

BRIEF REPORT

Female-Specific Cardiovascular Risk Factors in Severe Hypercholesterolemia



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Severe hypercholesterolemia, defined as low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL, affects over $\sim 3\%$ of the U.S. population.¹ Compared to those without severe hypercholesterolemia, individuals with severe hypercholesterolemia have a 6-fold risk of coronary artery disease, with further risk elevation if monogenic familial hypercholesterolemia (FH) mutations drive hypercholesterolemia.¹

Although current recommendations for preventive management in those with severe hypercholesterolemia are uniform, additional factors that further stratify risk within this population are emerging.² Male sex is a well-described atherosclerotic cardiovascular disease (ASCVD) risk factor.² Assessing the

impact of female-specific risk factors in this population is critical, as women receive less aggressive cholesterol treatment than men, and female-specific risk factors are routinely not considered among clinicians.^{1,3} As such, the International Atherosclerosis Society identified the uncertain relevance of female-specific risk factors in FH as a critical knowledge gap.² We and others have demonstrated that adverse pregnancy outcomes (APOs) and premature menopause (PM) are associated with incident coronary artery disease in the general population.^{1,3,4} Here, we extend this previous work by assessing if APOs and PM associate with incident ASCVD among women with severe hypercholesterolemia, including but not limited to women with monogenic FH.

METHODS

The UK Biobank is an observational, prospective cohort of $>500,000$ adults in the United Kingdom aged 40 to 69 years at study enrollment between the years 2006 and 2010. The UK Biobank was approved by the North West Multi-Center Research Ethics Committee. Analyses were conducted under the UK Biobank application 7089. We identified postmenopausal women who were ≥ 50 years at study entry without established ASCVD.⁴ Self-reported

What is the clinical question being addressed?

Are sex-specific risk factors predictive of atherosclerotic cardiovascular disease in patients with severe hypercholesterolemia?

What is the main finding?

Premature menopause and adverse pregnancy outcomes are independently and additively associated with incident atherosclerotic cardiovascular disease among women with severe hypercholesterolemia.

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ABBREVIATIONS
AND ACRONYMS

- aHR = adjusted HR
APO = adverse pregnancy outcome
ASCVD = atherosclerotic cardiovascular disease
BMI = body mass index
FH = familial hypercholesterolemia
LDL-C = low-density lipoprotein cholesterol
PM = premature menopause

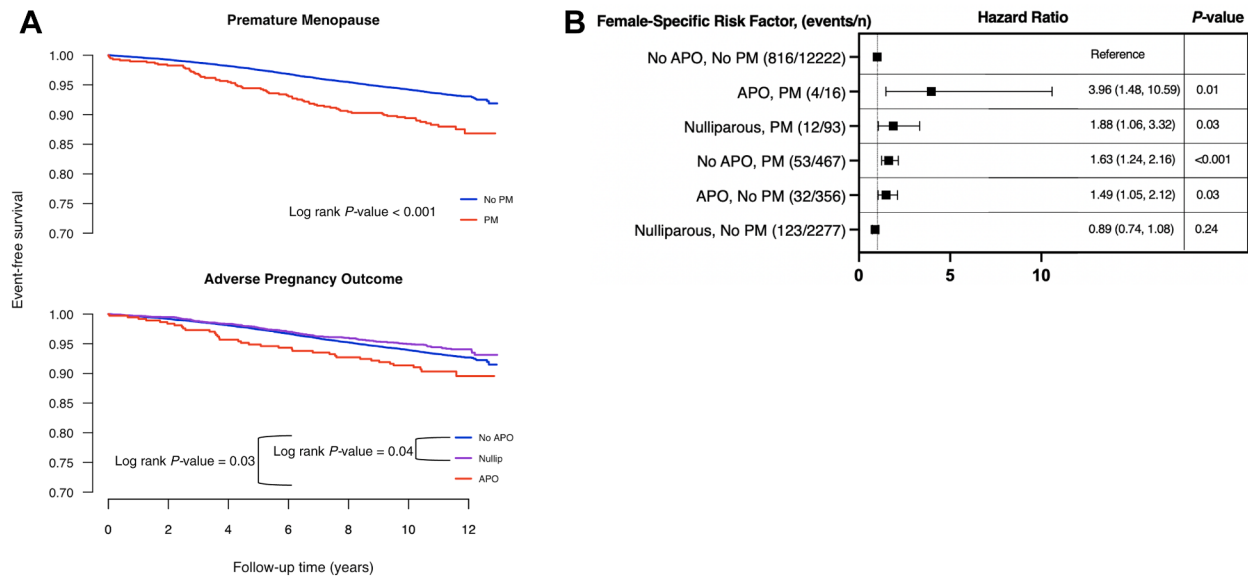
gender was used as a proxy for female sex. Using both linked primary care data and UK Biobank enrollment laboratory testing, we isolated women who had an LDL-C ≥ 190 mg/dL at or before UK Biobank study entry. We included women with severe hypercholesterolemia with or without monogenic FH to ensure adequate power. Female-specific risk factors (exposures) were (1) PM (<40 years at age of menopause) vs no PM and (2) APOs, which included hypertensive disorders of pregnancy and low birth weight of first child (<5 pounds), vs nulliparous vs parous without APOs. The primary outcome was incident ASCVD, defined as a composite of coronary artery disease, ischemic stroke, and peripheral artery disease using International Classification of Diseases or procedural codes. We used Cox regression to test the association of PM and APOs with incident ASCVD, adjusting for age, systolic blood pressure, diabetes, smoking, body mass index (BMI), use of lipid-lowering and antihypertensive medications, physical activity, and diet. The proportional hazards assumption was verified using Schoenfeld residuals. Diet and physical activity were quantified in accordance with the American Heart Association Life's Essential 8 framework, with a dietary score assigned

based on adherence to a Dietary Approaches to Stop Hypertension-style diet and a physical activity score assigned based on minutes of moderate-to-vigorous physical activity weekly.⁵ Missing data existed for systolic blood pressure, BMI, physical activity, and diet scores (N = 222-882). We addressed missingness using single imputation based on linear regression and confirmed the robustness of our imputation through sensitivity analyses. PM and APOs were included in the same mutually adjusted model. Using Cox regression analyses, we conducted an exploratory 6-way model to test the associations of various combinations of APOs, PM, and parity status with incident ASCVD. Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Among 15,431 women meeting inclusion criteria, 576 (3.7%) had a history of PM, 372 (2.4%) had APOs, 16 (0.1%) had both PM and APOs, and 2,370 (15.4%) were nulliparous. Mean (SD) age at enrollment was 61.5 (4.7) years. Women with PM and/or APOs had higher BMI (28.2 [4.8] vs 27.6 [4.4] kg/m², $P < 0.001$) and greater prevalence of diabetes (30 [3.2%] vs 226 [1.6%], $P < 0.001$), self-reported smoking history (445 [47.7%] vs 6,124 [42.2%], $P = 0.001$), lipid-lowering

FIGURE 1 Female-Specific Risk Factors and Incident Atherosclerotic Cardiovascular Disease



(A) Unadjusted Kaplan-Meier survival curves free from ASCVD among women with severe hypercholesterolemia, stratified by premature menopause and adverse pregnancy outcome. (B) Forest plot illustrating associations between various female-specific risk factors and incident ASCVD. APO = adverse pregnancy outcome; ASCVD = atherosclerotic cardiovascular disease; PM = premature menopause.

(173 [18.6%] vs 2,325 [16.0%], $P = 0.05$), and antihypertensive medication use (156 [16.7%] vs 1,793 [12.4%], $P < 0.001$). For women with vs without PM and/or APOs, no significant difference was observed in baseline LDL-C (210.8 mg/dL [19.3] vs 210.4 mg/dL [18.6], $P = 0.47$).

Over a median (IQR) of 11.1 (10.4–11.8) years of follow-up, 1,040 (6.8%) women developed incident ASCVD (860 [5.6%] coronary artery disease, 124 [0.8%] peripheral artery disease, and 105 [0.7%] ischemic stroke). Cumulative incidence of ASCVD was 69 (12.0%) in women with PM, 36 (9.7%) in women with APOs, and 816 (6.7%) in parous women without APOs or PM.

In unadjusted models, the HR for incident ASCVD was 1.89 (95% CI: 1.48–2.42, $P < 0.001$) for women with vs without PM, 1.46 (95% CI: 1.05–2.04, $P = 0.03$) for women with APOs vs parous women without APOs, and 0.83 (95% CI: 0.69–0.99, $P = 0.04$) for nulliparous women vs parous women without APOs.

In fully adjusted models, the adjusted HR (aHR) for incident ASCVD was 1.73 (95% CI: 1.36–2.22, $P < 0.001$) for women with vs without PM and 1.55 (95% CI: 1.11–2.17, $P = 0.01$) for women with APOs vs parous women without APOs (Figure 1A). Complete-case analysis restricted to individuals without imputed data yielded highly consistent results (data not shown). Hazards associated with PM and APOs appeared additive with no evidence of interaction ($P_{\text{interaction}} = 0.39$). Compared with parous women without APOs or PM, women with both APOs and PM had the highest aHR for incident ASCVD (aHR: 3.96; 95% CI: 1.48–10.59; $P = 0.006$), but all groups with APOs or PM demonstrated increased risk (Figure 1B).

CONCLUSIONS

In a large cohort of women with severe hypercholesterolemia, PM and APOs each additively enhanced ASCVD risk. We previously observed that hyperlipidemia does not mediate a significant proportion of the association between hypertensive disorders of pregnancy and cardiovascular events.⁴ Our results suggest that female-specific risk factors exert atherogenic effects independent of dyslipidemia, including among those with severe hypercholesterolemia.

Despite a Class I guideline recommendation to prescribe lipid-lowering therapy for patients with LDL ≥ 190 mg/dL, patients are widely undertreated. More than 80% of individuals treated for FH do not achieve target LDL-C reduction,² and women with

severe hypercholesterolemia are less likely to be treated with high-intensity statins compared to men.¹ Similarly, only 16.2% of our study population had ever received treatment with a lipid-lowering agent before UK Biobank entry. Clinicians also remain largely unaware of the significant risks that APOs and PM pose to women's future cardiovascular health.³ Women with APOs and/or PM are at uniquely high risk for ASCVD and would benefit from tailored screening, surveillance, and prevention strategies. APOs and PM occur early in life and can serve as an opportunity to assess risk and initiate long-term preventive measures. Although previous work suggests that female-specific risk factors do not materially improve 10-year risk prediction, understanding whether reproductive history improves prediction over longer (eg, 30-year) time horizons and in younger women remains an important area of future investigation.³

Although our study included a large cohort of women with severe hypercholesterolemia, it has limitations. APO phenotyping in the UK Biobank is limited, and preterm birth and gestational diabetes were not captured comprehensively. Use of International Classification of Diseases codes may lead to misclassification, and the prevalence of APOs in the UK Biobank is lower than population estimates, likely reflecting a healthy volunteer bias. Gestational age of first delivery was not available, and we used self-reported birth weight of the first child as a proxy for small-for-gestational-age status.

Overall, our research underscores the need for aggressive, tailored primary prevention for women with severe hypercholesterolemia and APOs and/or PM.

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