Concept and design: Wadhera, Figueroa, Joynt Maddox.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Wadhera, Figueroa.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Wadhera.
Administrative, technical, or material support: Wadhera.
Supervision: Figueroa, Yeh.

Conflict of Interest Disclosures: Dr Wadhera reported receiving research support from the National Heart, Lung, and Blood Institute (grant K23HL148525-1) and previously serving as a consultant for Regeneron. Dr Figueroa reported receiving research support from the National Center for Advancing Translational Sciences (grant KL2 TR002542) and the Commonwealth Fund. Dr Joynt Maddox reported receiving research support from the National Heart, Lung, and Blood Institute (grant R01HL143421) and the National Institute on Aging (grant R01AG060935); grant support from the Commonwealth Fund; and prior contract work for the Office of the Assistant Secretary for Planning and Evaluation. Dr Rosenbaum reported being a national correspondent for the *New England Journal of Medicine*. Dr Yeh reported receiving research support from the National Heart, Lung, and Blood Institute (grant R01HL136708) and the Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology; receiving personal fees from Biosense Webster; and receiving grants and personal fees from Abbott Vascular, AstraZeneca, Boston Scientific, and Medtronic. No other disclosures were reported.

Funding/Support: This work was supported by the Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

1. Blumenthal D, McGinnis JM. Measuring *Vital Signs*: an IOM report on core metrics for health and health care progress. *JAMA*. 2015;313(19):1901-1902. doi:10.1001/jama.2015.4862

2. MacLean CH, Kerr EA, Qaseem A. Time out: charting a path for improving performance measurement. *N Engl J Med*. 2018;378(19):1757-1761. doi:10.1056/NEJMp1802595

3. Casalino LP, Gans D, Weber R, et al. US physician practices spend more than $15.4 billion annually to report quality measures. *Health Aff (Millwood)*. 2016;35(3):401-406. doi:10.1377/hlthaff.2015.1258

4. US Government Accountability Office. Health care quality: CMS could more effectively ensure its quality measurement activities promote its objectives. Accessed December 20, 2019. https://www.gao.gov/assets/710/701512.pdf

5. Wadhera RK, Joynt Maddox KE, Wasfy JH, Haneuse S, Shen C, Yeh RW. Association of the hospital readmissions reduction program with mortality among Medicare beneficiaries hospitalized for heart failure, acute myocardial infarction, and pneumonia. *JAMA*. 2018;320(24):2542-2552. doi:10.1001/jama.2018.19232

6. Joynt Maddox KE. Financial incentives and vulnerable populations: will alternative payment models help or hurt? *N Engl J Med*. 2018;378(11):977-979. doi:10.1056/NEJMp1715455

COMMENT & RESPONSE

Premature Menopause and Risk for Cardiovascular Disease

To the Editor Venous thromboembolism (VTE) is a global health concern because of its significant morbidity and mortality. To our knowledge, few studies have investigated the associations of reproductive life characteristics with VTE risk in women.[1] Analysis of UK Biobank data by Dr Honigberg and colleagues[2] highlights the role of premature natural or surgical menopause in increasing both atherosclerotic and nonatherosclerotic cardiovascular risk, including VTE risk.

The analysis failed to show the well-established increased VTE risk in relation to menopausal hormone therapy (eTable 13 in Supplement 2 in the article[2]). Menopausal hormone use was ascertained only at the baseline study visit and was not updated during follow-up. Because previous studies have found that the increase in VTE risk is restricted to current users at the time of a clinical event,[3] incomplete capture of exposed cases may have occurred in this study, resulting in underestimating VTE risk. Also, it is unclear whether only the first VTE event was considered as a clinical outcome. Inclusion of recurrent VTE could have also introduced a bias in estimating VTE risk. Details of the definition and validation criteria of VTE events would be of great interest.

Premature menopause appears to be a new VTE risk factor, which could improve risk stratification and disease prevention among postmenopausal women. Women with premature menopause often consider menopausal hormone therapy. Such women should avoid oral estrogen. The most recent clinical guides recommend transdermal estrogen combined with progesterone for women who need menopausal hormone therapy and are at high VTE risk.[4]

Pierre Yves Scarabin, MD, MSc

Author Affiliation: INSERM U1018, Villejuif, France.

Corresponding Author: Pierre Yves Scarabin, MD, MSc, INSERM U1018, 16 Paul Vaillant-Couturier Ave, Villejuif 94807, France (pierre-yves.scarabin@inserm.fr).

Conflict of Interest Disclosures: None reported.

1. Canonico M, Plu-Bureau G, O'Sullivan MJ, et al. Age at menopause, reproductive history, and venous thromboembolism risk among postmenopausal women: the Women's Health Initiative Hormone Therapy clinical trials. *Menopause*. 2014;21(3):214-220. doi:10.1097/GME.0b013e31829752e0

2. Honigberg MC, Zekavat SM, Aragam K, et al. Association of premature natural and surgical menopause with incident cardiovascular disease. *JAMA*. 2019;322(24):2411-2421. doi:10.1001/jama.2019.19191

3. Scarabin PY, Oger E, Plu-Bureau G; EStrogen and THromboEmbolism Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet*. 2003;362(9382):428-432. doi:10.1016/S0140-6736(03)14066-4

4. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(11):3975-4011. doi:10.1210/jc.2015-2236

To the Editor The cohort study by Dr Honigberg and colleagues[1] found that natural and surgical premature menopause were associated with increased risks of cardiovascular diseases among postmenopausal women. Some important issues were not addressed.

First, a limitation of this study is that cancer history was not incorporated into the adjusted models. Cancer is tightly linked with cardiovascular diseases.[2] In the fully adjusted models in Table 3 and eTable 5 of Supplement 2 in the article,[1] in the surgical premature menopause group, 5 cardiovascular outcomes had significant *P* values when patients with cancer were retained, while only 2 cardiovascular outcomes were significant when all patients with cancer were removed. Thus, the variable of cancer history should be included in the fully adjusted models.

Second, other factors, such as chronic kidney disease, hysterectomy, and alcohol consumption, are closely correlated with cardiovascular diseases.[3,4] Because these covariates were unbalanced in the 3 groups, we suggest the authors adjust for these covariates in their multivariable models.

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Canberra User on 05/02/2020

Third, Honigberg and colleagues[1] stated that the incidence of "type 2 diabetes was greatest among women with history of surgical premature menopause and lowest among women without premature menopause." However, we do not fully agree with this statement. In Figure 3C in the article, when the age of patients was younger than 50 years, the cumulative incidence curve for type 2 diabetes in the surgical premature menopause group was below the curves of the other 2 groups, meaning that the group with the lowest incidence of type 2 diabetes was the surgical premature menopause group rather than the group without premature menopause.

Fourth, Honigberg and colleagues[1] developed fully adjusted models for the risks of premature menopause associated with cardiovascular diseases, but the performance of the models and the internal and external validity of the models were not reported. Thus, the reliability and veracity of the models are unknown.[5]

Xianshi Zhou, MD
Guanghua Tang, PhD

Author Affiliations: Emergency Department, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China.

Corresponding Author: Xianshi Zhou, MD, Emergency Department, Guangdong Provincial Hospital of Chinese Medicine, 111 Dade Rd, Yuexiu District, Guangzhou, 510120 China (drxianshizhou@163.com).

Conflict of Interest Disclosures: Drs Zhou and Tang reported receiving grants from Guangdong Provincial Key Laboratory of Research on Emergency in TCM.

1. Honigberg MC, Zekavat SM, Aragam K, et al. Association of premature natural and surgical menopause with incident cardiovascular disease. *JAMA*. 2019;322 (24):2411-2421. doi:10.1001/jama.2019.19191

2. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016;133(11):1104-1114. doi:10.1161/CIRCULATIONAHA.115.020406

3. Di Angelantonio E, Chowdhury R, Sarwar N, Aspelund T, Danesh J, Gudnason V. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. *BMJ*. 2010; 341:c4986. doi:10.1136/bmj.c4986

4. Ingelsson E, Lundholm C, Johansson AL, Altman D. Hysterectomy and risk of cardiovascular disease: a population-based cohort study. *Eur Heart J*. 2011;32 (6):745-750. doi:10.1093/eurheartj/ehq477

5. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J*. 2014;35 (29):1925-1931. doi:10.1093/eurheartj/ehu207

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.

Drs Zhou 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 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.

Michael C. Honigberg, MD, MPP
Pradeep Natarajan, MD, MMSc

Author Affiliations: Cardiology Division, Massachusetts General Hospital, Boston.

Corresponding Author: Pradeep Natarajan, MD, MMSc, Massachusetts General Hospital, 185 Cambridge St, CPZN 3.184, Boston, MA 02114 (pnatarajan@mgh.harvard.edu).

Conflict of Interest Disclosures: Dr Honigberg reported receiving a grant from the National Heart, Lung, and Blood Institute. Dr Natarajan reported receiving grant support from Amgen, Apple, Boston Scientific, the National Heart, Lung,

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Canberra User on 05/02/2020

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.

and Blood Institute, and Fondation Leducq; receiving a Hassenfeld award from Massachusetts General Hospital; receiving consulting income from Apple; and receiving personal fees from Blackstone Life Sciences.

1. Honigberg MC, Zekavat SM, Aragam K, et al. Association of premature natural and surgical menopause with incident cardiovascular disease. *JAMA*. 2019;322(24):2411-2421. doi:10.1001/jama.2019.19191

2. Manson JE, Hsia J, Johnson KC, et al; Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med*. 2003;349(6):523-534. doi:10.1056/NEJMoa030808

3. Klarin D, Busenkell E, Judy R, et al; INVENT Consortium; Veterans Affairs' Million Veteran Program. Genome-wide association analysis of venous thromboembolism identifies new risk loci and genetic overlap with arterial vascular disease. *Nat Genet*. 2019;51(11):1574-1579. doi:10.1038/s41588-019-0519-3

4. Canonico M, Plu-Bureau G, O'Sullivan MJ, et al. Age at menopause, reproductive history, and venous thromboembolism risk among postmenopausal women: the Women's Health Initiative Hormone Therapy clinical trials. *Menopause*. 2014;21(3):214-220. doi:10.1097/GME.0b013e31829752e0

Health Outcomes With Vitamin D Supplementation

To the Editor In an Editorial, Drs Lucas and Wolf[1] stated that randomized clinical trials (RCTs) of vitamin D and health outcomes have failed to confirm observational study findings. However, that is not the case for several health outcomes. Secondary analyses of the Vitamin D and Omega-3 Trial (VITAL) revealed significant reductions in overall cancer incidence with supplementation with 2000 IU/d of vitamin D_3 in participants with a body mass index (BMI) of less than 25 and in black individuals and reduced overall cancer mortality when the first 1 or 2 years of data were omitted.[2] Secondary analyses of the Vitamin D and Type 2 Diabetes (D2d) trial showed significant reductions in progression from prediabetes to type 2 diabetes with 4000 IU/d of vitamin D_3 supplementation in participants with a BMI less than 30, in those not taking calcium supplements, in males, in those older than 60.9 years, and in non-Hispanic individuals.[3] Most such findings can be explained by vitamin D axis effects. For example, those with higher BMI have smaller increases in serum 25-hydroxyvitamin D (25[OH]D) concentration with supplementation than individuals with comparable supplementation and lower BMI.

The primary problem with many RCTs is their reliance on vitamin D dosage rather than on improvement in inadequate vitamin D status (from baseline to achieved serum 25[OH]D concentrations).[4] An example of the usefulness of basing RCTs on 25(OH)D concentrations comes from an article on vitamin D supplementation and breast cancer incidence. Data from 3 studies were pooled; 2 RCTs provided vitamin D and calcium to the treatment group and the third study was an observational follow-up cohort of volunteers taking variable vitamin D supplemental doses.[5] All 3 studies measured 25(OH)D concentrations 6 months to 2 years before follow-up ended. Four-year Kaplan-Meier plots for the pooled data showed increasing breast cancer–free rates with increasing achieved 25(OH)D concentrations from less than 20 ng/mL to greater than 60 ng/mL, with a risk reduction for breast cancer between the highest and lowest groups of 82%. Similarly, the risk reduction was 80% in the RCTs with achieved supplementation values of greater than 60 ng/mL vs less than 20 ng/mL (hazard ratio, 0.20 [95% CI, 0.05-0.82]; $P = .04$ for trend). Thus, the use of study designs that allow assessment of outcomes against the changes in vitamin D status achieved may improve the chances of being able to detect any genuine health benefits of correcting vitamin D deficiency.

William B. Grant, PhD
Barbara J. Boucher, MD

Author Affiliations: Sunlight, Nutrition, and Health Research Center, San Francisco, California (Grant); Blizard Institute, Barts and the London School of Medicine and Dentistry, London, England (Boucher).

Corresponding Author: William B. Grant, PhD, Sunlight, Nutrition, and Health Research Center, PO Box 641603, San Francisco, CA 94164 (wbgrant@infionline.net).

Conflict of Interest Disclosures: Dr Grant reported receiving funding from Bio-Tech Pharmacal Inc and supporting GrassrootsHealth.net. Dr Boucher reported receiving a donation from the Supreme Master Ching Hai International Association, Los Angeles Chapter, and travel expense reimbursement from conference organizers for presenting at vitamin D conferences in Germany.

1. Lucas A, Wolf M. Vitamin D and health outcomes: then came the randomized clinical trials. *JAMA*. 2019;322(19):1866-1868. doi:10.1001/jama.2019.17302

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Canberra User on 05/02/2020