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Premature Menopause and Risk for Cardiovascular Disease-Reply.

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In Reply Dr Scarabin highlights our finding that menopausal hormone therapy use at study enrollment was not associated with incident VTE.[1] At enrollment, women in the UK Biobank reported whether they had ever used menopausal hormone therapy, the age at which they started and (if applicable) stopped using therapy, and whether they were currently using hormones. In our postmenopausal cohort, it is unlikely that women who were never users of menopausal hormone therapy at enrollment subsequently started using it after the study began—particularly in the era following publication of the Women's Health Initiative results.[2] Women with any prevalent cardiovascular disease diagnoses at baseline, including VTE, were excluded from the analysis, and a secondary analysis evaluated development of a first VTE event.

Lack of new menopausal hormone use after enrollment and exclusion of women with prevalent VTE may explain the lack of association between hormone use and VTE because women who experienced prevalent hormone-related VTE would have been excluded. Incident VTE was defined according to the appearance of a qualifying *International Classification of Diseases* code in the patient's medical record, which we recently validated with human genetic analyses.[3] Of note, the magnitude of association we observed for premature menopause with incident VTE was the same as that observed for non-procedure-associated VTE in an analysis from the Women's Health Initiative, which also adjusted for menopausal hormone therapy use.[4] Nearly identical associations were observed in models that did and did not incorporate ever use of menopausal hormone therapy (eTable 12 in the Supplement).[1] We agree that our findings strengthen evidence that premature menopause represents a risk factor for VTE.

DrsZhou and Tang note that cancer and nontraditional cardiovascular risk factors may be correlated with both premature menopause and cardiovascular disease risk, and we refer to the sensitivity analyses in the article to address these issues. In eTable 5 in the Supplement,[1] we provided analyses in which women with prevalent cancer were excluded, and effect estimates remained similar for the primary analyses. In addition, eTable 7 in the

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Supplement[1] provided models with and without inclusion of women who underwent hysterectomy; our primary findings were again robust in these analyses.

Furthermore, at Zhou and Tang's request, we now provide results of the analyses incorporating chronic kidney disease, alcohol intake, prevalent cancer, and hysterectomy, in addition to covariates previously used in the primary analysis (Table). The results again are similar to the adjusted models presented in the article. In Figure 3C in the article, the y-axis is cumulative incidence and shows that the cumulative incidence of type 2 diabetes over the follow-up period was numerically greatest among women with premature surgical menopause. This association was confirmed in models in eTables 15 and 16 in the Supplement.[1]

Significant differences in diabetes risk were present among the older age strata but not the younger age strata, which may reflect lower absolute diabetes risk and risk differences at younger ages; future research is necessary to understand these differences. Findings were robust to multivariable adjustment and numerous sensitivity analyses, underscoring their internal validity. We replicated established associations previously reported in smaller limited data sets, indicating external validity. Similarly, large data sets are needed for replication of novel disease associations.

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Table.

Hazard Ratios for Incident Cardiovascular Disease Diagnoses in Expanded Multivariable Models[a]

	Surgical premature menopause		Natural premature menopause	
Diagnosis	**Hazard ratio (95% CI)**	***P* value[b]**	**Hazard ratio (95% CI)**	***P* value[b]**
First cardiovascular disease diagnosis[c]	1.74(1.25–2.42)	<.001	1.30(1.13–1.51)	<.001
Coronary artery disease	2.34(1.35–4.06)	.002	1.34(1.01–1.78)	.04
Heart failure	2.65(1.22–5.79)	.01	1.24(0.81–1.89)	.32
Aortic stenosis	4.20(1.26–13.95)	.02	2.72(1.61–4.60)	<.001
Mitral regurgitation	4.10(1.60–10.53)	.003	0.72(0.33–1.56)	.40
Atrial fibrillation	1.52(0.85–2.72)	.15	1.22(0.96–1.55)	.11
Ischemic stroke	0.50(0.07–3.61)	.49	1.62(1.07–2.47)	.02
Peripheral artery disease	1.26(0.30–5.26)	.75	1.30(0.75–2.25)	.35
Venous thromboembolism	2.28(1.19–4.36)	.01	1.56(1.14–2.13)	.005

[a]Models are adjusted for age, race/ethnicity, prevalent type 2 diabetes, ever having smoked, systolic blood pressure, use of antihypertensive medication, non-high-density lipoprotein cholesterol, use of cholesterol-lowering medication, body mass index, C-reactive protein, history of menopausal hormone therapy use, chronic kidney disease, frequency of alcohol intake, history of cancer, and history of hysterectomy.

[b]Derived from Cox proportional hazards models.

[c]Composed of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism.