Premature menopause is associated with the development of high blood pressure: a UK Biobank cohort study

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Abstract

Objectives: Hormonal fluctuations during menopause may contribute to an increased risk of hypertension. Evidence of a direct association is not well defined. The objective of this study was to analyze the association between premature (< 40 y of age) and early menopause (40-45 y) and the onset of hypertension in the UK Biobank database.

Methods: A prospective observational cohort study was conducted in postmenopausal women in the UK Biobank database. Enrollment was between 2006 and 2010, with follow-up until the end of 2023. The outcome variable was the diagnosis of hypertension during follow-up. Lifestyle behaviors, comorbidities, and laboratory tests were collected. Survival models with Weibull distribution were fitted to the time of onset of hypertension.

Results: Of a total of 107,836 women with a mean follow-up of 14.5 years, 18,508 cases of hypertension were observed (17.2%). The cumulative incidence increased with earlier menopause onset: 16.6% in normal menopause, 18.8% in early menopause, and 22.6% in premature menopause (χ^2 test, $P < 0.001$). Incidence of hypertension was higher in women with surgical menopause, but there was no association in the multivariate model. The effect of premature menopause was maintained in the multivariate model, with a 12.3% higher risk of developing hypertension.

Conclusions: Premature menopause had a significant effect on the development of hypertension during follow-up. Surgical menopause did not have a significant, independent effect.

Key Words: Cardiovascular disease, Cardiovascular risk, High blood pressure, Menopause.

(*Menopause* 2027;34:000–000)

Received for publication January 4, 2026; accepted April 9, 2026.

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Funding/Support: This study has been funded by a public grant, GIGE_2023_162, from the Ministry of Education, Culture, Universities, and Employment of the Generalitat Valenciana, Spain.

Financial disclosure/Conflicts of interest: None reported.

Author contributions: V.A.: served as the PI of the research and drafted and edited the entire original document. J.A.Q.: proposed the initial idea based on the evidence gap, developed the methodology, and carried out both the statistical analysis of the UK Biobank and the drafting of the results. The other authors assisted in the review of the final article and contributed their comments and bibliographies.

Ethical Considerations: The UK Biobank has been approved by the North West Multi-Centre Research Ethics Committee, the National Board for Information Governance in Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland. This study complies with the Declaration of Helsinki and was approved by the UMH Office for Responsible Research, dated November 11, 2023, with reference code AUT.DMC.JAQR.231109.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.menopause.org.

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eISSN: 1530-0374
DOI: 10.1097/GME.0000000000002834

The hormonal changes accompanied by the onset of menopause trigger wide-ranging impacts on disease risk in middle-aged and older women; however, the relationship between the onset of menopause and the risk of specific diseases is somewhat murky, including in cardiovascular health. Early and premature menopause are positively associated with coronary heart disease and stroke.[1] This association is likely indirect, with hormonal changes in menopause acting on the main risk factors for these diseases, such as the development of metabolic syndrome, an increased waist-to-hip ratio, elevated triglycerides, and elevated plasma glucose.[2] The hormonal fluctuations women experience throughout their lives can contribute to weight gain and female-specific fat distribution patterns, which are associated with their increased risk of diabetes and hypertension.[3]

However, the evidence for a direct association between the onset of menopause and diabetes or hypertension is not fully defined. Any association may be secondary to the development of confounding factors such as those described above. We recently published in this journal the absence of a direct association between diabetes and menopause, thus addressing a gap in evidence still described in clinical guidelines.[4] Some meta-analyses have found a slight association between menopause and the development of high blood pressure,[2] which could suggest that an earlier onset of the former would translate to similar effects in the latter. On the contrary, in a meta-analysis involving over 900,000 women, a more marked association was observed between the onset of menopause and diabetes, hyperlipidemia, and cardiovascular events, but no significant differences were observed in the development of high blood pressure.[5]

With specific regard to hypertension, its prevalence is lower in premenopausal women than in men, but this difference reverses after menopause for reasons that are not entirely clear. On the one hand, visceral fat theoretically increases the risk of salt sensitivity in blood pressure; this is more common in men than in premenopausal women due to the protective effects of estrogen. On the other hand, salt sensitivity is also higher in premenopausal women compared with men,[6] so the involvement of other modulators is necessary to confirm the relationship. Brain-derived neurotrophic factor plays a crucial role in modulating the response of target tissues to estrogen stimuli. Brain-derived neurotrophic factor and estrogen work cooperatively to prevent obesity by promoting lipolysis and, conversely, regulate blood pressure to adapt to the environment. Estrogen deficiency during menopause would lead to an imbalance in this equilibrium, so it would theoretically participate in the development of obesity and hypertension in postmenopausal women.[7] However, we cannot rule out the effect at other levels, such as environmental effects from pollution, which could increase the secondary risk of arterial hypertension to a greater degree in peri- or postmenopausal compared with premenopausal women.[8] Changes in lifestyle could also be strongly related to the development of hypertension after the onset of menopause, so no direct association can be confirmed. In fact, combined aerobic and resistance exercise would be an effective way not only to control hypertension, but also to prevent its onset in postmenopause.[9] Hormone therapy (HT) during menopause may also be associated with the development of hypertension. Combined formulations of conjugated equine estrogens with progestins appear to have a stronger association than estradiol alone or in combination with tibolone.[10]

Despite the great potential for differences in risk profiles between sexes, and the evidence pointing to a higher number of cardiovascular events with lower blood pressure levels in women than in men,[11] treatments for men and women are still identical. The latest guidelines reflect a certain broadening of perspectives regarding hypertension, disease risk, and sex-specific characteristics, although to date this has not significantly affected treatment recommendations.[12] Published data suggest the plausibility of a direct relationship between age of menopause and the development of hypertension, but the available evidence is limited. Thus, this study aims to assess the link between early or premature menopause (including surgical menopause) and the development of high blood pressure. We consider the use of a large population-based database (the UK Biobank) to investigate this relationship to be sufficiently substantiated.

METHODS

A prospective observational cohort study was conducted in postmenopausal women over 40 years of age. The sample was drawn from the UK Biobank database,[13] a large cohort of 502,129 volunteer participants (228,973 men and 273,156 women) aged 40 years or older and residing in the United Kingdom at the time of inclusion. The database collects data on lifestyle, comorbidities, and blood tests. Participants consented to long-term health monitoring through linkage to their medical records. Participants were enrolled between 2006 and 2010, and the follow-up time is carried out until 2023.

The inclusion criteria for the present study were female sex and postmenopausal status at the time of inclusion in the UK Biobank, that is, those who answered "yes" to the question "Have you had menopause?" (data field: 2724). Women were excluded if they had been diagnosed with high blood pressure before inclusion in the study or before menopause; were lost to follow-up due to moving; dropped out of the cohort by their own choice; or had missing data for menopause, age at menopause, or type of menopause. The follow-up period was from the date of enrollment (between March 2006 and December 2010) until the end of follow-up, measured on December 31, 2023.

The outcome variable was a diagnosis of high blood pressure (ICD10: I10-I15) during follow-up, along with the date of diagnosis. Explanatory variables were as follows:

- *Sociodemographics*: age at recruitment (years), Townsend Deprivation Index (unit), educational level (upper secondary education/university degree/lower secondary education/technical vocational training/ compulsory secondary education/ higher vocational education/basic education or less).
- *Behavioral factors*: frequency of alcohol intake (never/ previous/current), tobacco use (no/only occasionally/ yes, most days), daily hours of sleep (≤ 7 h/7-9 h/ > 9 h), IPAQ activity (low/moderate/high).
- *Anthropometric variables*: total metabolic equivalent of task per week (high $> 6{,}272$ kJ/moderate 5,027-6,272 kJ/low $< 5{,}027$ kJ), waist circumference (≤ 80 cm/80-88 cm/ > 88 cm), body mass index (normal < 25 kg/m^2/overweight 25-30 kg/m^2/obese > 30 kg/m^2), percentage of fat mass (normal $< 21\%$/moderate 21%-32%/high $> 32\%$).
- *Physiological variables*: forced vital capacity: calculated as normal or high if the observed value was greater than the theoretical value ($> 0.041 \times$ height $- 0.018 \times$ age $- 2.69$), and reduced if it was lower (normal-high/reduced),

diastolic blood pressure (normal < 90 mm Hg/high ≥ 90 mm Hg), systolic blood pressure (normal < 140 mm Hg/high ≥ 140 mm Hg), blood type (AA/AB/AO/BB/BO/OO).

- *Dietary variables*: cooked vegetable intake, tablespoons per day (none /1-2/3-4/ > 4), raw vegetable intake, tablespoons per day (none/1-2/3-4/ > 4), fresh fruit intake, pieces per day (none/1-2/3-4/ > 4), salt added to food (never or rarely/sometimes/frequently/always), cups of coffee consumed per day (none/ < 1/1-2/3-4/ > 4), glasses of water consumed per day (none/ < 1/1-2/3-4/ > 4), sugar intake (no/yes).
- *Health status*: overall self-perceived health (excellent/good/fair/poor), asthma, bronchitis, emphysema or lung clot (no/yes), cancer (no/yes), acute myocardial infarction, angina or stroke (no/yes), diabetes (no/yes), anxiety or depression (no/yes), cholesterol medication (no/yes), insulin use (no/yes), dental problems (no/yes).
- *Female-specific factors*: age at menopause, with early menopause defined as occurring between the ages of 40 and 45, and premature menopause before the age of 40; type of menopause (surgical: bilateral oophorectomy/natural); age at menarche in years (< 10/10-12/13-14/ > 14); ever taken oral contraceptive pills (no/yes), used HT (no/yes), hysterectomy (no/yes).
- *Family history*: father with diabetes (no/yes), father with hypertension (no/yes), mother with diabetes (no/yes), mother with hypertension (no/yes).
- *Analytical variables*: total cholesterol in mmol/L (normal < 5.2/high > 5.2), HDL cholesterol in mmol/L (high ≥ 1.6/normal 1.3-1.6/low < 1.3), LDL cholesterol in mmol/L (normal < 3/high ≥ 3), creatinine μmol/L (low < 61.9/normal 61.9-106.1/high > 106.1), glucose in mmol/L (low < 4.1/normal 4.1-5.9/high > 5.9), HbA1c (low < 5.7%/normal 5.7-6.49%/high > 6.49%), vitamin D in nmol (normal > 50/low ≤ 50), albumin in g/L (low < 35/normal 35-50/high > 50), triglycerides in mmol/L (normal < 1.7/high > 1.7), urate in μmol/L (low < 202/normal 202-416/high > 416), urea in mmol/L (low < 2.8/normal 2.8-8.2/high > 8.2), lipoprotein (a) in nmol/L (normal < 120/high > 120), calcium in nmol/L (low < 2.1/normal 2.1-2.6/ high > 2.6).

For the statistical analysis, a simple imputation process was performed using the mean (according to the presence of hypertension, yes/no) for the only quantitative variable that had missing data, which was the deprivation index (105 cases). The remaining variables were categorized as missing. A descriptive analysis was performed by calculating frequencies for qualitative variables, and means and SDs for quantitative variables.

Factors associated with the onset of hypertension were analyzed using the $\chi 2$ test for qualitative variables and the Student *t* test for quantitative variables. To analyze the association between age at menopause and type of menopause with the onset of hypertension, the $\chi 2$ test was applied, calculating the hypertension rate per 1,000 women-years, and survival models with Weibull distribution were fitted to the time to onset of hypertension. A crude adjustment, an age adjustment, and a multivariate model were fitted, considering all variables. In the multivariate adjustment, a variable selection process based on the Akaike information criterion was performed until the optimal model was reached. Potential multicollinearity was assessed using the variance inflation factor criterion. A continuous B-spline adjustment for age at menopause was also performed to observe the shape of the cardiovascular risk function. The crude analyses and adjustments for age were performed on the full sample, and the multivariate adjustment was performed on a random training sample of 70% the size of the original. The C-index predictive index, along with its 95% CI, was calculated in the testing sample, of 30% the size of the original. The goodness-of-fit of the Weibull distribution was assessed by plotting the log (−log ()) of the estimated survival against the log () of the follow-up time, fitting a regression line and showing the adjusted R^2. Points located on the line, and an $R^2 > 0.9$, indicate a good fit.[14,15] Analyses were performed using the R v.4.4.1 program.[16]

RESULTS

Of the 273,156 women in the UK Biobank database, 56,335 (20.6%) were excluded due to missing data on menopausal variables, 56,230 (20.6%) due to not being menopausal at inclusion, and 52,755 (19.3%) due to having hypertension before inclusion or before menopause. This left a sample of 107,836 women included in the analysis (Fig. 1). Their mean age was 59.5 years (range 40-70); 38% were overweight; 17% obese; 31% had a university education; 12%, low physical activity; 24%, < 7 hours of sleep per day; 10%, a history of cancer; 1.7%, diabetes; 38%, anxiety or depression; and 1.7%, acute myocardial infarction, angina pectoris, or stroke. Regarding variables specific to women, 37% had menarche before the age of 13, 79% were taking birth control pills, and 44% had taken HT. Regarding blood pressure, 13% had high diastolic pressure, and 36% high systolic pressure (Table 1). For the two study factors of interest, 82.2% had menopause after age 45, 14.2% between age 40 and 45, and 3.6% before age 40. Surgical menopause, by bilateral oophorectomy, was performed in 4.9% of women (Table 2).

Over a median follow-up of 14.8 years (mean 14.5 y), 18,508 women (17.2%) were diagnosed with hypertension, equivalent to a cumulative incidence of 10.6 cases per 1,000 person-years. The earlier the onset of menopause, the higher the incidence of hypertension, with rates of 16.6% in normal menopause (10.6 cases per 1,000 women-years), 18.8% in early menopause (10.9 cases per 1,000 women-years), and 22.6% in women with premature menopause (10.8 cases per 1,000 women-years) (χ^2 test, $P < 0.001$). The incidence of hypertension was higher in women with surgical menopause (23.0%, or 11.1 cases per 1,000 women-years) compared to natural menopause (16.9%, or 10.6 cases per 1,000 women-years) (χ^2 test, $P < 0.001$) (Table 2).

A significantly higher incidence of hypertension was also observed in women who smoked (22.1%), were obese

(26.7%), had a very high waist circumference (24.7%), had a high basal metabolic rate (24.9%), did not eat vegetables (20%) or fruit (21%), had a high intake of added salt (20%), had worse self-perceived health (28.9%), had a history of myocardial infarction, angina, or stroke (35%), had diabetes (37%), or were on insulin medication (39.4%). Analytical parameters showing an association with hypertension were high creatinine (29%), glucose (23%), high (35.5%) or very high (41.9%) glycosylated hemoglobin levels, high triglycerides (21.2%), high urate (29%), high diastolic blood pressure (34.8%), and high systolic blood pressure (28.8%) (Table 1 and Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/MENO/B551).

Table 3 shows the risks (hazard ratios, HRs) for the onset of hypertension, according to the type and timing of menopause. In both the crude (model I) and age-adjusted analysis (model II), a significantly greater risk of hypertension was observed in women with early (HR: 1.19; 95% CI: 1.14-1.23) and premature (HR: 1.58; 95% CI: 1.48-1.68) menopause compared to menopause at ages older than 45 years. Similarly, surgical menopause was associated with a higher risk (HR: 1.31; 95% CI: 1.24-1.39) than natural menopause. The effect of premature menopause on hypertension held in the multivariate model III adjusted for 50 variables, where the risk of onset of hypertension was 12.3% higher in women with premature menopause compared with menopause after age 45 (HR: 1.12; 95% CI: 1.03-1.23). On the other hand, the multivariate model did not show an independent association between hypertension and surgical menopause compared to natural menopause (HR: 0.98; 95% CI: 0.90-1.07). The Weibull model fit the data well, showing good predictive capacity, with a C-index of 0.704 (95% CI: 0.698-0.711) in the testing sample. On the other hand, a risk curve by age of menopause as a continuous variable, estimated by splines, also shows a higher risk before 40 years, but it is not linear; the maximum risk occurs between 25 and 35 years (Fig. 2 and Table 4).

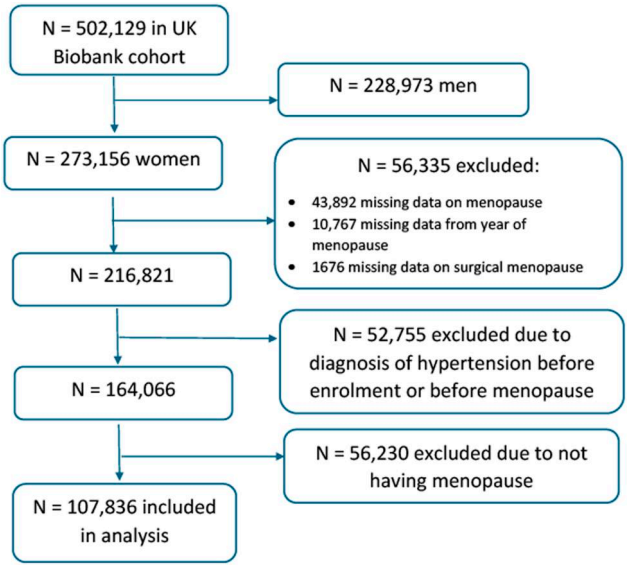

FIG. 1. Patient flow chart.

DISCUSSION

In this large study of more than 107,000 women followed for an average of 14 years, menopause before the age of 40 was shown to have a significant effect on the subsequent development of high blood pressure. These results shed light on the evidence gap mentioned in the 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice[17] regarding the lack of sufficient data to draw conclusions about a possible increased risk of hypertension or diabetes with premature menopause. Our study finds a direct association between natural menopause and high blood pressure, confirming that this association is not due to confounding by other cardiovascular risk factors, which are more common in women during menopause.

These data are in line with those obtained by Chikwati et al[2] in a meta-analysis of 16 studies and 40,517 women, as well as in the meta-analysis of 23 studies and 66,801 women by Hallajzadeh et al.[18] In the latter, the impact of arterial hypertension and the strength of the association with postmenopause was even more marked than in the former (OR: 3.95, 95% CI: 2.01-7.78). In our study, we tried to confirm the direct, independent relationship between premature menopause and arterial hypertension, considering it essential to identify and control for the effect of possible confounders that we know could cause an indirect association. In addition to the association between premature menopause and the presence of high blood pressure during follow-up, after adjusting for all confounders, we used a continuous risk curve for age at menopause estimated by splines to further elucidate that the increased risk before age 40 is nonlinear. The peak risk occurs between the ages of 25 and 35 years. This finding opens the door to redefining the concept of premature menopause, at least in the context of cardiovascular disease, reducing it to less than age 35.

Regarding the type of menopause, surgical menopause was associated with high blood pressure in the crude analysis, but this association lost its significance once adjusted for confounders. Surgical menopause has been linked to high blood pressure in laboratory animals. The effect on female mice suggested a relationship between ovariectomy and an angiotensin II–induced increase in blood pressure and pathophysiological changes in the kidneys.[19] That study raised the hypothesis that selective inhibitors could be useful to treat possible surgically induced hypertension in postmenopausal women. Another possible causal relationship could be increased salt sensitivity, which can even double 4 months after surgical menopause, according to the study by Hernández and colleagues.

TABLE 1. Sample characteristics and incidences of hypertension at each level of the explanatory variables

	n (%)			
	Total	**No hypertension**	**Hypertension**	***P***
Age, mean (SD), y	59.5 (5.5)	59.1 (5.5)	61.4 (5.2)	< 0.001
Alcohol intake				
Never	5,707 (5.3)	4,500 (78.9)	1,207 (21.1)	< 0.001
Previously	3,673 (3.4)	2,905 (79.1)	768 (20.9)	
Currently	98,375 (91.2)	81,870 (83.2)	16,505 (16.8)	
DK/NA	81 (0.1)	53 (65.4)	28 (34.6)	
Tobacco				
No	98,643 (91.5)	82,089 (83.2)	16,554 (16.8)	< 0.001
Only occasionally	2,043 (1.9)	1,665 (81.5)	378 (18.5)	
Yes, every or most days	7,097 (6.6)	5,530 (77.9)	1,567 (22.1)	
DK/NA	53 (0.0)	44 (83.0)	9 (17.0)	
BMI				
Normal < 25 kg/m^2	47,593 (44.1)	41,645 (87.5)	5,948 (12.5)	< 0.001
Overweight 25-30 kg/m^2	40,846 (37.9)	33,422 (81.8)	7,424 (18.2)	
Obese > 30 kg/m^2	18,706 (17.3)	13,715 (73.3)	4,991 (26.7)	
NA	691 (0.6)	546 (79.0)	145 (21.0)	
Waist circumference				
< 80 cm normal	45,521 (42.2)	40,014 (87.9)	5,507 (12.1)	< 0.001
80-88 high	31,950 (29.6)	26,461 (82.8)	5,489 (17.2)	
> 88 very high	30,076 (27.9)	22,636 (75.3)	7,440 (24.7)	
NA	289 (0.3)	217 (75.1)	72 (24.9)	
Educational level				
Upper secondary education	12,028 (11.2)	10,275 (85.4)	1,753 (14.6)	< 0.001
College or university degree	33,730 (31.3)	29,289 (86.8)	4,441 (13.2)	
Lower secondary education	4,455 (4.1)	3,734 (83.8)	721 (16.2)	
Technical vocational training	4,793 (4.4)	3,872 (80.8)	921 (19.2)	
Compulsory secondary education	24,489 (22.7)	20,295 (82.9)	4,194 (17.1)	
Higher vocational education	6,993 (6.5)	5,682 (81.3)	1,311 (18.7)	
DK/NA	1,684 (1.6)	1,263 (75.0)	421 (25.0)	
None	19,664 (18.2)	14,918 (75.9)	4,746 (24.1)	
IPAQ activity				
Low	13,109 (12.2)	10,785 (82.3)	2,324 (17.7)	< 0.001
Moderate	34,767 (32.2)	29,124 (83.8)	5,643 (16.2)	
High	32,790 (30.4)	27,643 (84.3)	5,147 (15.7)	
DK/NA	27,170 (25.2)	21,776 (80.1)	5,394 (19.9)	
Self-perceived health status				
Excellent	22,383 (20.8)	19,701 (88.0)	2,682 (12.0)	< 0.001
Good	66,526 (61.7)	55,427 (83.3)	11,099 (16.7)	
Tight	15,892 (14.7)	12,030 (75.7)	3,862 (24.3)	
Low	2,676 (2.5)	1,903 (71.1)	773 (28.9)	
DK/NA	359 (0.3)	267 (74.4)	92 (25.6)	
Diabetes				
No	105,914 (98.2)	88,111 (83.2)	17,803 (16.8)	< 0.001
Yes	1,794 (1.7)	1,131 (63.0)	663 (37.0)	
DK/NA	128 (0.1)	86 (67.2)	42 (32.8)	
Cholesterol medication				
No	98,500 (91.3)	82,662 (83.9)	15,838 (16.1)	< 0.001
Yes	8,127 (7.5)	5,751 (70.8)	2,376 (29.2)	
DK/NA	1,209 (1.1)	915 (75.7)	294 (24.3)	

TABLE 1. (*continued*)

	n (%)			
	Total	**No hypertension**	**Hypertension**	***P***
Age of menarche				
< 10 y	4,421 (4.1)	3,552 (80.3)	869 (19.7)	< 0.001
10-12 y	35,712 (33.1)	29,486 (82.6)	6,226 (17.4)	
13-14 y	47,411 (44.0)	39,605 (83.5)	7,806 (16.5)	
> 14 y	17,946 (16.6)	14,708 (82.0)	3,238 (18.0)	
DK/NA	2,346 (2.2)	1,977 (84.3)	369 (15.7)	
Oral contraceptive use (ever)				
No	21,810 (20.2)	17,253 (79.1)	4,557 (20.9)	< 0.001
Yes	85,828 (79.6)	71,923 (83.8)	13,905 (16.2)	
DK/NA	198 (0.2)	152 (76.8)	46 (23.2)	
HT (ever)				
No	60,532 (56.1)	51,335 (84.8)	9,197 (15.2)	< 0.001
Yes	47,089 (43.7)	37,825 (80.3)	9,264 (19.7)	
DK/NA	215 (0.2)	168 (78.1)	47 (21.9)	
Hysterectomy				
No	97,689 (90.6)	81,666 (83.6)	16,023 (16.4)	< 0.001
Yes	10,092 (9.4)	7,620 (75.5)	2,472 (24.5)	
DK/NA	55 (0.1)	42 (76.4)	13 (23.6)	
Father with hypertension				
No	90,699 (84.1)	75,129 (82.8)	15,570 (17.2)	0.94
Yes	17,137 (15.9)	14,199 (82.9)	2,938 (17.1)	
Mother with hypertension				
No	79,120 (73.4)	65,810 (83.2)	13,310 (16.8)	< 0.001
Yes	28,716 (26.6)	23,518 (81.9)	5,198 (18.1)	
Diastolic blood pressure				
Normal < 90 mm Hg	86,805 (80.5)	74,230 (85.5)	12,575 (14.5)	< 0.001
High ≥ 90 mm Hg	13,669 (12.7)	8,919 (65.2)	4,750 (34.8)	
NA	7,362 (6.8)	6,179 (83.9)	1,183 (16.1)	
Systolic blood pressure				
Normal < 140 mm Hg	61,877 (57.4)	55,665 (90.0)	6,212 (10.0)	< 0.001
High ≥ 140 mm Hg	38,595 (35.8)	27,483 (71.2)	11,112 (28.8)	
NA	7,364 (6.8)	6,180 (83.9)	1,184 (16.1)	
Total cholesterol				
Normal < 5.2 mmol/L	18,121 (16.8)	14,778 (81.6)	3,343 (18.4)	< 0.001
High > 5.2 mmol/L	82,557 (76.6)	68,714 (83.2)	13,843 (16.8)	
NA	7,158 (6.6)	5,836 (81.5)	1,322 (18.5)	
Creatinine				
Low < 61.9 μmol/L	45,122 (41.8)	37,302 (82.7)	7,820 (17.3)	< 0.001
Normal 61.9-106.1 μmol /L	55,251 (51.2)	45,972 (83.2)	9,279 (16.8)	
High > 106.1 μmol /L	255 (0.2)	181 (71.0)	74 (29.0)	
NA	7,208 (6.7)	5,873 (81.5)	1,335 (18.5)	
Glucose				
Low < 4.1 mmol/L	4,056 (3.8)	3,459 (85.3)	597 (14.7)	< 0.001
Normal 4.1-5.9 mmol/L	80,568 (74.7)	67,071 (83.2)	13,497 (16.8)	
High > 5.9 mmol/L	6,911 (6.4)	5,316 (76.9)	1,595 (23.1)	
NA	16,301 (15.1)	13,482 (82.7)	2,819 (17.3)	
HbA1c				
Normal < 5.7%	99,792 (92.5)	82789 (83.0)	17,003 (17.0)	< 0.001
High 5.7%-6.49%	152 (0.1)	98 (64.5)	54 (35.5)	
Very high > 6.49%	167 (0.2)	97 (58.1)	70 (41.9)	
NA	7,725 (7.2)	6,344 (82.1)	1,381 (17.9)	

HDL cholesterol				
High > 1.6 mmol/L	47,812 (44.3)	40,811 (85.4)	7,001 (14.6)	< 0.001
Normal 1.3-1.6 mmol/L	34,961 (32.4)	28,362 (81.1)	6,599 (18.9)	
Low ≤ 1.3 mmol/L	8,833 (8.2)	6,729 (76.2)	2,104 (23.8)	
NA	16,230 (15.1)	13,426 (82.7)	2,804 (17.3)	
LDL cholesterol				
Normal < 3 mmol/L	17,539 (16.3)	14,227 (81.1)	3,312 (18.9)	< 0.001
High ≥ 3 mmol/L	73,969 (68.6)	61,594 (83.3)	12,375 (16.7)	
NA	16,328 (15.1)	13,507 (82.7)	2,821 (17.3)	
Triglycerides				
Normal < 1.7 mmol/L	68,800 (63.8)	58,386 (84.9)	10,414 (15.1)	< 0.001
High > 1.7 mmol/L	31,823 (29.5)	25,062 (78.8)	6,761 (21.2)	
NA	7,213 (6.7)	5,880 (81.5)	1,333 (18.5)	
Vitamin D				
Normal > 50 nmol/L	45,112 (41.8)	37,939 (84.1)	7,173 (15.9)	< 0.001
Low ≤ 50 nmol/L	47,710 (44.2)	39,183 (82.1)	8,527 (17.9)	
NA	15,014 (13.9)	12,206 (81.3)	2,808 (18.7)	
Albumin				
Low < 35 g/L	42 (0.0)	28 (66.7)	14 (33.3)	0.005
Normal 35-50 g/L	89,081 (82.6)	73,739 (82.8)	15,342 (17.2)	
High > 50	2,516 (2.3)	2,162 (85.9)	354 (14.1)	
NA	16,197 (15.0)	13,399 (82.7)	2,798 (17.3)	
Lipoprotein A				
Normal < 120 nmol/L	70,831 (65.7)	58,930 (83.2)	11,901 (16.8)	< 0.001
High > 120 nmol/L	10,332 (9.6)	8,510 (82.4)	1,822 (17.6)	
NA	26,673 (24.7)	21,888 (82.1)	4,785 (17.9)	
Calcium				
Low < 2.1 nmol/L	123 (0.1)	98 (79.7)	25 (20.3)	0.012
Normal 2.1-2.6 nmol/L	89,441 (82.9)	74,166 (82.9)	15,275 (17.1)	
High > 2.6 nmol/L	2,048 (1.9)	1,644 (80.3)	404 (19.7)	
NA	16,224 (15.0)	13,420 (82.7)	2,804 (17.3)	

BMI, body mass index; DK/NA, don't know/no answer; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HT, hormone therapy; IPAQ, International Physical Activity Questionnaire; LDL, low-density lipoprotein; NA, data not available.

TABLE 2. Timing and type of onset of menopause and incidence of hypertension

	n (%)				
	Total	No hypertension	Hypertension	*P*	IR
Age at menopause					
Normal > 45 y	88,649 (82.2)	73,904 (83.4)	14,745 (16.6)	< 0.001	10.6
Early 40-45 y	15,266 (14.2)	12,391 (81.2)	2,875 (18.8)		10.9
Premature < 40 y	3,921 (3.6)	3,033 (77.4)	888 (22.6)		10.8
Type of menopause					
Natural	102,570 (95.1)	85,273 (83.1)	17,297 (16.9)	< 0.001	10.6
Surgical	5,266 (4.9)	4,055 (77.0)	1,211 (23.0)		11.1

IR, incidence rate of hypertension per 1,000 women-years.

However, the development of high blood pressure was not directly observed in that study either. The possible delay of more than 5-10 years for this mechanism could influence the lack of a significant association in our study.[20]

The relationship between menopause and hypertension justifies preventive interventions in women during menopause and perimenopause. However, this is not reflected in routine clinical practice. An Australian study examined health center–based prevention in more than 50,000 patients. Women were less likely than men to have their cardiovascular risk factors recorded and assessed. These data suggest that female-specific risk factors may not be detected in women at earlier stages of life, entailing missed opportunities for early preventive measures to avoid the development of cardiovascular disease.[21]

Optimizing health during menopause is the gateway to healthy aging for women. The silent effects of the menopause transition can be substantial, as reflected in our study with the increased incidence of high blood pressure. Women with menopausal symptoms should be actively assessed for prevention, counseled on treatment options, and offered preventive measures and evidence-based therapies, such as HT.[22] However, the timing of these measures is also relevant, as the cardiovascular risk associated with HT appears to depend on the timing of initiation relative to menopause. Starting hormone treatment early in menopause reduces the risk compared to prescribing it 10 years after onset.[23] Similarly, acting early to detect and treat high blood pressure increases the chances of preventing future cardiovascular events.

Fortunately, although the main preventive guidelines still do not draw out the major differences in the control of risk factors such as high blood pressure in diseases and physiological conditions specific to women, the body of literature is reporting expert consensus and evidence-based guidelines that, like our study, focus on the importance of prevention in women.[24,25] More research is needed to deepen our understanding of this important stage of a woman's life.

TABLE 3. Risks of developing hypertension, as estimated by Weibull models for the age at menopause

	Age and type of menopause	HR[a] (95% CI)	*P*
Model I	Normal > 45 y	1	
	Early 40-45 y	1.14 (1.09-1.18)	< 0.001
	Premature < 40 y	1.42 (1.33-1.51)	< 0.001
	Natural	1	
	Surgical	1.43 (1.35-1.51)	< 0.001
Model II	Normal > 45 y	1	
	Early 40-45 y	1.19 (1.14-1.23)	< 0.001
	Premature < 40 y	1.58 (1.48-1.68)	< 0.001
	Natural	1	
	Surgical	1.31 (1.24-1.39)	< 0.001
Model III[b]	Normal > 45 y	1	
	Early 40-45 y	1.03 (0.98-1.08)	0.22
	Premature < 40 y	1.12 (1.03 -1.23)	0.010
	Natural	1	
	Surgical	0.98 (0.90-1.07)	0.66

HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein.

Model I: crude fit. Model II: age-adjusted model. Model III: Multivariate model adjusted for age, deprivation index, tobacco and alcohol use, body mass index, waist circumference, basal metabolic rate, educational level, physical activity, forced vital capacity, hours of sleep, salad-vegetable intake, cooked vegetable intake, fruit intake, salt intake, coffee intake, water intake, sugar intake, self-rated health, asthma/bronchitis/emphysema/pulmonary clot, cancer, acute myocardial infarction/angina pectoris/stroke, diabetes, nerves/anxiety/tension/depression, cholesterol medication, age at menarche, use of birth control pill, use of hormone therapy, hysterectomy, paternal and maternal history of diabetes, paternal and maternal history of hypertension, dental problems, blood type, systolic blood pressure, urea, creatinine, glucose, HbA1c, total cholesterol, HDL and LDL cholesterol, triglycerides, urate, vitamin D, albumin, lipoprotein a, and calcium.

[a]Adjusted for training sample, n = 75,555; hypertension n = 13,013.

[b]C-index of model III in testing sample: 0.704 and 95% CI (0.698-0.711); n = 32,281; hypertension n = 5,495.

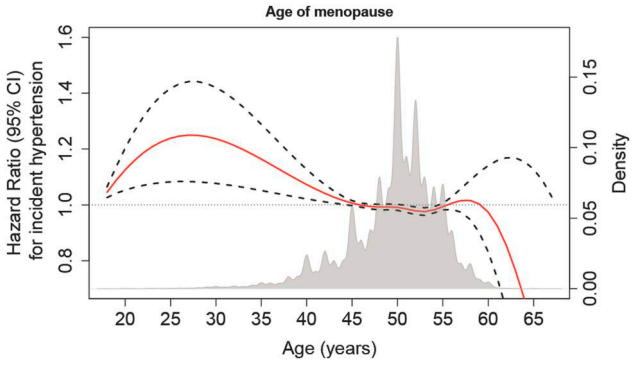

FIG. 2. Risk curve according to age at menopause (continuous) for incident hypertension, estimated by splines.

TABLE 4. Multivariate Weibull model for the onset of hypertension, with age and type of menopause as study factors

	HR (95% CI)	*P*
Age of menopause		
Normal > 45 y	1	
Early 40-45 y	1.03 (0.98-1.08)	0.22
Premature < 40 y	1.12 (1.03-1.23)	0.010
Menopause type		
DK/NA	1	
Surgical	0.98 (0.90-1.07)	0.66
Age, y	1.08 (1.07-1.08)	< 0.001
Townsend Deprivation Index, unit	1.02 (1.01-1.02)	< 0.001
Alcohol intake		
Never	1	
Previously	0.97 (0.87-1.09)	0.64
Currently	0.99 (0.92-1.07)	0.85
DK/NA	1.59 (1.02-2.48)	0.042
Tobacco		
No	1	
Only occasionally	1.18 (1.05-1.33)	0.007
Yes, every or most days	1.22 (1.14-1.31)	< 0.001
DK/NA	0.99 (0.49-2.01)	0.97
Body mass index		
Normal < 25 kg/m^2	1	
Overweight 25-30 kg/m^2	1.15 (1.09-1.21)	< 0.001
Obese > 30 kg/m^2	1.32 (1.22-1.42)	< 0.001
NA	0.98 (0.75-1.29)	0.90
Waist circumference		
< 80 cm normal	1	
80-88 high	1.15 (1.09-1.21)	< 0.001
> 88 very high	1.20 (1.13-1.29)	< 0.001
NA	1.56 (1.08-2.24)	0.017
Basal metabolic rate		
Low < 5,027 kJ	1	
Normal 5,027-6,272 kJ	0.99 (0.94-1.05)	0.83
High > 6,272 kJ	1.12 (1.03-1.21)	0.005
NA	1.11 (0.96-1.29)	0.16
Level of education		
Level A/AS or equivalent	1	
College or University Degree	0.98 (0.92-1.05)	0.54
CSEs or equivalent	1.18 (1.06-1.31)	0.002
NUQ, HND, HNC or equivalent	1.11 (1.01-1.22)	0.036
Level 0/GCSEs or equivalent	1.10 (1.03-1.17)	0.006
Others	1.10 (1.01-1.20)	0.024
DK/NA	1.34 (1.14-1.57)	< 0.001
None	1.21 (1.13-1.30)	< 0.001
IPAQ activity		
Low	1	
Moderate	0.99 (0.93-1.05)	0.64
High	1.00 (0.94-1.06)	1.00
DK/NA	1.01 (0.95-1.07)	0.72
Forced vital capacity		
Normal-high	1	
Reduced	1.18 (1.14-1.23)	< 0.001
NA	1.25 (1.17-1.32)	< 0.001
Sleep duration		
< 7 h	1	
7-9 h	0.92 (0.89-0.96)	< 0.001
> 9 h	0.85 (0.75-0.97)	0.015
DK/NA	0.96 (0.78-1.17)	0.66
Intake of cooked vegetables		
None	1	
1-2 tablespoons per day	0.94 (0.84-1.06)	0.33
3-4 tablespoons per day	0.96 (0.85-1.08)	0.52
> 4 tablespoons per day	0.92 (0.81-1.04)	0.19
DK/NA	1.03 (0.87-1.21)	0.76

TABLE 4. (*continued*)

	HR (95% CI)	*P*
Intake of raw vegetables in salad		
None	1	
1-2 tablespoons per day	0.99 (0.92-1.06)	0.78
3-4 tablespoons per day	0.99 (0.92-1.07)	0.86
> 4 tablespoons per day	0.97 (0.89-1.05)	0.44
DK/NA	0.96 (0.86-1.07)	0.46
Fresh fruit intake		
None	1	
1-2 pieces per day	0.92 (0.84-1.00)	0.062
3-4 pieces per day	0.94 (0.86-1.03)	0.18
> 4 pieces per day	0.97 (0.87-1.07)	0.53
DK/NA	0.83 (0.72-0.97)	0.019
Intake of added salt		
Never or rarely	1	
Sometimes	1.01 (0.97-1.05)	0.66
Frequently	1.00 (0.95-1.06)	0.92
Always	1.08 (1.00-1.17)	0.052
Coffee intake		
None	1	
< 1	0.89 (0.82-0.96)	0.004
1-2 cups a day	0.96 (0.91-1.00)	0.068
3-4 cups a day	0.94 (0.89-0.99)	0.018
> 4 cups a day	0.99 (0.93-1.06)	0.80
DK/NA	1.09 (0.75-1.60)	0.65
Water intake		
None	1	
< 1	0.97 (0.88-1.07)	0.53
1-2 glasses a day	0.98 (0.91-1.05)	0.57
3-4 glasses a day	1.02 (0.94-1.10)	0.67
> 4 glasses a day	1.09 (1.00-1.17)	0.044
DK/NA	0.83 (0.65-1.04)	0.11
Sugar intake		
No	1	
Yes	0.97 (0.93-1.01)	0.16
DK/NA	1.01 (0.63-1.59)	0.98
Self-perceived health status		
Excellent	1	
Good	1.23 (1.17-1.30)	< 0.001
Tight	1.58 (1.48-1.68)	< 0.001
Low	1.79 (1.62-1.99)	< 0.001
DK/NA	1.49 (1.15-1.94)	0.003
Asthma, bronchitis, emphysema, and blood clot		
No	1	
Yes	1.07 (1.03-1.11)	0.001
DK/NA	0.85 (0.53-1.35)	0.49
Cancer		
No	1	
Yes	0.99 (0.94-1.05)	0.77
DK/NA	0.90 (0.66-1.25)	0.54
AMI, angina, and stroke		
No	1	
Yes	1.41 (1.28-1.55)	< 0.001
DK/NA	1.93 (1.47-2.54)	< 0.001
Diabetes		
No	1	
Yes	1.53 (1.38-1.71)	< 0.001
DK/NA	1.44 (0.99-2.10)	0.057
Anxiety or depression		
No	1	
Yes	1.09 (1.05-1.13)	< 0.001
DK/NA	0.96 (0.78-1.18)	0.68
Cholesterol medication		
No	1	
Yes	1.23 (1.15-1.31)	< 0.001
DK/NA	1.05 (0.83-1.33)	0.66
Age of menarche		
< 10	1	
10-12	0.99 (0.91-1.08)	0.82

TABLE 4. (*continued*)

	HR (95% CI)	*P*
13-14	0.98 (0.90-1.07)	0.67
≥15	1.04 (0.95-1.14)	0.42
DK/NA	0.97 (0.84-1.13)	0.70
Oral contraceptive use (ever)		
No	1	
Yes	0.99 (0.95-1.04)	0.71
DK/NA	1.02 (0.70-1.49)	0.92
HT (ever)		
No	1	
Yes	1.11 (1.07-1.15)	<0.001
DK/NA	0.94 (0.65-1.37)	0.76
Hysterectomy		
No	1	
Yes	1.18 (1.10-1.26)	<0.001
DK/NA	0.91 (0.47-1.76)	0.79
Father with DM, yes	0.93 (0.87-1.00)	0.042
Mother with DM, yes	1.05 (0.99-1.11)	0.13
Father with hypertension, yes	1.16 (1.10-1.21)	<0.001
Mother with hypertension, yes	1.25 (1.20-1.30)	<0.001
Dental problems		
No	1	
Yes	1.06 (1.02-1.10)	0.002
DK/NA	1.08 (0.79-1.48)	0.63
Blood type		
AA	1	
AB	0.99 (0.88-1.10)	0.83
AO	0.99 (0.92-1.06)	0.71
BB	1.07 (0.85-1.34)	0.58
BO	0.91 (0.84-1.00)	0.044
OO	0.98 (0.92-1.05)	0.57
NA	0.95 (0.82-1.09)	0.47
Diastolic blood pressure		
Normal < 90 mm Hg	1	
High ≥ 90 mm Hg	2.51 (2.41-2.62)	0
NA	1.02 (0.95-1.10)	0.56
Urea		
Low <2.8 mmol/L	1	
Normal 2.8-8.2 mmol/L	0.91 (0.73-1.13)	0.38
High >8.2 mmol/L	0.91 (0.71-1.17)	0.47
NA	1.02 (0.49-2.11)	0.97
Creatinine		
Low <61.9 μmol/L	1	
Normal 61.9-106.1 μmol/L	0.95 (0.92-0.99)	0.009
High >106.1 μmol/L	1.39 (1.06-1.83)	0.019
NA	0.82 (0.31-2.16)	0.69
Glucose		
Low <4.1 mmol/L	1	
Normal 4.1-5.9 mmol/L	0.98 (0.88-1.08)	0.62
High >5.9 mmol/L	1.05 (0.93-1.17)	0.44
NA	1.33 (0.74-2.39)	0.34
HbA1c		
Normal <5.7%	1	
High 5.7%-6.49%	0.91 (0.65-1.26)	0.56
Very high >6.49%	1.22 (0.90-1.64)	0.20
NA	0.98 (0.90-1.05)	0.52
Total cholesterol		
Normal ≤ 5.2 mmol/L	1	
High > 5.2 mmol/L	1.00 (0.94-1.07)	0.93
NA	0.62 (0.27-1.40)	0.25
HDL		
High >1.6 mmol/L	1	
Normal 1.2-1.6 mmol/L	1.02 (0.98-1.07)	0.33
Low ≤1.3 mmol/L	1.12 (1.05-1.20)	0.001
NA	1.00 (0.38-2.66)	1.00
LDL		
Normal ≤3 mmol/L	1	
High >3 mmol/L	0.97 (0.91-1.04)	0.37
NA	0.93 (0.42-2.07)	0.86

TABLE 4. (*continued*)

	HR (95% CI)	*P*
Triglycerides		
Normal < 1.7 mmol/L	1	
Height > 1.7 mmol/L	1.05 (1.01-1.10)	0.025
NA	1.11 (0.37-3.32)	0.86
Urate		
Low < 202 µmol/L	1	
Normal 202-416 µmol/L	1.01 (0.95-1.07)	0.80
High > 416 µmol/L	1.15 (1.00-1.31)	0.044
NA	1.58 (1.06-2.36)	0.025
Vitamin D		
Normal > 50 mmol/L	1	
Low < 50 nmol/L	0.99 (0.95-1.03)	0.64
NA	1.03 (0.96-1.10)	0.47
Calcium		
Low < 2.1 nmol/L	1	
Normal 2.1-2.6 nmol/L	0.95 (0.58-1.56)	0.83
High > 2.6 nmol/L	1.04 (0.62-1.73)	0.89
NA	0.66 (0.30-1.44)	0.30
Albumin		
Normal < 35 nmol/L	1	
Normal-high 35-50 nmol/L	0.70 (0.37-1.33)	0.28
High > 50 nmol/L	0.70 (0.36-1.34)	0.28
NA	0.80 (0.34-1.91)	0.62
Lipoprotein A		
Normal ≤ 120 nmol/L	1	
Height > 120 nmol/L	1.05 (0.99-1.11)	0.13
NA	1.04 (0.99-1.09)	0.091

AMI, acute myocardial infarction; DK/NA, don't know/no answer; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HR, hazard ratio; HT, hormone therapy; IPAQ, International Physical Activity Questionnaire; LDL, low-density lipoprotein; NA, data not available.

Our study has significant strengths, such as high statistical power, richness, and standardization of the data (Fig. 3). These characteristics allow for a comprehensive analysis of risk factors and exploration of the temporality of associations. However, the study also has certain limitations. The inherent selection bias in UK Biobank participants (who may not be representative of the general population), potential survival bias, self-reported age at menopause, possible heterogeneity in the definition of hypertension, and the existence of residual confounding factors, as well as the relatively homogeneous population of predominantly European descent, should all be considered when interpreting the results. Despite these limitations, the study's strengths contribute to the existing evidence on the association between early menopause and hypertension and provide a solid foundation for future research.

CONCLUSIONS

Our study confirms a significant association between premature menopause (before age 40) and an increased risk of developing high blood pressure, with the risk peaking between

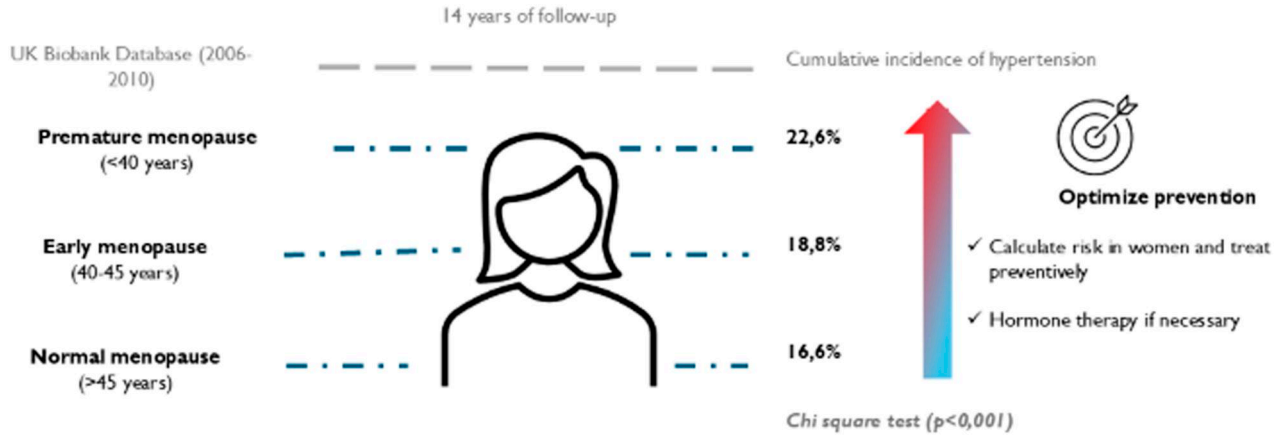

FIG. 3. Menopause and high blood pressure.

ages 25 and 35. This association persists even after adjusting for other known cardiovascular risk factors, highlighting the importance of considering the age at menopause as a cardiovascular risk factor when assessing women's health.

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