WHI.^{17, 18} We postulate that our observations may relate to pattern of estrogen exposure. Estrogen can affect cardiac ion channel dynamics,²⁴ and postmenopausal women have different repolarization kinetics and atrial electrophysiological properties compared to their premenopausal counterparts.^{25–28} Use of estrogen-alone PHT has been associated with QT-interval prolongation, while no change in the QT-interval was observed in women on estrogen and progesterone PHT.²⁵ Presumably, these changes in ventricular repolarization also reflect atrial repolarization, possibly leading to AF via increased atrial early afterdepolarizations.²⁹ PHT use has also been linked to increased inflammation, which is an important purported mechanism in AF pathogenesis.³⁰ Based upon our findings, the pattern of estrogen exposure (opposed versus unopposed) and pattern of estrogen decline (abrupt versus natural) may be important components of the underlying mechanism.

The strengths of our study include the large sample size, long follow-up duration and the adjudication of AF and CVD events. Our study adds to an important body of literature examining the relationship between menopausal age, PHT and AF risk. Women with AF remain at an increased risk of stroke and AF-related complications compared to their male counterparts, and a greater understanding of the relationship between hormonal factors and AF risk may lead to novel preventive, risk-modifying, and management strategies in women. Given that 3 separate studies^{20, 21} have found a modestly elevated AF risk associated with estrogen-only PHT, this risk may need to be disclosed when initiating and following women on estrogen-alone PHT.

Several limitations need to be considered. First, the study population was comprised entirely of female health professionals, the majority of whom were of European descent; thus, these results may not be generalizable to study populations with less access to health care or to women of other races or ethnicities. Second, age of menopause, surgical menopause and PHT use were self-reported and may be subject to misclassification; however, there is literature to support that data in this context is reproducible.¹⁴ If present, such misclassification would likely be non-differential and would have biased our results toward the null. Third, PHT start and stop dates were not provided by participants and may have led to misclassification of the exposure, which if differential, may have biased the results away from the null. However, it is unlikely that reporting of PHT use would have differed between women with and without AF. Fourth, AF cases were ascertained by self-report, and as with any AF ascertainment method, there may be biases as to which cases are more likely to be detected by this method. Further, due to the episodic and sometimes asymptomatic nature of AF, some AF episodes may not have been detected. These factors, if non-differential, again would have likely biased our results towards the null. Finally, given the observational nature of WHS, and the divergence between observational studies and randomized controlled trials with respect to the relationship between PHT and CVD,^{17, 18} we cannot exclude the possibility that uncontrolled confounding could have contributed to the findings we observed.

Conclusions

In this large prospective study of initially healthy women, we found that estrogen monotherapy in the setting of PHT use was associated with an increase in incident AF risk, while women with younger age at menopause had relatively lower hazards for AF, a finding which was no longer significant after accounting for baseline age. Our findings suggest a possible pathophysiological link between pattern of estrogen exposure and AF in women. Future studies to evaluate the underlying mechanisms behind these relationships are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources

This study was supported by grant HL-093613 from the NHLBI to CMA. The WHS was supported by grants HL-043851, HL-080467, and HL-099355 from the NHLBI and grant CA-047988 from the National Cancer Institute. JAW is supported by a Canadian Institutes of Health Research Fellowship award and the Arthur J.E. Child Cardiology Fellowship. DC was supported by a grant of the Swiss National Science Foundation (PP00P3_133681 and PP00P3_159322).

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Key questions

What is already known about this subject?

Younger menopausal age, and estrogen and progesterone postmenopausal hormone therapy (PHT) have been associated with an increased risk of incident coronary heart disease. Although coronary heart disease is strongly associated with incident atrial fibrillation (AF), limited data exist regarding the relationship between age of menopause, PHT use and incident AF.

What does this study add?

We examined the association between menopausal age, PHT use and incident AF among a cohort of 30,034 women free of cardiovascular disease and AF at baseline within the Women's Health Study. We found that menopausal age was not associated with incident AF after adjustment for relevant covariates, including age and use of PHT. In addition, consistent with a prior study performed in the Women's Health Initiative, we found that estrogen-alone PHT, but not estrogen and progesterone combination therapy, was associated with AF risk. The observed relationship between estrogen monotherapy and incident AF was not mediated by interim cardiovascular events.

How might this impact on clinical practice?

These data suggest that the pattern of estrogen exposure may be associated with AF risk in women. In combination with results from prior studies, women treated with estrogen-alone PHT may be at a modest increased risk for developing AF, and education surrounding this potential risk may be provided to women beginning estrogen-alone PHT.

Figure 1.
Schematic depicting the study population within the Women's Health Study.

Table 1A

Baseline participant characteristics by menopausal status.

	Premenopausal (n=11180)	Age at menopause				P-trend*
		<45 (n=5071)	45 – 49 (n=5931)	50 – 54 (n=6570)	>54 (n=1247)	
Age, years	48.7 (47.1 – 50.8)	55.7 (49.8 – 62.7)	55.5 (51.3 – 61.7)	58.5 (55.1 – 63.6)	62.1 (59.0 – 66.1)	<0.0001
BMI, Kg/m ²	24.7 (22.3 – 28.3)	25.2 (22.7 – 29.0)	24.8 (22.3 – 28.3)	24.9 (22.5 – 28.2)	25.4 (22.8 – 29.1)	0.67
Height, cm	165.1 (160 – 168)	165.1 (160 – 168)	165.1 (160 – 168)	162.6 (160 – 168)	162.6 (160 – 168)	0.0003
Weight, Kg	67.1 (59.0 – 77.1)	68.0 (60.8 – 77.1)	67.1 (59.0 – 77.1)	67.1 (59.9 – 76.2)	68.0 (61.2 – 77.1)	0.32
White race, n (%)	10572 (94.6)	4735 (93.4)	5617 (94.7)	6224 (94.7)	1187 (95.2)	0.19
Hypertension, n (%)	1885 (16.9)	1559 (30.7)	1647 (27.8)	2021 (30.8)	450 (36.1)	<0.0001
Diabetes, n (%)	195 (1.7)	166 (3.3)	146 (2.5)	173 (2.6)	48 (3.9)	<0.0001
Hypercholesterolemia, n (%)	1989 (17.8)	1965 (38.8)	1996 (33.7)	2287 (34.8)	462 (37.1)	<0.0001
Smoking, n (%)						
Current	1149 (10.3)	826 (16.3)	846 (14.3)	702 (10.7)	84 (6.7)	<0.0001
Former	3796 (34.0)	1792 (35.4)	2253 (38.0)	2578 (39.2)	445 (35.7)	
Never	6228 (55.7)	2445 (48.3)	2828 (47.7)	3286 (50.1)	717 (57.5)	
Hormone replacement therapy, n (%)						
Current	1264 (11.4)	3265 (64.5)	3500 (59.1)	3219 (49.0)	547 (43.9)	<0.0001
Former	310 (2.8)	741 (14.6)	671 (11.3)	730 (11.1)	143 (11.5)	
Never	9571 (85.9)	1055 (20.9)	1751 (29.6)	2615 (39.8)	555 (44.6)	
Alcohol consumption, n (%)						
Rarely/never	4603 (41.2)	2516 (49.6)	2611 (44.1)	2873 (43.7)	565 (45.4)	0.73
1–3 drinks /month	1531 (13.7)	680 (13.4)	749 (12.6)	826 (12.6)	152 (12.2)	
1–6 drinks / week	3940 (35.3)	1425 (28.1)	1905 (32.1)	2070 (31.5)	369 (29.6)	
>1 drink/day	1103 (9.9)	448 (8.8)	664 (11.2)	798 (12.2)	160 (12.8)	
Exercise, n (%)						
Rarely/never	3848 (34.4)	2047 (40.4)	2388 (40.3)	2562 (39.0)	505 (40.5)	0.0001
<1 times /week	2369 (21.2)	1038 (20.5)	1091 (18.4)	1191 (18.1)	220 (17.6)	
1–3 times /week	3728 (33.4)	1487 (29.3)	1806 (30.5)	2030 (30.9)	380 (30.5)	
>4 times /week	1229 (11.0)	497 (9.8)	645 (10.9)	782 (11.9)	142 (11.4)	
Highest education level, n (%)						

	Premenopausal (n=11180)	Age at menopause				P-trend [*]
		<45 (n=5071)	45 – 49 (n=5931)	50 – 54 (n=6570)	>54 (n=1247)	
Less than a bachelor's degree	5577 (49.9)	3257 (64.2)	3472 (58.5)	3676 (56.0)	720 (57.7)	<0.0001
Bachelor's degree	2985 (26.7)	1017 (20.1)	1246 (21.0)	1511 (23.0)	279 (22.4)	
Master's or Doctorate	2618 (23.4)	797 (15.7)	1213 (20.5)	1383 (21.1)	248 (19.9)	
Age at Menarche, n (%)						
11 years	2730 (24.4)	1328 (26.2)	1417 (23.9)	1476 (22.5)	248 (19.9)	<0.0001
12 – 14 years	7643 (68.4)	3331 (65.7)	4067 (68.7)	4544 (69.3)	861 (69.2)	
15 years	797 (7.1)	408 (8.1)	440 (7.4)	538 (8.2)	135 (10.9)	
Prior birth control use, n (%)	9272 (83.0)	3090 (61.0)	3804 (64.2)	3581 (54.6)	579 (46.5)	<0.0001
Surgical / chemotherapy-induced menopause, n (%)	0 (0)	3097 (61.0)	1645 (27.7)	670 (10.2)	125 (10.0)	<0.0001

Data presented as medians (interquartile range) for continuous variables or n (%) for categorical variables.

* Trends in categorical variables compared using the Mantel-Haenszel trend test. Trends in continuous variables were compared using linear regression.

Table 1B

Baseline participant characteristics by baseline postmenopausal hormone therapy use.

	Postmenopausal hormone therapy			P-value *
	Never (n=15,561)	Previous (n=2,604)	Current (n=11,811)	
Age, years	50.7 (47.8 – 57.4)	59.3 (53.3 – 65.5)	54.8 (51.0 – 60.0)	<0.0001
BMI, Kg/m ²	25.0 (22.5 – 28.9)	25.6 (22.9 – 29.3)	24.4 (22.3 – 27.5)	<0.0001
Height, cm	165.1 (160 – 168)	162.6 (160 – 168)	165.1 (160 – 168)	<0.0001
Weight, Kg	68.0 (59.9 – 77.6)	68.0 (61.2 – 79.4)	65.8 (59.0 – 74.8)	<0.0001
White race, n (%)	14626 (94.0)	2445 (93.9)	11238 (95.2)	<0.0001
Hypertension, n (%)	3598 (23.1)	883 (33.9)	3080 (26.1)	<0.0001
Diabetes, n (%)	428 (2.8)	90 (3.5)	207 (1.8)	<0.0001
Hypercholesterolemia, n (%)	3804 (24.5)	998 (38.3)	3888 (32.9)	<0.0001
Smoking, n (%)				
Current	1907 (12.3)	381 (14.7)	1319 (11.2)	<0.0001
Former	5323 (34.2)	1014 (39.0)	4516 (38.3)	
Never	8318 (53.5)	1204 (46.3)	5971 (50.6)	
Alcohol consumption, n (%)				
Rarely/never	6895 (44.3)	1276 (49.0)	4984 (42.2)	<0.0001
1–3 drinks /month	2070 (13.3)	325 (12.5)	1543 (13.1)	
1–6 drinks / week	5022 (32.3)	721 (27.7)	3958 (33.5)	
>1 drink/day	1567 (10.1)	282 (10.8)	1324 (11.2)	
Exercise, n (%)				
Rarely/never	5957 (38.3)	1148 (44.1)	4228 (35.8)	<0.0001
<1 times /week	3167 (20.4)	480 (18.4)	2261 (19.2)	
1–3 times /week	4820 (31.0)	713 (27.4)	3894 (32.3)	
>4 times /week	1607 (10.3)	262 (10.1)	1425 (12.1)	
Highest education level, n (%)				
Less than a bachelor's degree	8433 (54.2)	1726 (66.3)	6528 (55.3)	<0.0001
Bachelor's degree	3750 (24.1)	507 (19.5)	2779 (23.5)	
Master's or Doctorate	3378 (21.7)	371 (14.3)	2504 (21.2)	
Age of menopause, n (%)				

	Postmenopausal hormone therapy			P-value*
	Never (n=15,561)	Previous (n=2,604)	Current (n=11,811)	
<45 years	1092 (7.4)	746 (29.1)	3301 (28.2)	<0.0001
45 – 49 years	3363 (22.6)	740 (28.9)	3772 (32.2)	
50 – 54 years	8130 (54.7)	884 (34.5)	3810 (32.6)	
>54 years	2275 (15.3)	195 (7.6)	820 (7.0)	
Age at menarche, n (%)				
11 years	3718 (23.9)	635 (24.4)	2846 (24.1)	0.19
12 – 14 years	10640 (68.5)	1734 (66.7)	8042 (68.2)	
15 years	1180 (7.6)	231 (8.9)	911 (7.7)	
Postmenopausal Hormone Therapy, n (%)				
Estrogen alone	0 (0)	1210 (52.3)	4932 (43.6)	<0.0001
Estrogen and progesterone	0 (0)	1019 (44.0)	6120 (54.1)	
Other	0 (0)	87 (3.8)	253 (2.2)	
Prior birth control use, n (%)	10678 (68.7)	1411 (54.3)	8213 (69.6)	<0.0001
Surgical / chemotherapy-induced menopause, n (%)	564 (3.6)	725 (27.8)	4250 (36.0)	<0.0001

Data presented as medians (interquartile range) for continuous variables or n (%) for categorical variables.

* Differences in categorical variables examined using the Chi squared test, while the Kruskal-Wallis test was used to compare continuous variables.

Table 2

Multivariable adjusted HR and 95%-CI of incident AF according to age of menopause categories

	Age of menopause (years)				
	Premenopausal	<45	45-49	50-54	>54
Number of AF cases	17	255	361	544	160
Person-Years	2,222	94,334	149,164	245,451	62,757
AF incidence rate[*]	7.65	2.70	2.42	2.22	2.55
Model 1[†]	0.32 (0.19 – 0.54), p<0.0001	0.90 (0.74 – 1.09), p=0.28	0.87 (0.72 – 1.05), p=0.14	0.84 (0.70 – 1.00), p=0.046	Reference
Model 2[‡]	0.31 (0.19 – 0.53), p<0.0001	0.81 (0.66 – 1.01), p=0.06	0.84 (0.70 – 1.01), p=0.068	0.83 (0.70 – 0.99), p=0.041	Reference
Model 3[§]	0.31 (0.18 – 0.52), <0.0001	0.80 (0.65 – 0.99), p=0.042	0.83 (0.69 – 1.00), p=0.05	0.83 (0.69 – 0.98), p=0.031	Reference
Model 4	0.71 (0.42 – 1.20), p=0.20	0.82 (0.67 – 1.02), p=0.07	0.90 (0.74 – 1.08), p=0.24	0.89 (0.75 – 1.06), p=0.18	Reference

Covariates were updated over time as necessary. Data represent hazard ratios and 95%-confidence intervals. P-value for trend across categories of age of menopause shown.

^{*} per 1000 patient-years.[†]Model 1: adjusted for body mass index, height, hypertension, diabetes, hypercholesterolemia, race, smoking status, alcohol consumption, education, exercise, age at menarche and history of oral contraceptive use.[‡]Model 2: additionally adjusted for surgical/chemotherapy-induced menopause and postmenopausal hormone therapy use.[§]Model 3: additionally adjusted for cardiovascular events occurring prior to AF onset.^{||}Model 4: additionally adjusting for age.

Table 3

Multivariable adjusted HR and 95%-CI for incident AF according to age of menopause categories, stratified by type of menopause.

Strata	Age of menopause (years)				p-trend	p-interaction
	<45	45-49	50-54	>54		
Natural menopause (N=21,739)						
N	1,557	5,447	11,179	2,942		
AF cases	74	224	455	135		
Model 1 [*]	0.95 (0.72 – 1.27)	0.83 (0.67 – 1.03)	0.84 (0.70 – 1.02)	Reference	0.93	
Model 2 [†]	0.96 (0.72 – 1.27)	0.83 (0.67 – 1.03)	0.84 (0.70 – 1.02)	Reference	0.97	
Model 3 [‡]	0.94 (0.71 – 1.25)	0.82 (0.67 – 1.02)	0.83 (0.69 – 1.01)	Reference	0.88	
Model 4 [§]	0.96 (0.72 – 1.27)	0.89 (0.72 – 1.10)	0.89 (0.74 – 1.08)	Reference	0.96	
Surgical / chemotherapy-induced menopause (N=8,295)						
N	3,592	2,435	1,657	351		0.45//
AF cases	181	137	89	25		
Model 1 [*]	0.70 (0.46 – 1.06)	0.78 (0.51 – 1.20)	0.76 (0.49 – 1.19)	Reference	0.12	
Model 2 [†]	0.70 (0.46 – 1.06)	0.79 (0.51 – 1.21)	0.76 (0.49 – 1.19)	Reference	0.12	
Model 3 [‡]	0.69 (0.45 – 1.05)	0.78 (0.51 – 1.19)	0.76 (0.49 – 1.18)	Reference	0.11	
Model 4 [§]	0.72 (0.47 – 1.09)	0.85 (0.55 – 1.30)	0.84 (0.54 – 1.31)	Reference	0.06	

Covariates were time updated as necessary. Data represent hazard ratios and 95%-confidence intervals.

^{*} Model 1: adjusted for body mass index, height, hypertension, diabetes, hypercholesterolemia, race, smoking status, alcohol consumption, education, exercise, age at menarche and history of oral contraceptive use.

[†] Model 2: Additionally adjusted for postmenopausal hormone therapy use

[‡] Model 3: Additionally adjusted for cardiovascular events occurring prior to AF onset

[§] Model 4: Additionally adjusted for age

//p for interaction for Model 4.

Table 4

Risk of incident atrial fibrillation by pattern of postmenopausal hormone use.

	Postmenopausal Hormone Use		
	Never (n= 7078)	Previous (n= 19386)	Current (n= 3569)
Unadjusted	Reference	1.03 (0.90 – 1.19), p=0.63	0.88 (0.76 – 1.02), p=0.09
Age adjusted	Reference	1.11 (0.97 – 1.27), p=0.14	1.11 (0.95 – 1.29), p=0.19
Model 1 *	Reference	1.15 (1.00 – 1.32), p=0.049	1.20 (1.02 – 1.41), p=0.025
Model 2 †	Reference	1.14 (0.99 – 1.31), p=0.067	1.18 (1.00 – 1.40), p=0.047
Model 3 ‡	Reference	1.14 (0.99 – 1.31), p=0.075	1.18 (1.00 – 1.40), p=0.046

Pattern of postmenopausal hormone use was updated over time in Cox models. Other covariates were time updated as necessary. Data represent hazard ratios and 95%-confidence intervals.

* Model 1: Additionally adjusted for body mass index, height, hypertension, diabetes, hypercholesterolemia, race, smoking status, alcohol consumption, education, exercise, age of menarche, birth control use, age of menopause.

† Model 2: Additionally adjusted for surgical menopause

‡ Model 3: Additionally adjusted for CV events prior to AF onset

Table 5

Risk of incident atrial fibrillation by type postmenopausal hormone therapy.

	None	Estrogen	Estrogen and progesterone	Other
Age-adjusted	Reference	1.19 (1.02 – 1.39), p=0.029	0.96 (0.79 – 1.15), p=0.63	0.92 (0.70 – 1.22), p=0.56
Model 1 *	Reference	1.21 (1.02 – 1.45), p=0.032	1.04 (0.86 – 1.26), p=0.70	1.02 (0.77 – 1.34), p=0.92
Model 2 †	Reference	1.22 (1.02 – 1.45), p=0.028	1.04 (0.86 – 1.26), p=0.69	1.01 (0.77 – 1.34), p=0.93

Type of postmenopausal hormone used was updated over time in Cox models. Other covariates were time updated as necessary. Data represent hazard ratios and 95%-confidence intervals.

* Additionally adjusted for body mass index, height, hypertension, diabetes, hypercholesterolemia, race, smoking status, alcohol consumption, education, exercise, surgical/chemotherapy-induced menopause, age of menopause, age of menarche, and history of oral contraceptive use.

† Additionally adjusting for cardiovascular events occurring prior to AF events