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Reproductive History, Hormone Replacement, and Incidence of Venous Thromboembolism: The Longitudinal Investigation of Thromboembolism Etiology

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Summary

Numerous studies have established that hormone replacement therapy increases the risk of venous thromboembolism (VTE), but an association of endogenous estrogen exposure with the incidence of VTE is not fully established. Using a prospective design combining the Atherosclerosis Risk in Communities and the Cardiovascular Health Study cohort, we studied the 12-year risk of VTE in relation to hormone replacement therapy use, age at menopause, parity number, and type of menopause in 8,236 post-menopausal women. There were no significant associations of age at menopause, parity number, or type of menopause with incidence of VTE. Women currently using hormone replacement had a 1.6-times higher multivariate-adjusted rate ratio (RR) of VTE compared with those without hormone use in the time-dependent model (RR=1.60, 95% CI, 1.06-2.36; Population attributable fraction=6.7%, 95%CI, 1.0-10.3). When we excluded women with 1-year or more duration of hormone therapy at baseline, the associations was stronger (RR=2.02, 95%CI, 1.31-3.12). The multivariate-adjusted RRs of VTE for current users tended to be higher in those with idiopathic VTE (RR=2.40, 95%CI, 1.40-4.12) than those with secondary VTE (RR=1.08, 95%CI, 0.63-1.85). Hormone replacement therapy is associated with increased risk of VTE, but reproductive history markers of endogenous estrogen exposure were not associated with VTE.

Keywords

Epidemiology; Hormone therapy; Menopause; Risk factors; Venous thrombosis

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Introduction

Previous prospective studies and clinical trials have established that hormone replacement therapy (HRT) increases the risk of venous thromboembolism (VTE). For example, in the Nurses' Health Study cohort, use of oral contraceptives and postmenopausal hormone therapy were associated with increased risk of pulmonary embolism (Grodstein, *et al* 1996). Further, in clinical trials, such as the Heart and Estrogen/progestin Replacement Study (HERS) (Grady, *et al* 2000) and the Women's Health Initiative (WHI) (Cushman, *et al* 2004a), HRT increased the risk of VTE 2.1- to 2.7-fold.

A recent hospital-based case-control study indicated that reproductive markers of lifetime endogenous estrogen exposure also might affect VTE risk in women (Simon, *et al* 2006). Specifically, VTE risk was associated positively with age at menopause and number of children. Compared with normal age at menopause (46-54 years), the multivariate-adjusted odds ratio (OR) of VTE for late menopause (≥ 55 years) was 2.53 (95% CI, 1.28, 4.99) (Simon, *et al* 2006). The adjusted OR for VTE was 1.6-fold higher for women with more than two children when compared with those with two children or fewer (Simon, *et al* 2006). Other studies have reported similar results that women with late menopause and a history of more than three pregnancies had increased risk of VTE (Grady, *et al* 2000) (Samama 2000). Since the subjects of previous studies were predominantly whites and from hospital-based studies, these findings need confirmation in the general population. Rates of VTE are higher in African Americans than whites (Tsai, *et al* 2002a) (White, *et al* 2005), so confirmation among this population is especially relevant.

To examine the association of reproductive history measures of endogenous estrogen exposure, hormone replacement, and incident VTE among American Africans and whites, we used data from women in two population-based prospective studies.

Methods

Study population

The Longitudinal Investigation of Thromboembolism Etiology (LITE) study is a prospective study of VTE occurrence in 2 pooled, multi-center, longitudinal population-based cohort studies: the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study (CHS). The LITE study design, methods, and VTE incidence rates have been described in detail elsewhere (Tsai, *et al* 2002a) (Cushman, *et al* 2004b) (Ohira, *et al* 2007) (Yamagishi, *et al* 2009). In brief, 15,792 men and women aged 45 to 64 years enrolled in the ARIC study in 1987-1989 and 5,201 men and women aged ≥65 years enrolled in the CHS in 1989-1990 underwent assessments of cardiovascular risk factors. An additional 687 African Americans were recruited to CHS using similar methods in 1992-1993. The basic characteristics of the combined LITE sample, and the justification for pooling ARIC and CHS, have been published (Tsai, *et al* 2002a). Informed consent was obtained from participants, with approval of methods from the institutional review committees at each study center.

We first excluded participants who were not white or black or were scarcely represented in some field centers (n=103), men (n=9,572), and pre or peri-menopausal women at baseline (n=2,436). We then excluded participants who at baseline had a history of VTE (n=395) or cancer (n=908), were missing menopausal data (n=25) or were taking warfarin (n=57). The remaining 8,236 post-menopausal women were included in the analyses. Up to three follow-up examinations were performed every 3 years in ARIC and up to nine follow-up examinations were performed annually in CHS. Reexamination rates were 78, 66, and 51 percent for ARIC, and 81, 80, 76, 87, 85, 85, 77, 76, and 70 percent for CHS, respectively.

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Subjects were followed to determine the incidence of VTE through December 31, 2002 for ARIC and December 31, 2001 for CHS, after a median follow up of 13.1 years in ARIC and 11.7 years in CHS.

Measurements

Baseline cardiovascular risk factors and additional hemostatic factors included in this paper were measured comparably in ARIC and CHS, as described elsewhere (Tsai, *et al* 2002a) (Folsom, *et al* 1997) (Folsom, *et al* 2002) (Cushman, *et al* 1995). Blood was drawn from participants in the morning in both studies, promptly centrifuged for 30,000g-min, and stored in -70°C freezers. Factor VIIIc (FVIII) coagulant activity was measured as previously reported (Tsai, *et al* 2002b). Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Diabetes mellitus was defined at baseline as a fasting glucose of ≥126mg/dL, nonfasting glucose ≥200mg/dL, a history of physician-diagnosed diabetes, or current use of diabetes medication.

Menopause was defined on the basis of baseline interview data. A woman was considered premenopausal if she had menstruated in the last 2 years. Women less than 55 years of age with a hysterectomy and at least one intact ovary could not be categorized on ovarian status. The remaining women were considered postmenopausal. Postmenopausal women were further classified as having undergone a surgical menopause if they had had a bilateral oophorectomy. Natural menopause included (1) non-menstruating women with an intact uterus and at least one intact ovary and (2) women who had had a hysterectomy, had at least one intact ovary but were 55 years of age or older (Szklo, *et al* 1996). Participants were also interviewed about parity and use and duration of hormone replacement therapy. Hormone replacement therapy included the use of estrogen or estrogen and progestin preparations. In the present study, “current hormone use” was defined as use of oral estrogen or estrogen and progestin preparations, and thus did not include transdermal administration because it does not increase risk of VTE (Canonico, et al 2008). ‘Never hormone use” was defined as never having used oral estrogen or estrogen and progestin preparations, and “former hormone use” was defined as previously using oral contraceptives or an estrogen, progestin, or androgen therapy by oral or transdermal administration.

Endpoint determination

All participants were contacted annually by phone and asked about all hospitalizations in the previous year. Hospital records were obtained and VTE events validated by two physicians, as previously reported (Cushman, *et al* 2004b). Diagnosis of deep venous thrombosis (DVT) or pulmonary embolism (PE) required positive imaging tests. Cases were classified as idiopathic (no obvious cause) or secondary (associated with cancer, major trauma, surgery, marked immobility). From the ARIC study, 110 post-menopausal women with VTE were identified (51 idiopathic, and 59 secondary). In CHS, there were 80 post-menopausal women with VTE events; 33 were idiopathic, and 47 secondary. Of the 190 events, 153 had DVT only and 37 had PE.

Statistical analysis

Age- and race-adjusted mean values or prevalences of baseline variables of interest were compared between participants with VTE and without VTE, using analysis of covariance (ANCOVA) or logistic regression models (Wilcosky and Chambless 1985). Data were analyzed by classifying participants into three groups according to age at menopause defined as early (≤ 45 years), normal (46-54 years) and late menopause (≥ 55 years); according to hormone therapy as current users of estrogen (alone or in combination with progestin), former users, and never users; and according to parity as nulliparous, one or two children, and more than two children (Simon, *et al* 2006). Differences among these categories in age-

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and race-adjusted mean values or prevalences of potential confounding factors at baseline were also calculated using ANCOVA or logistic regression models. Rate ratios (RR) and 95% confidence intervals (CI) of VTE were calculated with adjustment for age and other potential confounding factors using the Cox proportional hazards model. Adjustment was made for factors previously associated with VTE in this study, including age (continuous), race, BMI (continuous), diabetes status (yes, no), and FVIII (continuous). Because hormone use often changed during follow-up, we also used time-dependent Cox models (updating information on hormone use at follow-up examinations). For participants with missing information on hormone use for a given follow-up examination visit, the hormone use status from the prior examination was carried forward. In order to evaluate the effect of duration of hormone therapy on the incidence of VTE, the incidence data excluding women with 1-year or more duration of hormone therapy at baseline were also analyzed.

Results

The sample consisted of postmenopausal women 45 years and older followed for an average of 11.8 years for VTE occurrence. Table 1 shows means or prevalences of risk characteristics at baseline for incident cases of VTE and for those who remained free of VTE. Mean values of age, BMI, and FVIII and the prevalence of diabetes were significantly higher among women with VTE than those without VTE, and African Americans were more likely than whites to suffer VTE. There were no significant differences in age at menopause, parity number, or type of menopause between women with VTE and those without VTE in either whites and Africans Americans (Table S1 and S2).

Table 2 presents age- and race-adjusted mean values or prevalences of VTE risk factors at baseline according to the categories of age at menopause, parity, hormone therapy, and type of menopause. Women with late menopause (≥ 55 years) had a higher mean BMI compared with women with early or normal menopause. The prevalence of diabetes and mean BMI were lower among women with parity of one to two than among women who were nulliparous or had parity of more than two. Current users of estrogen and/or progesterone had a lower mean BMI and factor VIII, and lower prevalence of diabetes compared with never and former users.

Compared with normal menopause, the multivariate-adjusted RRs of VTE for early menopause was 1.16 (95% CI, 0.83, 1.63) and for late menopause was 1.49 (95% CI, 0.89, 2.58), neither being statistically significant (Table 3). Further, when modeled as continuous variables, there were no associations of age at menopause or parity number with the risk of VTE (P=0.23 and P=0.62, respectively). There were no significant associations of parity or type of menopause with incidence of VTE. Women currently using hormone replacement had a 1.6-fold higher multivariate-adjusted RR of VTE compared with those not taking hormones in the time-dependent model (RR = 1.60, 95% CI, 1.06, 2.36). When we excluded women with 1-year or more duration of hormone therapy at baseline, the associations of current hormone use with the incidence of VTE was stronger; the multivariate-adjusted RR for current hormone use was 2.02 (95%CI, 1.31, 3.12). When we analyzed the associations of estrogen alone or estrogen in combination with progestin, separately, the association of current hormone use with the incidence of VTE was similar between estrogen/progestin and estrogen alone; the RRs were 1.60 (95%CI, 0.97-2.62) for estrogen/progestin and 1.59 (95%CI, 1.06-2.37) for estrogen alone. Furthermore, we calculated population attributable risk, the percentage of VTE occurrence in the population associated with current hormone use, using the formula $p(RR-1)/[1-p(RR-1)]$, where p is the prevalence of current hormone use among participants. The population attributable risk was 6.7% (95%CI, 1.0-10.3). The associations of hormone replacement with the incidence of VTE did not differ among the categories of menopause age, parity, or type of menopause (P for interactions >0.30).

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As shown in Table 4, the multivariate-adjusted RRs of VTE for current users of hormone replacement tended to be higher in those with idiopathic VTE (RR=2.40, 95%CI, 1.40, 4.12) than secondary VTE (RR=1.08, 95%CI, 0.63, 1.85). Women with late menopause had a 1.8-fold higher multivariate-adjusted RR of idiopathic VTE compared with normal menopause, but this did not reach statistically significance (RR = 1.85, 95% CI, 0.87, 3.94).

Discussions

Although previous hospital-based studies reported that late menopause and a history of having more than two children were associated with increased risk of VTE (Grady, *et al* 2000) (Simon, *et al* 2006) (Samama 2000), in this population-based prospective study, there were no associations of parity or late menopause with incidence of VTE. On the other hand, women currently using hormone replacement had an increased risk of VTE, consistent with previous studies (Grodstein, *et al* 1996) (Grady, *et al* 2000) (Cushman, *et al* 2004a). Therefore, effects of estrogen exposure on incidence of VTE differ between endogenous production and exogenous administration.

The ESTHER study, in which more than 95% of subjects were whites, indicated that markers of lifetime endogenous estrogen exposure, such as age at menopause and number of children, were positively associated with the risk of VTE (Simon, *et al* 2006). As in previous studies (Tsai, *et al* 2002a) (White, *et al* 2005), we found that compared with whites, African Americans have a higher risk of VTE, and they tend to have earlier menopause and more children. In analysis stratified by race, there were no significant associations of age at menopause or parity with the incidence of VTE in either whites and Africans Americans. Many studies have reported that oral estrogen use can induce an acquired activated protein C resistance and activate blood coagulation (Hoibraaten, *et al* 2001) (Oger, *et al* 2003) (Cushman, *et al* 2001). However, to our knowledge, the associations of late menopause and the number of children with hemostatic variables have not been reported. We previously reported that endogenous estrogen was associated with increased levels of inflammatory markers, such as C reactive protein and white cell count in ARIC (Folsom, *et al* 2005), but these inflammatory markers were not associated with the risk of VTE in LITE (Tsai, *et al* 2002b). Therefore, further study is needed to confirm whether there is any association of markers of lifetime endogenous estrogen exposure with the incidence of VTE, especially among African Americans.

In the present study, women currently using hormone replacement had a 1.6-fold higher risk of VTE. This RR is somewhat lower than reported by other observational studies. A recent meta-analysis of hormone replacement therapy and risk of VTE (Canonico, *et al* 2008), assessing seven case-control studies and one cohort study, showed that the pooled odds ratio of current oral estrogen use for VTE was 2.5 (95%CI, 1.9, 3.4) compared with non-users. Our confidence interval overlapped that of the meta-analysis. Differences of the duration of treatment may contribute to between-study differences of effect (Hernán, *et al* 2008). In the meta-analysis, the risk of VTE was significantly higher for treatment within the first year (pooled odds ratio, 4.0, 95%CI, 2.9, 5.7) than for treatment later (pooled odds ratio, 2.1, 95%CI, 1.3, 3.8) (Canonico, *et al* 2008). In the present study, the mean duration of hormone therapy use was about five years at baseline, and this could attenuate an effect of hormone therapy on the risk of VTE, even though we updated information on hormone use at follow-up examinations. Further, when we excluded women with one or more years duration of hormone therapy at baseline, the associations of current hormone use with the VTE grew stronger, which also supports the above hypothesis (Hernán, *et al* 2008).

A strength of the present study is that the cohorts studied are typical of general US adult populations, including both African Americans and whites. Potential limitations of this study

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warrant consideration. First, as in most clinical studies, we ascertained only clinically recognized VTE. This depended on participants' accurate reporting of hospitalizations and on their physicians' diagnostic work-up of suspected VTE events. During this study period, few VTEs were likely diagnosed and treated as outpatient events, but they would not be detected. However, misclassification of the VTE outcome was probably too rare to significantly alter our findings. Second, in the present study, because of limited numbers, we did not fully investigate the impact of unopposed and opposed estrogen therapy on VTE separately. However, as well as our findings, others suggested that there is little difference in the risk of VTE between users of estrogen alone and estrogen plus progestin (Canonico, *et al* 2008). Third, we did not analyze the association between transdermal hormone use and VTE, but transdermal hormone use does not seem to increase risk of VTE. In the meta-analysis, the risk of VTE was clearly elevated for treatment by oral estrogen (pooled odds ratio, 2.5, 95%CI, 1.9, 3.4) but not for treatment by transdermal estrogen (pooled odds ratio, 1.2, 95%CI, 0.9, 1.7) (Canonico, *et al* 2008). Fourth, the number of VTE events in the present study was relatively small. We therefore may have missed a modest association of late menopause with incidence of VTE (RR, 1.49, CI, 0.89, 2.58) due to low power. A larger study would be needed to verify whether such a modest association exists. Fifth, among the post-menopausal women in this study, younger women may have been more likely to have had non-natural menopause compared with older women, which may have affected the associations. However, when we excluded women ages 54 and less from the analyses, the associations of reproductive history and hormone replacement with the incidence of VTE were unchanged; the multivariate-adjusted RR were 1.44 (95%CI, 0.83, 2.51) for late menopause and 1.67 (95%CI, 1.08, 2.57) for current hormone use. Finally, although we analyzed the associations of hormone use with the incidence of VTE using information on hormone use updated at follow-up examinations, some participants who were not re-examined missed updating. This could have led to an underestimate of the association of current hormone use with the risk of VTE.

In conclusion, women currently using hormone replacement had a 1.6-fold higher risk of VTE than those without a history of hormone therapy use during 12 years of follow-up in this general population study. However, there were no associations of reproductive markers, such as greater parity and late menopause, with incidence of VTE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ. 2008; 336:1227–1231. [PubMed: 18495631]

Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. Laboratory methods and quality assurance in the Cardiovascular Health Study. Clin Chem. 1995; 41:264–270. [PubMed: 7874780]

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Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, Sidney S, Rosendaal FR. Estrogen plus progestin and risk of venous thrombosis. JAMA. 2004a; 292:1573–1580. [PubMed: 15467059]

Cushman M, Psaty BM, Meilahn EN, Dobs AS, Kuller LH. Post-menopausal hormone therapy and concentrations of protein C and antithrombin in elderly women. Br J Haematol. 2001; 114:162–168. [PubMed: 11472362]

Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med. 2004b; 117:19–25. [PubMed: 15210384]

Folsom AR, Cushman M, Tsai MY, Aleksic N, Heckbert SR, Boland LL, Tsai AW, Yanez ND, Rosamond WD. A prospective study of venous thromboembolism in relation to factor V Leiden and related factors. Blood. 2002; 99:2720–2725. [PubMed: 11929758]

Folsom AR, Golden SH, Boland LL, Szklo M. Association of endogenous hormones with C-reactive protein, fibrinogen, and white blood count in post-menopausal women. Eur J Epidemiol. 2005; 20:1015–1022. [PubMed: 16331433]

Folsom AR, Wu KK, Rosamond WD, Sharrett AR, Chambless LE. Prospective study of hemostatic factors and incidence of coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 1997; 96:1102–1108. [PubMed: 9286936]

Grady D, Wenger NK, Herrington D, Khan S, Furberg C, Hunninghake D, Vittinghoff E, Hulley S. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. Ann Intern Med. 2000; 132:689–696. [PubMed: 10787361]

Grodstein F, Stampfer MJ, Goldhaber SZ, Manson JE, Colditz GA, Speizer FE, Willett WC, Hennekens CH. Prospective study of exogenous hormones and risk of pulmonary embolism in women. Lancet. 1996; 348:983–987. [PubMed: 8855854]

Hernán MA, Alonso, Logan R, Grodstein F, Michels KB, Willett WC, Manson JE, Robins JM. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology. 2008; 19:766–779. [PubMed: 18854702]

Hoibraaten E, Qvigstad E, Andersen TO, Mowinckel MC, Sandset PM. The effects of hormone replacement therapy (HRT) on hemostatic variables in women with previous venous thromboembolism--results from a randomized, double-blind, clinical trial. Thromb Haemost. 2001; 85:775–781. [PubMed: 11372667]

Oger E, Alhenc-Gelas M, Lacut K, Blouch MT, Roudaut N, Kerlan V, Collet M, Abgrall JF, Aiach M, Scarabin PY, Mottier D. Differential effects of oral and transdermal estrogen/progesterone regimens on sensitivity to activated protein C among postmenopausal women: a randomized trial. Arterioscler Thromb Vasc Biol. 2003; 23:1671–1676. [PubMed: 12869355]

Ohira T, Cushman M, Tsai MY, Zhang Y, Heckbert SR, Zakai NA, Rosamond WD, Folsom AR. ABO blood group, other risk factors and incidence of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE). J Thromb Haemost. 2007; 5:1455–1461. [PubMed: 17425663]

Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. Arch Intern Med. 2000; 160:3415–3420. [PubMed: 11112234]

Simon T, Beau Yon de Jonage-Canonico M, Oger E, Wahl D, Conard J, Meyer G, Emmerich J, Barrellier MT, Guiraud A, Scarabin PY. Indicators of lifetime endogenous estrogen exposure and risk of venous thromboembolism. J Thromb Haemost. 2006; 4:71–76. [PubMed: 16409454]

Szklo M, Cerhan J, Diez-Roux AV, Chambless L, Cooper L, Folsom AR, Fried LP, Knopman D, Nieto FJ. Estrogen replacement therapy and cognitive functioning in the Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol. 1996; 144:1048–1057. [PubMed: 8942436]

Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med. 2002a; 162:1182–1189. [PubMed: 12020191]

Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Tracy RP, Aleksic N, Folsom AR. Coagulation factors, inflammation markers, and venous thromboembolism: the longitudinal investigation of thromboembolism etiology (LITE). Am J Med. 2002b; 113:636–642. [PubMed: 12505113]

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White RH, Zhou H, Murin S, Harvey D. Effect of ethnicity and gender on the incidence of venous thromboembolism in a diverse population in California in 1996. Thromb Haemost. 2005; 93:298–305. [PubMed: 15711746]

Wilcosky TC, Chambless LE. A comparison of direct adjustment and regression adjustment of epidemiologic measures. J Chronic Dis. 1985; 38:849–856. [PubMed: 4044770]

Yamagishi K, Cushman M, Heckbert SR, Tsai MY, Folsom AR. Lack of association of soluble endothelial protein C receptor and PROCR 6936A/G polymorphism with the risk of venous thromboembolism in a prospective study. Br J Haematol. 2009; 145:221–226. [PubMed: 19222470]

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Table 1

Baseline characteristics among post-menopausal women who did or did not develop incident venous thromboembolism, LITE

Baseline characteristics†	Venous thromboembolism (n=190)	No venous thromboemolism (n=8,046)	p value
Age (years)*	64.0	61.0	<0.001
Race (% African American)**	37.0	29.1	0.02
Mean age at the menopause (years)	44.8	45.2	0.51
Age at menopause (%)			
Early menopause (≤ 45 years)	44.4	43.4	0.44
Normal menopause (46-54 years)	48.3	51.2	
Late menopause (≥ 55 years)	7.3	5.4	
Parity (%)			
Nulliparous	12.6	11.2	0.83
One to two children	38.1	38.4	
Greater than two children	49.3	50.4	
Hormone therapy use (%)			
Never use	63.4	63.3	0.93
Former use of estrogen or progesterone	18.2	19.2	
Current use of estrogen and/or progesterone	18.2	17.5	
Duration of hormone therapy use (years) ‡	5.1	5.4	0.77
Type of menopause (%)			
Natural	81.4	83.4	0.47
Surgical	18.6	16.6	
BMI (kg/m^2)	29.3	27.6	<0.001
Diabetes Mellitus (%)	14.2	9.6	0.03
Factor VIII (%)	151	132	<0.001

Sample sizes vary somewhat among characteristics because some women had indefinable menopause status.

*Race-adjusted,

**Age-adjusted.

†Age- and race-adjusted,

‡Current user only.

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Table 2

Age- and race-adjusted baseline characteristics according to age at menopause, parity, hormone therapy use, and cause of menopause, LITE

Baseline characteristics	No. at risk	Race (% African American)*	*P*	BMI (kg/m^2)	*P*	Diabetes Mellitus (%)	*P*	Factor VIII (%)	*P*
Age at menopause (%)									
Early menopause (=< 45 years)	3,577	64.0	<0.001	27.5	0.001	9.8	0.88	132	0.02
Normal menopause (46-54 years)	3,464	76.7		27.7		9.8		135	
Late menopause (>= 55 years)	452	69.6		28.5		10.5		134	
Parity (%)									
Nulliparous	926	67.2	<0.001	27.1	<0.001	10.3	0.01	132	0.23
One to two children	3,095	77.2		27.0		8.4		132	
Greater than two children	4,150	67.3		28.2		10.5		134	
Hormone therapy use (%)									
Never use	5,025	68.0	<0.001	28.0	<0.001	10.8	<0.001	135	<0.001
Former use of estrogen or progesterone	1,579	75.2		27.6		9.0		130	
Current use of estrogen and/or progesterone	1,439	79.3		26.2		5.9		128	
Type of menopause (%)									
Natural	6,238	73.0	<0.001	27.6	0.53	9.4	0.01	133	0.76
Surgical	1,248	59.3		27.7		11.8		133	

Sample sizes vary somewhat among characteristics because some women had indefinable menopause status.

*Age-adjusted.

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Table 3

Multivariate-adjusted rate ratios (RRs) and 95% confidence intervals (CIs) of incident venous thromboembolism, LITE, 1987-2002

Variable	No. at risk	No. of cases	Person-years of follow up	Model 1*		Model 2**	
				RR	95%CI	RR	95%CI
Age at menopause							
Early menopause (=< 45 years)	3,577	82	42,433	1.16	(0.84-1.60)	1.16	(0.83-1.63)
Normal menopause (46-54 years)	3,464	77	40,695	1		1	
Late menopause (>= 55 years)	452	16	4,975	1.44	(0.84-2.48)	1.49	(0.89-2.58)
Parity							
Nulliparous	926	27	10,068	1.14	(0.71-1.83)	1.15	(0.72-1.84)
One to two children	3,095	71	36,158	1		1	
Greater than two children	4,150	90	49,990	0.89	(0.64-1.25)	0.90	(0.64-1.26)
Hormone therapy use †							
Never use	5,025	120	58,159	1		1	
Former use of estrogen or progesterone	1,579	36	18,435	0.96	(0.63-1.46)	1.07	(0.72-1.62)
Current use of estrogen and/or progesterone	1,439	30	17,761	1.58	(1.08-2.32)	1.60	(1.06-2.36)
Type of menopause							
Natural	6,238	143	72,918	1		1	
Surgical	1,248	31	15,095	1.03	(0.67-1.59)	0.91	(0.58-1.44)

Sample sizes vary somewhat among characteristics because some women had indefinable menopause status.

*Adjusted for age, race, body mass index, diabetes mellitus, and factor VIII at baseline.

**Further adjusted for other reproductive variables.

†Time dependent analysis

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Table 4

Multivariate-adjusted rate ratios (RRs) and 95% confidence intervals (CIs) of venous thromboembolism for current users of estrogen and/or progesterone[†] compared with non-users, LITE, 1987-2002

		Multivariate-adjusted[*]	
Stratum	**No. of cases**	**RR**	**95% CI**
ARIC	106	1.44	(0.90-2.32)
CHS	80	1.86	(1.01-3.46)
Whites	123	1.63	(1.07-2.49)
Non-whites	63	1.25	(0.53-2.97)
Idiopathic	84	2.40	(1.40-4.12)
Secondary	102	1.08	(0.63-1.85)

[*] Adjusted for age, sex, (race), body mass index, diabetes mellitus and factor VIII.

[†] Time dependent analysis.