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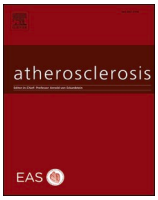

Risk factors for major adverse cardiovascular events in postmenopausal women: UK Biobank prospective cohort study

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ABSTRACT

Background and aims: Cardiovascular risk increases during menopause, so the medical and scientific community should consider women's specific risk factors to prevent cardiovascular disease. This study aims to assess the risk factors for the incidence of major adverse cardiovascular events (MACE) exclusive to postmenopausal women.
Methods: We conducted a prospective cohort study in postmenopausal women aged 40 years and older, who were included in the UK Biobank cohort between 2006 and 2010 and followed to 2021 (12 years). A total of 156,787 women were followed for a median of 12.5 years (nearly 2 million person-years), and MACE risk was assessed using Fine-Gray competing risk models.
Results: The cumulative incidence of cardiovascular morbidity and mortality was 1.2% (0.97 cases per 1000 women-years). Not having taken birth control pills, not having children, and early menarche (≤12 years) were independently associated with cardiovascular morbidity and mortality.
Conclusions: Risk factors for cardiovascular disease that are specific to women include early menarche, not having taken oral contraceptives, and reproductive history, and this relationship is independent of classic cardiovascular risk factors.

1. Introduction

Cardiovascular disease is the leading cause of mortality worldwide in both men and women [1]. While different prevention and treatment strategies have effectively decreased cardiovascular mortality in recent years [2,3], these impacts have not necessarily been equal between the sexes. For example, the incidence of acute myocardial infarction has decreased more in men than in women [4,5].

The relatively late development of acute coronary syndrome in women is largely attributed to the protective role of estrogen during the childbearing age. In postmenopause, estrogen deficiency is associated with a higher prevalence of diabetes mellitus, metabolic syndrome, hypercholesterolemia, and weight gain with an increased percentage of body fat—all cardiovascular risk factors in their own right [6]. Thus, in this clinical panorama, postmenopause is considered just as important as male sex in terms of cardiovascular risk [7].

Estrogen has numerous potentially protective mechanisms. In the circulatory system, these include vasodilation mediated by nitric oxide, inhibition of coronary vasospasm, increased vascular flow and lower resistance, increased cardiac output, facilitation of angiogenesis, and an antiapoptotic effect on cardiomyocytes [8]. Other protective mechanisms include antioxidant and anti-inflammatory properties, favorable changes in the lipid profile, increased sensitivity to insulin, attenuation of weight gain typical of menopause, and less abdominal adiposity. In contrast, negative factors related to estrogens have also been described: increased triglycerides, C-reactive protein, and coagulation factors [9].

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Studies of hormone replacement therapy for reducing cardiovascular risk in postmenopausal women show inconsistent results, and meta-analyses suggest that the effects of the therapy depend on the woman's individual characteristics [10].

Although traditional cardiovascular risk factors are common in both men and women, predictive models of cardiovascular risk rarely consider the risk factors unique to women. Some are related to gynecological history, such as age at menarche, age at menopause, surgical menopause (hysterectomy), history of polycystic ovarian syndrome, and premature ovarian failure. Others are related to pregnancy history, such as gestational diabetes, preeclampsia, intrauterine growth restriction, spontaneous abortions, or premature birth [11]. Previous studies suggest that these factors could be early markers of cardiovascular disease in women; however, there is little evidence on the magnitude of the associations [12], or for that matter, on the importance of traditional risks and the impact of the interactions between all these factors in postmenopausal women [13].

Regarding the management of cardiovascular disease, most guidelines are based on studies in predominantly male populations, especially in coronary disease and heart failure. Previous research has shown that symptoms, disease management, and response to treatment may differ between sexes and that there is underdiagnosis and undertreatment of cardiovascular disease among women [14].

Cardiovascular risk increases during menopause, so female-specific risk factors and pathophysiological characteristics should be considered in cardiovascular disease prevention. This study aims to assess the association between factors exclusive to postmenopausal women and the incidence of major adverse cardiovascular events.

2. Patients and methods

2.1. Study design and population

This prospective observational cohort study included postmenopausal women aged 40 years and older. The sample was drawn from the UK Biobank database, a large cohort of 502,413 voluntary participants (229,085 men and 273,328 women) aged 40 or over and living in the UK at the time of inclusion. The database includes behavioral data, comorbidities, and blood tests. Participants consented to long-term health monitoring by linkage to their medical records; they were included from 2006 to 2010 and followed to 2021. The study design and methods for data collection of UK Biobank cohort are well described elsewhere [15]. The UK Biobank was approved by the North West Multi-centre Research Ethics Committee, the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland. All participants gave their written informed consent before their data were collected. The present study complies with the Declaration of Helsinki and was approved by the UMH Office for Responsible Research on 10 May 2022 (reference AUT.DMC.DMR.01.22.CC).

The inclusion criteria were: female sex and having menopause at the time of inclusion in the UK Biobank cohort, that is, those who answered "Yes" to the question "Have you had your menopause (periods stopped)?" (data-field 2724) when they completed the touchscreen questionnaire during the baseline data collection. Women who had experienced any cardiovascular event or disease before their inclusion were excluded (International Classification of Diseases, 10th revision [ICD10] Cardiovascular Accident: I60-I64 or Ischemic Heart Disease ICD10: I20-I25), as were those with an unknown cause of death, loss to follow-up due to change of address, or who left the cohort of their own accord.

2.2. Variables

The outcome variable was a composite endpoint consisting of any major adverse cardiovascular event (MACE): death from cardiovascular causes (ICD10: I00-I99), cerebrovascular accident (ICD10: 60-I64), or ischemic heart disease (ICD10: I20-I25), which was recorded together with its date of occurrence during follow-up.

The female-specific exposure variables were: ever taken oral contraception (no/yes/missing); bilateral oophorectomy (both ovaries removed) (not sure/no/yes/missing); ever used hormone replacement therapy (no/yes/missing); hysterectomy (womb removed) (no/yes/missing); number of live births (0/1/2/≥3/missing); age at menarche, in years (≤10/11-12/13-14/≥15/missing); age at menopause, in years (last menstrual period) (<40/40-44/45-49/50-54/≥55/missing).

A wide variety of other explanatory variables were also analyzed, including sociodemographic data (age, country of birth, socioeconomic status, family), behavioral variables (alcohol and tobacco use, sleep, daily activities, energy expenditure), anthropometric variables (waist and hip circumference, body mass index, body fat, heel bone mineral density), physiological variables (forced vital capacity, blood pressure, heart rate), dietary intake of different foods and drinks, comorbidities (sleeplessness, irritability, anxiety, feelings of depression, diabetes, hypertension, cancer, asthma, allergies), analytic variables (cholesterol, creatinine, glucose, HbA1c, albumin, triglycerides, urea), medication use, and family history of heart disease/stroke. See Supplementary materials for a comprehensive list of all variables and their categorization.

The follow-up period was 11–15 years, from the date of inclusion (between March 2006 and December 2010) to the end of follow-up on 31 December 2021.

2.3. Statistical methods

A descriptive analysis of all the study variables was performed. Categorical variables were expressed as frequencies and quantitative variables as mean, standard deviation (SD), and range. The factors associated with the incidence of the cardiovascular event were determined using contingency tables, applying the chi-squared test to compare categorical variables and the Student's *t*-test to compare the mean values of quantitative ones. The normality of the distribution was verified using the Kolmogorov-Smirnov test.

Fine-Gray subdistribution hazard models were adjusted to estimate the magnitude of change in the function of cardiovascular events, considering competing risks of mortality from other causes [16]. Subdistribution hazard ratios (HRs) were estimated for the composite outcome, along with their 95% confidence interval (CIs). An optimal model was fitted using a backwards stepwise approach, starting from the complete model with all exposure and explanatory variables, which were gradually eliminated based on the Akaike information criterion (AIC) until obtaining the final model. The model adjustment was carried out on a random training sample of 70% of the original sample, and Harrell's C-index of goodness-of-fit was calculated as a measure of model discrimination in a testing sample of 30% of the original size [17]. We set a 2-sided *p*-value <0.05 as the threshold for statistical significance. Analyses were performed using the SPSS v.28 program (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp) and the R program v.4.2.2 (R Core Team, 2022. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) using the *cmprsk*, *riskRegression* and *pec* libraries.

3. Results

A total of 156,787 women with menopause and without coronary or cerebrovascular disease at the time of inclusion were included (Fig. 1). The mean follow-up period was 12.5 years (1,965,546 person-years), during which time 1915 MACE occurred (cumulative incidence 1.2%, or 0.97 cases per 1000 women-years), along with 7721 deaths from other causes (cumulative incidence 4.9%; 3.9 cases per 1000 women-years).

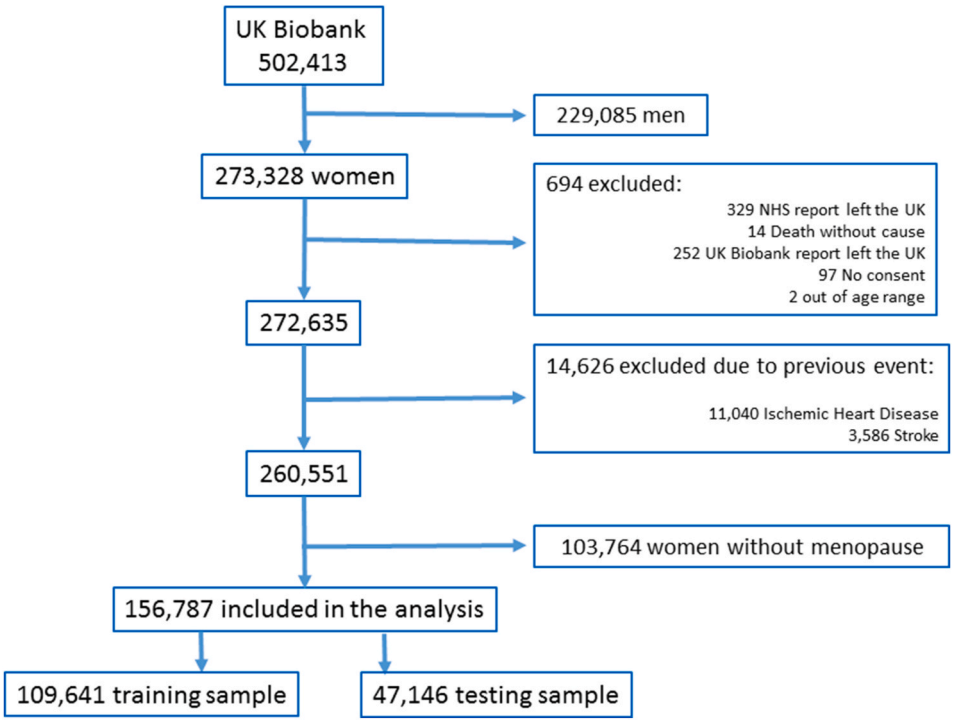

Fig. 1. Participant flowchart.

The women analyzed had a mean age of 60.1 years (SD 5.4, range 40–70 years). Most (77.6%) lived in England, 95.6% were white, 29.2% university educated, and 25% had a high deprivation index. Regarding behavioral variables, 58.1% had never smoked, 33.5% were ex-smokers, and 38.4% reported drinking alcohol every day or 3 to 4 times a week. About 10.3% drove more than 1 h a day, 16% used the computer for more than 1 h a day, and 31.8% watched television for more than 3 h a day. The majority did at least some physical activity (just 13.4% reported doing none or very little), and 25% said they slept 6 h or less per night. Regarding risk factors and comorbidities, 24% had a waist circumference of over 93 cm, 22.4% were obese, 22% had a heart rate over 77 bpm, 3.6% had diabetes, 26.4% hypertension, 10.6% some type

Table 1
Prevalence of female-specific exposure factors and cumulative incidence of major adverse cardiovascular events (MACE) over follow-up.

		Total (N = 156,787)		No event (N = 147,151)		MACE (N = 1915)		Death (other causes) (N = 7721)		
		n	%	n	%	n	%	n	%	*p*-value
Ever taken oral contraception	No	34,225	21.8%	31,448	91.9%	638	1.9%	2139	6.2%	<0.001
	Yes	122,221	78.0%	115,393	94.4%	1271	1.0%	5557	4.5%	
	Missing	341	0.2%	310	90.9%	6	1.8%	25	7.3%	
Bilateral oophorectomy	Not sure	1454	0.9%	1345	92.5%	26	1.8%	83	5.7%	<0.001
	No	146,802	93.6%	137,995	94.0%	1749	1.2%	7058	4.8%	
	Yes	8461	5.4%	7751	91.6%	137	1.6%	573	6.8%	
	Missing	70	0.0%	60	85.7%	3	4.3%	7	10.0%	
Ever used hormone-replacement therapy	No	83,448	53.2%	78,600	94.2%	925	1.1%	3923	4.7%	<0.001
	Yes	72,937	46.5%	68,185	93.5%	985	1.4%	3767	5.2%	
	Missing	402	0.3%	366	91.0%	5	1.2%	31	7.7%	
Hysterectomy	No	138,944	88.6%	130,685	94.1%	1620	1.2%	6639	4.8%	<0.001
	Yes	17,676	11.3%	16,317	92.3%	291	1.6%	1068	6.0%	
	Missing	167	0.1%	149	89.2%	4	2.4%	14	8.4%	
Number of live births	0	26,132	16.7%	24,428	93.5%	349	1.3%	1355	5.2%	<0.001
	1	19,816	12.6%	18,552	93.6%	268	1.4%	996	5.0%	
	2	71,420	45.6%	67,407	94.4%	744	1.0%	3269	4.6%	
	≥3	39,300	25.1%	36,656	93.3%	552	1.4%	2092	5.3%	
	Missing	119	0.1%	108	90.8%	2	1.7%	9	7.6%	
Age at menarche, years	≤10	6905	4.4%	6423	93.0%	107	1.5%	375	5.4%	<0.001
	11–12	52,659	33.6%	49,389	93.8%	686	1.3%	2584	4.9%	
	13–14	67,457	43.0%	63,549	94.2%	755	1.1%	3153	4.7%	
	≥15	25,320	16.1%	23,674	93.5%	300	1.2%	1346	5.3%	
	Missing	4446	2.8%	4116	92.6%	67	1.5%	263	5.9%	
Age at menopause (last menstrual period), years	<40	5630	3.6%	5176	91.9%	104	1.8%	350	6.2%	<0.001
	40–44	13,232	8.4%	12,302	93.0%	203	1.5%	727	5.5%	
	45–49	35,286	22.5%	33,122	93.9%	434	1.2%	1730	4.9%	
	50–54	70,476	45.0%	66,575	94.5%	721	1.0%	3180	4.5%	
	≥55	22,070	14.1%	20,675	93.7%	268	1.2%	1127	5.1%	
	Missing	10,093	6.4%	9301	92.2%	185	1.8%	607	6.0%	

of cancer, and 10.4% asthma. In terms of diet, 19.4% reported consuming processed meat more than twice a week, 23% ate pork at least once a week, 49% ate no more than two servings of cooked vegetables per week, 26.6% no more than one serving of fresh fruit a day, 25% two bowls or less of cereal a week, 19% at least six cups of tea a day, and 17% at least four cups of coffee a day; 12% said they did not drink water. Blood tests showed that 42% had high total cholesterol, 8% HDL values below 1.17 mmol/L, 31% LDL values greater than 4.1 mmol/L, 2.6 values of HbA1c greater than 6.5, and 45.5% levels of vitamin D less than 50 nmol/L. In addition, 13.1% reported taking cholesterol-lowering medication and 19.2% blood pressure medication, while 30.4% had a family history of heart disease/stroke (Supplementary Table S1).

Table 1 shows the prevalence of female-specific exposure factors and the cumulative incidence of MACE during follow-up. The 22% of women who had never taken oral contraception showed a cumulative incidence of MACE almost double that of those who had ever taken it. Incidence of MACE was also higher in women who had undergone bilateral oophorectomy (1.6% *versus* 1.2%), ever used hormone replacement therapy (1.4% *versus* 1.1%), had undergone hysterectomy (1.6% *versus* 1.2 %), had early menarche (≤10 years, 1.5%; 11-12 years, 1.3%; 13-14 years, 1.1%), or had early menopause (≤40 years, 1.8%, 40–44 years, 1.5%, 45–49 years, 1.2%, 50–54 years, 1.0%, ≥55 years, 1.2%).

Table 2 shows the estimated risks of cardiovascular morbidity and mortality using Fine-Gray models, taking into account the competing risks of death from other causes. A crude analysis was fitted for each exposure variable, and a multivariable adjustment for the rest of the explanatory variables. In the crude analysis, a significantly higher risk of MACE was observed in women who had not taken oral contraception (HR 1.79, 95% CI 1.60–2.00; $p < 0.001$) compared to those who had taken it, and this risk remained significant in the multivariable adjustment (HR 1.24, 95% CI 1.10–1.40; $p = 0.001$). Regarding the number of live births, the effect is modified from the crude to the multivariable adjustment due to confounding: in the crude analysis, a protective effect was observed for having had two live births compared to three (HR 0.72, 95% CI 0.64–0.83; $p < 0.001$), while in the multivariable model a higher risk was observed in women with no live births (HR 1.22, 95% CI 1.04–1.44; $p = 0.016$). Menarche before the age of 10 years was associated with a higher risk, both in the crude model (HR 1.31, 95% CI 1.01–1.70; $p = 0.046$) and in the multivariable adjustment (HR 1.33, 95% CI 1.02–1.74; $p = 0.034$). Menarche at 11-12 years of age was also independently associated with a higher risk (HR 1.24, 95% CI 1.05–1.47; $p = 0.010$) compared to those who were 15 or older when they first had their period. In the crude model, bilateral oophorectomy (HR 1.44, 95% CI 1.18–1.76; $p < 0.001$), hormone replacement therapy (HR 1.16, 95% CI 1.05–1.30; $p = 0.006$), and hysterectomy (HR 1.32, 95% CI 1.13–1.54; $p < 0.001$) were all significantly associated with MACE, but this association lost significance in the multivariable adjustment. The multivariable model was adjusted in the training sample (n = 109,641) for age at recruitment, tobacco use, waist circumference, sleep duration, heel bone mineral density, hours/day watching TV, total MET, heart rate, pork intake, cereal intake, coffee intake, frequency of feeling depressed, diabetes, hypertension, emphysema/chronic bronchitis, forced vital capacity, HDL and LDL cholesterol, vitamin D, cholesterol-lowering medication, and family history of heart disease/stroke. Supplementary Table S2 shows the complete multivariable model, which presented good performance, with a C-index in the test sample (n = 47,146) of 0.726.

Table 2
Crude and multivariable adjustment models for female-specific factors.

		Crude analysis			Multivariable model[a]		
		HR	95 % CI	*p*-value	HR	95 % CI	*p*-value
Ever taken	Yes	1			1		
Oral contraception	No	1.79	(1.60–2.00)	<0.001	1.24	(1.10–1.40)	0.001
	Missing	2.08	(0.86–5.04)	0.10	0.74	(0.24–2.33)	0.61
Bilateral oophorectomy	No	1					
	Not sure	0.90	(0.49–1.62)	0.71	NS		
	Yes	1.44	(1.18–1.76)	<0.001			
	Missing	1.77	(0.25–12.76)	0.57			
Ever used hormone-replacement therapy	No	1					
	Yes	1.16	(1.05–1.30)	0.006	NS		
	Missing	1.23	(0.46–3.28)	0.685			
Hysterectomy	No	1					
	Yes	1.32	(1.13–1.54)	<0.001	NS		
	Missing	2.36	(0.76–7.36)	0.14			
Number of live births	≥3	1			1		
	2	0.72	(0.64–0.83)	<0.001	0.91	(0.79–1.04)	0.17
	1	0.92	(0.77–1.10)	0.35	1.05	(0.87–1.25)	0.63
	0	0.93	(0.79–1.09)	0.36	1.22	(1.04–1.44)	0.016
	Missing	1.67	(0.42–6.67)	0.47	1.14	(0.28–4.63)	0.86
Age at menarche, years	≥15	1			1		
	13–14	0.95	(0.81–1.11)	0.49	1.09	(0.92–1.28)	0.30
	11–12	1.11	(0.95–1.31)	0.19	1.24	(1.05–1.47)	0.010
	≤10	1.31	(1.01–1.70)	0.046	1.33	(1.02–1.74)	0.034
	Missing	1.26	(0.92–1.73)	0.15	1.21	(0.89–1.70)	0.24
Age at menopause (last menstrual period), years	<40	1					
	40–44	0.81	(0.61–1.09)	0.16			
	45–49	0.72	(0.56–0.93)	0.013	NS		
	50–54	0.58	(0.45–0.74)	<0.001			
	≥55	0.73	(0.56–0.96)	0.025			
	Missing	1.05	(0.79–1.40)	0.75			

NS: not significant; HR: hazard ratio; CI: confidence interval.
Training sample: n = 109,641; n cardiovascular event = 1,347; n death other causes = 5,360
Testing sample: n = 47,146; n cardiovascular event = 568; n death other causes = 2,361
C-index in testing sample = 0.726
[a] Model adjusted for: age at recruitment, tobacco use, waist circumference, sleep duration, heel bone mineral density, hours/day watching TV, total metabolic equivalent of tasks, heart rate, pork intake, cereal intake, coffee intake, frequency of feeling depressed, diabetes mellitus, hypertension, emphysema/chronic bronchitis, forced vital capacity, HDL and LDL cholesterol, vitamin D, cholesterol-lowering medication and family history of heart disease/stroke.

4. Discussion

Our results, based on a large sample with a follow-up of almost 2 million person-years, clearly show that postmenopausal women have significant, female-specific risks for cardiovascular morbidity and mortality. Independent predictors of a major cardiovascular event included not having taken birth control pills, not having children, and having early menarche (Fig. 2).

The incidence of classic, or type 1, myocardial infarction is up to three times higher in men than in women; however, there is less difference between sexes in older age groups, revealing the critical role that menopause plays in cardiovascular risk. On the other hand, in other coronary diseases, such as type 2 infarcts, coronary dissections, ischemia with no obstructive coronary artery disease, and myocardial infarction with no obstructive coronary arteries, the figures indicate a clearly higher incidence in women compared to men [18,19]. Moreover, mortality in young women with acute coronary syndrome is higher than in men of the same age [20]. This study addresses two of the most relevant research topics today: identification and primary prevention of cardiovascular disease in people with the highest risk, and the study of female-specific risk factors. Scientific societies such as the European Society of Cardiology have made explicit calls for research to reduce the gap in the prevention, diagnosis, and treatment of cardiovascular disease in women [21].

Consensus papers have promoted coordinated efforts to improve cardiovascular health in postmenopausal women [22]. Optimal cardiovascular care in this population requires better representation of women in clinical trials, generation and dissemination of knowledge on the specific signs and symptoms of cardiovascular diseases in women, and reductions in the great disparity in the morbidity and mortality of women between different European countries [23].

Menopause is a key process in a woman's life, setting off important physical, psychological, and social changes. The average age of its onset is 50 years, albeit with considerable variability between women [24]. Biological aspects driving the increased incidence of cardiovascular disease include the loss of regulation of vascular reactivity, endothelial function, and cardiac remodeling. At the pathophysiological level, the lesions found in women with cardiovascular disease are not the same as those in men: women have a lower burden of atheromatosis, fewer vascular calcifications, a more diffuse pattern of atherosclerosis, more frequent erosive plaques, more vasomotor alterations such as coronary vasospasm, and more microvascular involvement [25,26]. The reduction in estrogen levels after menopause has been associated with alterations in endothelial function, inflammation, activation of the renin-angiotensin-aldosterone and sympathetic systems, and reduced vasodilatation dependent on nitric oxide [27,28].

Data from both the literature and the present study clearly indicate that estrogens protect women against cardiovascular disease. But our results also illustrate the complexity of this relationship: we found a higher risk both in women who started menopause at younger ages and in women with early menarche. Therefore, we cannot infer that having more total years of life with a menstrual cycle lowers cardiovascular risk, but rather that the later the menstrual cycles start and end, the lower the risk will be. These results are supported by other studies that have shown increased mortality from cardiovascular disease associated with early menopause [29]. Early menarche has also been associated with increased levels of glucose, triglycerides, nonalcoholic steatosis, and metabolic syndrome [30,31].

The exogenous administration of estrogens also shows paradoxical behavior: taking oral contraceptives reduces cardiovascular risk, but hormone replacement therapy in menopause has a neutral effect. In a simplistic analysis, one would expect that giving estrogens to women who stop producing them endogenously would be beneficial, and that no benefits would arise on giving them to women with normal menstrual cycles, but the pathophysiology of cardiovascular disease, especially in women, seems anything but simple. In a detailed analysis of the existing scientific evidence, the European Society of Cardiology suggests that hormone replacement therapy could reduce cardiovascular risk when administered early in menopause, but this benefit is lost if treatment is started 10 years later than onset [32]. This conclusion would support the results of our study, that is, the benefit of oral contraceptive treatment is related to the administration of estrogens in younger women, and the

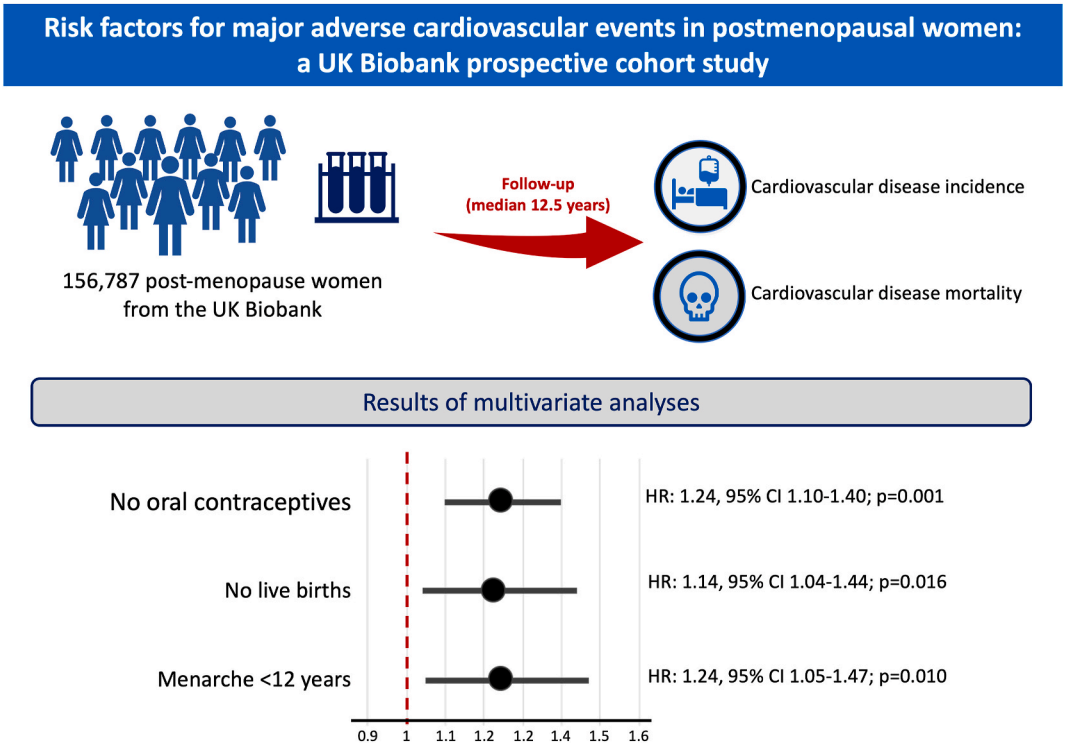

Fig. 2. Graphical abstract.

harm of hormone replacement treatment is associated with its administration in later phases [29,33].

Many published studies have analyzed factors related to the appearance of cardiovascular disease, and some have specifically focused on those that are more relevant in women than in men. But most have used the same cardiovascular risk factors already known in men, without contemplating female-specific predictors [34,35] like reproductive history. A large observational study showed that younger age at first live birth, number of stillbirths or spontaneous abortions, and lack of breastfeeding were associated with cardiovascular disease [36]. The reasons that live births are associated with lower risk could reside in the increased risk of miscarriage in women with classical risk factors such as obesity, high blood pressure and diabetes, in the protection conferred by breastfeeding, or in a higher level of social and familial support received by large families as Jacobs et al. [37] hypothesized previously. Conversely, a previous meta-analysis of cohort studies [38] reported that a higher number of parity was associated with increased CVD risk suggesting that cardiometabolic changes during pregnancy might permanently impact the cardiovascular system. Thus, more evidence is needed to elucidate this relationship. Regarding early menopause, its positive relationship with the development of cardiovascular disease has been repeatedly and consistently shown [39].

In addition to the risk factors related to women, we find other data that merit discussion: important aspects like diet, physical activity, sleep quality, and depression are closely related to the appearance of cardiovascular disease. These factors frequently occur together, their impacts mutually amplify each other, and they are closely related to menopause [40]. Menopause has been related to hyperphagia and obesity [41], which in turn is closely related to reduced physical activity and depression [42]. Thus, strategies as simple, accessible, and affordable as physical exercise can produce beneficial effects across different risk factors and also reduce cardiovascular risk specifically in postmenopausal women [43,44]. In our study we found a positive relationship between cardiovascular risk and hours watching television, and a tendency toward a negative relationship with energy expenditure.

Among the limitations of this study, we found that due to the voluntary sampling used to recruit study participants, the cohort might not adequately represent the general UK population. In addition, the entire population included in this study resided in the UK, so extrapolation of the results to populations in other countries warrants caution. Strengths include the prospective design, large sample size, and numerous variables, many of them objectively measured by qualified research personnel.

Cardiovascular disease presents differential characteristics in women compared to men, and these deserve recognition and attention in cardiovascular risk assessment. Aspects such as early menarche, taking oral contraceptives, and reproductive history are closely tied to the development of cardiovascular disease, and this relationship is independent of classic cardiovascular risk factors.

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CRediT authorship contribution statement

Vicente Bertomeu-Gonzalez: Conceptualization, Methodology, Writing – original draft. **Alberto Cordero:** Conceptualization, Methodology, Writing – review & editing. **Juan Miguel Ruiz-Nodar:** Conceptualization, Methodology, Writing – review & editing. **Francisco Sánchez-Ferrer:** Conceptualization, Methodology, Writing – review & editing. **Adriana López-Pineda:** Conceptualization, Methodology, Writing – review & editing. **José Antonio Quesada:** Formal analysis, Conceptualization, Data curation, Funding acquisition, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] World Health Organization, Cardiovascular Diseases (CVDs), 2020. https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases (1 June 2023).
[2] A. Timmis, Acute coronary syndromes, BMJ 351 (2015) h5153.
[3] R.W. Yeh, S. Sidney, M. Chandra, et al., Population trends in the incidence and outcomes of acute myocardial infarction, N. Engl. J. Med. 362 (23) (2010) 2155–2165.
[4] G. Graham, Acute coronary syndromes in women: recent treatment trends and outcomes. Clinical medicine insights, Cardiology (2016) 101–110.
[5] M. Schmidt, J.B. Jacobsen, T.L. Lash, et al., 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study, BMJ (2012) 344e356.
[6] S. Chakrabarti, J.S. Morton, S.T. Davidge, Mechanisms of estrogen effects on the endothelium: an overview, Can. J. Cardiol. 30 (7) (2014) 705–712.
[7] S.M. Grundy, Guidelines for cholesterol management: recommendations of the national cholesterol education Program's adult treatment panel II, Heart Dis. Stroke 3 (1994) 123–127.
[8] S. Salerni, S.Q. Francescomarino, C. Cadeddu, et al., The different role of sex hormones on female cardiovascular physiology and function: not only estrogens, Eur. J. Clin. Invest. 45 (2015) 634–645.
[9] E. Arteaga Urzúa, Menopause and cardiovascular risk, Rev. Med. Chile 144 (11) (2016) 1375–1376.
[10] J.E. Kim, J.H. Chang, M.J. Jeong, et al., A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases, Sci. Rep. 10 (1) (2020 Nov 26), 20631.
[11] S. Maffei, L. Guiducci, L. Cugusi, et al., Working Group on "Gender difference in cardiovascular disease" of the Italian Society of Cardiology. Women-specific predictors of cardiovascular disease risk - new paradigms, Int. J. Cardiol. 286 (2019 Jul 1) 190–197.
[12] The Lancet, Cardiology's problem women, Lancet 393 (10175) (2019 Mar 9) 959.
[13] F. Mauvais-Jarvis, N. Bairey Merz, P.J. Barnes, R.D. Brinton, J.J. Carrero, D. L. DeMeo, G.J. De Vries, C.N. Epperson, R. Govindan, S.L. Klein, A. Lonardo, P. M. Maki, L.D. McCullough, V. Regitz-Zagrosek, J.G. Regensteiner, J.B. Rubin, K. Sandberg, A. Suzuki, Sex and gender: modifiers of health, disease, and medicine, Lancet 396 (10250) (2020 Aug 22) 565–582.
[14] C.M. Norris, C.Y.Y. Yip, K.A. Nerenberg, et al., State of the science in women's cardiovascular disease: a Canadian perspective on the influence of sex and gender, J. Am. Heart Assoc. 9 (4) (2020 Feb 18), e015634.
[15] Uk Biobank, Protocol for a Large-Scale Prospective Epidemiological Resource, 2006. http://www.ukbiobank.ac.uk/resources (1 June 2023).
[16] J.P. Fine, R.J. Gray, A proportional hazards model for the subdistribution of a competing risk, J. Am. Stat. Assoc. 94 (1999) 496–509.
[17] F.E. Harrell, R.M. Califf, D.B. Pryor, K.L. Lee, R.A. Rosati, Evaluating the yield of medical tests, JAMA 247 (18) (1982) 2543–2546.
[18] A. Gabet, N. Danchin, Y. Juilliere, V. Olie, Acute coronary syndrome in women: rising hospitalizations in middle-aged French women, Eur. Heart J. 38 (2017) 1060–1065.
[19] V. Vaccarino, S. Sullivan, M. Hammadah, K. Wilmot, I. AlMheid, R. Ramadan, L. Elon, P.M. Pimple, E.V. Garcia, J. Nye, A.J. Shah, A. Alkhoder, O. Levantsevych, H. Gay, M. Obideen, M. Huang, T.T. Lewis, J.D. Bremner, A.A. Quyyumi, P. Raggi, Mental stress-induced-myocardial ischemia in young patients with recent myocardial infarction: sex differences and mechanisms, Circulation 137 (2018) 794–805.

[20] Ersilia M, DeFilippis. Women who experience a myocardial infarction at a young age have worse outcomes compared with men: the partners YOUNG-MI registry. Eur. Heart J..
[21] M. Stramba Badiale, Women and research on cardiovascular diseases in Europe: a report from the European heart health strategy (EuroHeart) project, Eur. Heart J. 31 (14) (2010) 1677–1681.
[22] Angela H.E. M. Maas, Giuseppe Rosano, Renata Cifkova, Alaide Chieffo, Dorenda van Dijken, Haitham Hamoda, Vijay Kunadian, Ellen Laan, Irene Lambrinoudaki, Kate Maclaran, et al., Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists, Eur. Heart J. 42 (10) (2021) 967–984.
[23] GBD 2016 Causes of Death Collaborators. Global, regional, and national ages exspecific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet 390 (2017) 1151–1210.
[24] InterLACE Study Team, Variations in reproductive events across life: a pooled analysis of data from 505 147 women across 10 countries, Hum. Reprod. 34 (5) (2019) 881–893.
[25] L.J. Shaw, J.K. Min, K. Nasir, J.X. Xie, D.S. Berman, M.D. Miedema, S.P. Whelton, Z.A. Dardari, A. Rozanski, J. Rumberger, C.N. Bairey Merz, M.H. Al-Mallah, M. J. Budoff, M.J. Blaha, Sex differences in calcified plaque and long-term cardiovascular mortality: observations from the CAC Consortium, Eur. Heart J. 39 (2018) 3727–3735.
[26] T. Padro, O. Manfrini, R. Bugiardini, J. Canty, E. Cenko, G. De Luca, D.J. Duncker, E.C. Eringa, A. Koller, D. Tousoulis, D. Trifunovic, M. Vavlukis, C. de Wit, L. Badimon, ESC Working Group on Coronary Pathophysiology and Microcirculation position paper on 'coronary microvascular dysfunction in cardiovascular disease', Cardiovasc. Res. 116 (2020) 741–755.
[27] P. Collins, A. Maas, M. Prasad, L. Schierbeck, A. Lerman, Endothelial vascular function as a surrogate of vascular risk and aging in women, Mayo Clin. Proc. 95 (2020) 541–553.
[28] K.L. Moreau, K.L. Hildreth, A.L. Meditz, K.D. Deane, W.M. Kohrt, Endothelial function is impaired across the stages of the menopause transition in healthy women, J. Clin. Endocrinol. Metab. 97 (2012) 4692–4700.
[29] D. Zhu, H.F. Chung, A.J. Dobson, N. Pandeya, G.G. Giles, F. Bruinsma, E. J. Brunner, D. Kuh, R. Hardy, N.E. Avis, E.B. Gold, C.A. Derby, K.A. Matthews, J. E. Cade, D.C. Greenwood, P. Demakakos, D.E. Brown, L.L. Sievert, D. Anderson, K. Hayashi, J.S. Lee, H. Mizunuma, T. Tillin, M.K. Simonsen, H.O. Adami, E. Weiderpass, G.D. Mishra, Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data, Lancet Public Health 4 (2019) e553–e64.
[30] C. Kim, J. Catov, P.J. Schreiner, D. Appiah, M.F. Wellons, D. Siscovick, R. Calderon-Margalit, H. Huddleston, I.A. Ebong, C.E. Lewis, Women's reproductive milestones and cardiovascular disease risk: a review of reports and opportunities from the CARDIA study, J. Am. Heart Assoc. 12 (5) (2023 Mar 7), e028132.
[31] H.W. Chan, S. Dharmage, A. Dobson, H.F. Chung, D. Loxton, J. Doust, G. Montgomery, E. Stamatakis, R.R. Huxley, M. Hamer, J. Abbott, B.B. Yeap, J. A. Visser, H. McIntyre, G.I. Mielke, G.D. Mishra, Cohort profile: a prospective Australian cohort study of women's reproductive characteristics and risk of chronic disease from menarche to premenopause (M-PreM), BMJ Open 12 (10) (2022 Oct 28), e064333.
[32] A.H.E.M. Maas, G. Rosano, R. Cifkova, A. Chieffo, D. van Dijken, H. Hamoda, V. Kunadian, E. Laan, I. Lambrinoudaki, K. Maclaran, N. Panay, J.C. Stevenson, M. van Trotsenburg, P. Collins, Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists, Eur. Heart J. 42 (10) (2021) 967–984.
[33] T. Muka, C. Oliver-Williams, S. Kunutsor, J.S. Laven, B.C. Fauser, R. Chowdhury, M. Kavousi, O.H. Franco, Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis, JAMA Cardiol. 1 (7) (2016) 767–776.
[34] R.B. D'agostino, M.W. Russell, D.M. Huse, R.C. Ellison, H. Silbershatz, P.W. F. Wilson, et al., Primary and subsequent coronary risk appraisal: new results from the Framingham Study, Am. Heart J. 139 (2000) 272–281.
[35] L.G. Goh, S.S. Dhaliwal, H. Leea, D. Bertolatti, P.R. Della, Utility of established cardiovascular disease risk score models for the 10-year prediction of disease outcomes in women, Expert Rev. Cardiovasc Ther. 11 (2013) 425–435.
[36] N.I. Parikh, R.P. Jeppson, J.S. Berger, C.B. Eaton, C.H. Kroenke, E.S. Leblanc, et al., Reproductive risk factors and coronary heart disease in the women's health initiative observational study, Circulation 133 (2016) 2149–2158.
[37] M.B. Jacobs, D. Kritz-Silverstein, D.L. Wingard, E. Barrett-Connor, The association of reproductive history with all-cause and cardiovascular mortality in older women: the Rancho Bernardo Study, Fertil. Steril. 97 (1) (2012 Jan) 118–124.
[38] W. Li, W. Ruan, Z. Lu, D. Wang, Parity and risk of maternal cardiovascular disease: a dose-response meta-analysis of cohort studies, Eur. J. Prev. Cardiol. 26 (6) (2019 Apr) 592–602.
[39] M.G. Van Der Meer, Y. Van Der Graaf, E. Schuit, L.M. Peelen, W.M.M. Verschuren, Boer Jma, et al., Added value of female-specific factors beyond traditional predictors for future cardiovascular disease, J. Am. Coll. Cardiol. 67 (2016) 2084–2086.
[40] M.M.I. Abdalla, M. Azzani, W. Atroosh, D. Anbazhagan, V. Kumarasamy, The association between mental health and obesity in postmenopausal women: a systematic review, Endocr. Regul. 56 (4) (2022) 295–310.
[41] L.M. Brown, D.J. Clegg, Central effects of estradiol in the regulation of food intake, body weight, and adiposity, J. Steroid Biochem. Mol. Biol. 122 (2010) 65–73.
[42] J.T. Bromberger, K.A. Matthews, L.L. Schott, S. Brockwell, N.E. Avis, zHM. Kravit, S.A. Everson-Rose, E.B. Gold, M. Sowers, J.F. Randolph Jr., Depressive symptoms during the menopausal transition: the study of women's health across the nation (SWAN), J. Affect. Disord. 103 (2007) 267–272.
[43] J.A. Quesada, V. Bertomeu-González, J.M. Ruiz-Nodar, A. López-Pineda, F. Sánchez-Ferrer, Lifestyle and cardiovascular mortality in menopausal women: a population-based cohort study, Rev. Esp. Cardiol. 75 (7) (2022 Jul) 576–584.
[44] fJ. Eigendor, A. Melk, S. Haufe, D. Boethig, D. Berliner, A. Kerling, M. Kueck, H. Stenner, C. Bara, M. Stiesch, C. Schippert, A. Hilfiker, C. Falk, J. Bauersachs, T. Thum, R. Lichtinghagen, A. Haverich, D. Hilfiker-Kleiner, U. Tegtbur, Effects of personalized endurance training on cellular age and vascular function in middle aged sedentary women, Eur. J. Prev. Cardiol. 26 (2019) 1903–1906.