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Neurology 2007;68;563-568
DOI: 10.1212/01.wnl.0000254473.88647.ca

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Abstract—*Objective:* To determine if levels of serum estradiol and testosterone can predict stroke in a population-based sample of elderly men. *Methods:* Serum 17β estradiol and testosterone were measured in 2,197 men aged 71 to 93 years who participated in the Honolulu-Asia Aging Study from 1991 to 1993. All were free of prevalent stroke, coronary heart disease, and cancer. Participants were followed to the end of 1998 for thromboembolic and hemorrhagic events. *Results:* During the course of follow-up, 124 men developed a stroke (9.1/1,000 person-years). After age adjustment, men in the top quintile of serum estradiol (≥125 pmol/L [34.1 pg/mL]) experienced a twofold excess risk of stroke vs men whose estradiol levels were lower (14.8 vs 7.3/1,000 person-years, $p < 0.001$). Among the lower quintiles, there were little differences in the risk of stroke. Findings were also significant and comparable for bioavailable estradiol and for thromboembolic and hemorrhagic events. After additional adjustment for hypertension, diabetes, adiposity, cholesterol concentrations, atrial fibrillation, and other characteristics, men in the top quintile of serum estradiol continued to have a higher risk of stroke vs those whose estradiol levels were lower (relative hazards = 2.2; 95% CI = 1.5 to 3.4, $p < 0.001$). Testosterone was not related to the risk of stroke. *Conclusions:* High levels of serum estradiol may be associated with an elevated risk of stroke in elderly men.

NEUROLOGY 2007;68:563–568

Information on the relationship between endogenous estrogen and atherosclerosis in men is limited and controversial.[1] In case-control studies, some have found that hyperestrogenemia is related to an elevated risk of coronary heart disease,[2,3] while others have not.[4,5] In a longitudinal follow-up in the Rancho Bernardo Study, there was no apparent relationship between estrogen and death from cardiovascular and ischemic heart disease.[6]

Less is known about the relationship between endogenous estrogen and the risk of stroke, particularly in elderly men. New evidence, however, suggests that high estrogen levels may be associated with ischemic brain injury. In a sample of elderly men who underwent MRI in the Honolulu-Asia Aging Study, elevated concentrations of serum estradiol were cross-sectionally associated with an increased frequency of lacunar infarcts.[7] In the Rotterdam Study, elevated estradiol was associated with an increased risk of dementia with a contributing cerebrovascular cause.[8] Although strokes are an important precursor of dementia,[9,10] it remains to be determined if pre- or coexisting cerebrovascular conditions in dementia are estrogen related.

The purpose of this report is to determine if levels of serum 17β estradiol and testosterone can predict the development of stroke (including thromboembolic and hemorrhagic events) in a sample of elderly men. Findings are based on longitudinal follow-up in the Honolulu-Asia Aging Study of a population-based sample of Japanese-American men without prevalent stroke, coronary heart disease, and cancer.

Methods. *Background and study sample.* From 1965 to 1968, the Honolulu Heart Program began following 8,006 men of Japanese ancestry living on the island of Oahu, HI, for the development of cardiovascular disease.[11,12] Beginning with examinations that were given from 1991 to 1993, the Honolulu-Asia Aging Study was launched by the National Institute on Aging as an expansion of the Honolulu Heart Program to study neurodegenerative diseases and cognitive function in the elderly.[13] Subjects

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Supported by a contract (N01-AG-4-2149) and grant (1-R01-AG17155-01A1) from the National Institute on Aging, a contract (N01-HC-05102) from the National Heart, Lung, and Blood Institute, a grant (1-R01-NS41265-01) from the National Institute of Neurologic Disorders and Stroke, a grant from the United States Department of the Army (DAMD17-98-1-8621), the Office of Research and Development, Medical Research Service, Department of Veterans Affairs, and the Japan Society for the Promotion of Science.

Disclosure: The authors report no conflicts of interest.

The information contained in this article does not necessarily reflect the position or the policy of the United States Government, and no official endorsement should be inferred.

Received August 17, 2006. Accepted in final form November 1, 2006.

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included 3,734 men aged 71 to 93 years (approximately 80% of the survivors in the original Honolulu Heart Program cohort).

For this report, follow-up began at the 1991 to 1993 examinations when blood was drawn and assayed for serum estradiol, testosterone, sex hormone binding globulin (SHBG), and albumin. Men with prevalent stroke (n = 183), coronary heart disease (n = 602), and cancer (n = 405) were excluded from follow-up as were those with missing hormone data (n = 347). The remaining sample comprised 2,197 men with follow-up to the end of 1998 for incident stroke. Procedures were in accordance with institutional guidelines and approved by an institutional review committee. Informed consent was obtained from the study participants.

Diagnosis of stroke. Stroke was ascertained from a comprehensive and ongoing system of surveillance by a panel of physician investigators who reviewed hospital discharges, medical records, death certificates, and autopsy reports. A diagnosis of definite stroke was made when a neurologic deficit was accompanied by blood in the CSF or by evidence of a brain infarct or hemorrhage based on CT or MRI. Although neuroimaging was not routinely performed on the 2,197 cohort members at the beginning of follow-up (1991–1993), access to hospital discharges, medical records, and data from serial physical examinations has been available for all participants since the beginning of the Honolulu Heart Program (1965–1968).

Probable strokes included neurologic deficits that persisted for at least 2 weeks or until death but were not accompanied by positive CSF or by findings based on available neuroimaging data. All diagnoses were reviewed and confirmed by a study neurologist and the Honolulu Heart Program Morbidity and Mortality Review Committee. Because of a lack of diagnostic certainty, neurologic deficits lasting at least 24 hours but less than 2 weeks were not included among the stroke events.

A stroke was most often considered thromboembolic if the focal neurologic deficit occurred without prolonged unconsciousness, nuchal rigidity, fever, pronounced leukocytosis, or blood in the spinal fluid. Identification of hemorrhagic stroke was made when the neurologic deficit was accompanied by a loss of consciousness, headache, and blood in the spinal fluid obtained by an atraumatic lumbar puncture or on the basis of neuroimaging or surgical findings. Subjects who experienced focal neurologic episodes attributed to other conditions, such as blood dyscrasias, neoplastic disease, head injury, surgical accident, meningoencephalitis, fat embolism, epilepsy, or cardiac arrest, were not included among the stroke victims. Further details on the diagnosis of stroke are provided elsewhere.[14]

Measurement of serum estradiol, testosterone, SHBG, and albumin. Fasting blood samples were drawn at the beginning of follow-up (1991–1993) and stored at −70 °C. A quantitative competitive immunoassay (Immulite 2000) was used to measure serum 17β estradiol and testosterone. For estradiol, the intra- and interassay coefficients of variation were 4.3 and 5.2%. Levels of estradiol <73.4 pmol/L (20 pg/mL) were estimated for 37% of the men (813/2,197) from a curve-fitting algorithm that converted the relative light unit from the immunoassay into an absolute unit using a standard master calibration curve. For testosterone, corresponding intra- and interassay coefficients of variation were 7.4 and 7.7%, with a sensitivity of 0.35 nmol/L (0.1 ng/mL).

Concentrations of SHBG were measured by an immunometric assay (Immulite 2000). Albumin determinations were based on the bromocresol green method using an immunoassay with intra- and interassay coefficients of variation of 2 and 3%. The more active bioavailable estradiol and testosterone (not bound to SHGB) consisted of free and albumin-bound hormones.[15,16] Bioavailable fractions were calculated following the methods of van den Beld et al. and Sodergard et al.[16,17]

Coexisting risk factors. Other risk factors that were measured at the beginning of follow-up (1991–1993) included age, hypertension, diabetes, body mass index, total and high-density lipoprotein cholesterol, a marker of peripheral vascular disease, an index of physical activity, daily alcohol intake, EKG evidence of atrial fibrillation, and dementia. A diagnosis of hypertension was made when a systolic blood pressure was ≥160 mm Hg or when a diastolic blood pressure was ≥95 mm Hg. A subject receiving medication for high blood pressure was also diagnosed as having hypertension. Diabetes was defined on the basis of a medical history or the use of insulin or oral hypoglycemic therapy. Based on guidelines from the World Health Organization,[18] diabetes was also considered to be present when fasting glucose concentrations were ≥7.0 mmol/L (126 mg/dL) or when glucose levels were ≥11.1 mmol/L (200 mg/dL) 2 hours after ingestion of a 75 g glucose load. Peripheral vascular disease was determined from the ratio of a systolic blood pressure measurement in the ankle divided by a systolic measurement in the arm.[19] Peripheral vascular disease was defined as present when the ratio was <0.9.[19] Assessment of physical activity was based on the use of the physical activity index, a common measure used to quantify overall metabolic output in a typical 24-hour period.[20] Low levels of the physical activity index (a marker of low physical activity) have been shown to increase the risk of stroke vs indices that are higher.[20] Methods for the measurement of total and high-density lipoprotein cholesterol are described elsewhere.[21] The diagnosis of dementia followed guidelines from the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised.[22] Further description of the diagnosis of dementia has been previously reported.[13] For this sample of elderly men, cigarette smoking was too infrequent to be included among the risk factors. Only 152 of the 2,197 men were current smokers. Control of past and current smoking had no effect on the reported findings.

Statistical methods. Crude and age-adjusted incidence rates of total, thromboembolic, and hemorrhagic stroke in person-years of follow-up were estimated across quintiles of serum estradiol and testosterone based on standard analysis of covariance methods.[23] Percents and average levels of the coexisting risk factors were also derived and age-adjusted across the quintile ranges. To test for an independent effect of estradiol and testosterone on the risk of total stroke and its subtypes, proportional hazards regression models were used.[24] Adjustments were made for age and the other risk factors. Regression models also included estradiol and testosterone as independent variables. In addition, tests were made for interaction effects between a hormone and each risk factor and for whether the effect of a hormone on the risk of stroke changed with time. Based on the estimated regression coefficients and standard errors, relative hazards (and 95% CIs) were derived by comparing the risk of stroke between quintile ranges of a hormone. All reported p values were based on two-sided tests of significance.

Results. In the course of follow-up, stroke occurred in 124 of the 2,197 elderly men (9.1/1,000 person-years). The average age at the time of a stroke was 81.9 years (range: 73 to 94 years), and the average time into follow-up when a stroke occurred was 3.3 years (range: 10 months to 7.5 years). Among the strokes, 85 were thromboembolic, 42 were hemorrhagic, and 1 was of unknown origin. For three of the men, a thromboembolic stroke was preceded by a hemorrhagic event by 8 months to 3.9 years. In one instance, a hemorrhagic stroke was preceded by a thromboembolic event by 1.4 years.

Among the endogenous hormones, only estradiol was associated with the risk of stroke. For testosterone, stroke risk varied negligibly from 10.4 to 9.0/1,000 person-years in the bottom to the top quintiles (≤12 nmol/L [346 ng/dL] and >21.5 nmol/L [620 ng/dL]). SHGB and albumin were also unrelated to the risk of stroke.

Table 1 describes details of the observed findings for estradiol. In the bottom four quintiles of total and bioavailable estradiol, there were no significant differences in the risk of stroke. The pooled age-adjusted incidence rates across these quintiles were 7.6 and 7.5/1,000 person-years for total and bioavailable estradiol. Relative to the bottom four quintiles, the incidence in the highest quintile increased twofold to 14.8/1,000 person-years for total estradiol and 15.5/1,000 person-years for bioavailable estradiol ($p < 0.001$). There were no apparent differences in the risk of stroke across estradiol concentrations in the top quintile.

The figure describes the age-adjusted findings for thromboembolic and hemorrhagic events. Regardless of the

Table 1 *Age-adjusted incidence of total stroke in elderly men within each quintile of total and bioavailable estradiol*

Quintile	Range, pmol/L*	Incidence/1,000 person-years	
		Unadjusted	Age-adjusted
Total estradiol			
1st	3.6–53.4	7.2 (20/439)†	7.3
2nd	53.5–75.6	7.8 (22/442)	8.0
3rd	76.0–96.5	6.9 (19/438)	6.9
4th	96.9–124.9	8.6 (23/439)	8.4
5th	125.0–473.6	15.1‡ (40/439)	14.8‡
Bioavailable estradiol			
1st	1.9–34.7	9.0 (25/439)	9.0
2nd	34.8–49.8	5.4 (15/440)	5.4
3rd	49.9–64.2	7.8 (21/439)	7.7
4th	64.3–82.8	7.9 (22/440)	7.9
5th	82.9–319.6	15.6‡ (41/439)	15.5‡

* To convert to pg/mL, divide by 3.671.
† Number of stroke events/sample at risk.
‡ Excess risk of stroke vs the bottom four quintiles ($p < 0.001$).

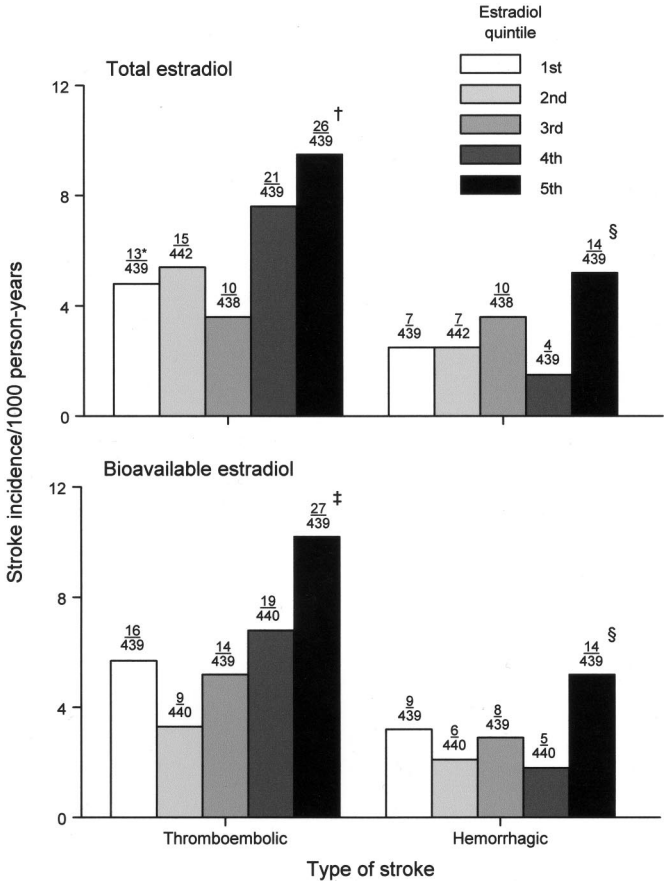

*Figure. Age-adjusted incidence of thromboembolic and hemorrhagic stroke in elderly men within each quintile of total and bioavailable estradiol. *Numbers above the bars are the number of stroke events/sample at risk. In all instances, there is an excess risk of stroke in the top vs bottom four quintiles of an estradial measure: †$p = 0.017$; ‡$p = 0.005$; §$p = 0.023$.*

stroke outcome, the risk of stroke remained nearly doubled for men in the top quintile of total estradiol vs estradiol levels that were lower. For total estradiol, incidence of thromboembolic stroke increased from 5.4/1,000 person-years in the bottom four quintiles to 9.5/1,000 person-years in the top quintile ($p = 0.017$). Incidence of hemorrhagic stroke increased from 2.5 to 5.2/1,000 person-years ($p = 0.023$). Findings were similar for bioavailable estradiol.

Table 2 describes the average age and age-adjusted relationships between total estradiol and other putative or concomitant stroke risk factors. Among the factors, men tended to be older ($p < 0.004$) and to have lower levels of total cholesterol ($p = 0.002$) in the higher estradiol ranges. Most notable is the increase in prevalence of atrial fibrillation ($p = 0.004$) and dementia ($p < 0.001$) with rising estradiol concentrations. The latter is consistent with findings from the Rotterdam Study.[8] Other characteristics were not significantly associated with estradiol.

Table 3 describes the relationship between estradiol levels and the risk of stroke after accounting for the risk factors in table 2. Here, relative hazards describe the risk of stroke for men in the top vs bottom four quintiles of total and bioavailable estradiol. In addition to the risk factors in table 2, relative hazards were also adjusted for testosterone. As can be seen, risk of stroke for men in the top quintile of each estradiol measurement is approximately twofold higher than for men in the lower quintiles. Similar and significant relationships were observed for total, thromboembolic, and hemorrhagic events. Although statistical power is limited, changes in the effect of estradiol on the risk of stroke across risk factor strata and with time were not apparent. Further adjustment for SHBG and albumin failed to alter these findings.

Discussion. Information on the association of endogenous estrogen and cerebrovascular disease in men is limited. In the current report, evidence suggests that elevated concentrations of total and bioavailable estradiol (in those who are elderly) are associated with an excess risk of stroke. In addition, estradiol determinations were made prior to the occurrence of stroke in men without prevalent coronary heart disease and cancer when follow-up began. Findings were similar for thromboembolic and hemorrhagic events. Testosterone, SHBG, and albumin were not related to the risk of stroke.

Risk of stroke appeared constant across the bottom four estradiol quintiles (particularly for hemorrhagic events). It doubled and also appeared homogeneous in the top quintile (≥125 pmol/L [34.1 pg/mL] for total estradiol). A computer scan for an optimal threshold yielded a modestly higher cutpoint of 134 pmol/L (36.5 pg/mL). Although there was a linear (dose-response) relationship across the entire range of estradiol ($p = 0.007$), the association was largely driven by the excess of stroke in the top estradiol quintile. There was no clear linear trend. Possibly due to a limited number of stroke events, tests for curvature were equally uninformative. While a clinical cutpoint is difficult to identify (and may not

Table 2 *Average age and age-adjusted percent and average levels of concomitant risk factors across total estradiol quintiles in elderly men*

	Total estradiol quintile				
	1st	2nd	3rd	4th	5th
Age, y*	77.1±4.5	77.1±4.3	77.6±4.7	78.1±4.6	78.1±4.9
Hypertension	51.8	54.5	54.6	57.4	46.9
Diabetes	26.6	29.8	27.9	25.3	25.5
Body mass index, kg/m^2	23.6±3.1	23.1±3.1	23.5±3.1	23.4±3.1	23.5±3.3
Total cholesterol,† mmol/L‡	5.0±0.8	4.9±0.8	5.0±0.9	4.9±0.8	4.8±0.8
HDL cholesterol, mmol/L‡	1.3±0.4	1.3±0.3	1.3±0.3	1.3±0.4	1.3±0.3
Peripheral vascular disease	9.5	10.3	12.8	10.5	12.2
Physical activity index	31.1±4.6	30.9±4.7	31.1±4.8	31.1±4.8	31.1±4.4
Alcohol intake, mL/d	16.3±33.1	16.7±28.4	20.6±43.0	18.3±39.8	19.4±47.5
Atrial fibrillation§	1.0	2.4	3.0	3.1	4.4
Dementia‖	2.3	3.7	4.3	6.7	7.4

Values are mean ± SD or %.

* Age increases with rising level of estradiol ($p = 0.004$).
† Total cholesterol declines with rising level of estradiol ($p = 0.002$).
‡ To convert to mg/dL, divide by 0.0259.
§ Prevalence of atrial fibrillation increases with rising level of estradiol ($p = 0.004$).
‖ Prevalence of dementia increases with rising level of estradiol ($p < 0.001$).

HDL = high-density lipoprotein.

exist), total estradiol concentrations <184 pmol/L (50 pg/mL) are often thought to be normal.[25] In the current sample, only 5.8% of the men had higher concentrations. Among this group, after age and risk factor adjustment, there continued to be a twofold excess in the risk of stroke vs men in the bottom four quintiles (relative hazards = 2.3; 95% CI = 1.2 to 4.4, $p = 0.008$). The latter is consistent with a leveling off of the effect of estradiol on the risk of stroke for concentrations that fall in the top quintile. While a dose-response relationship may still exist in this higher range, statistical power is limited by the small number of stroke events.

Findings are also in contrast with evidence for a neuroprotective effect of estrogen on stroke and ischemic brain injury in both in vitro and animal studies.[26-28][26-28] In humans, the direction of association is less clear, particularly in elderly men. Most reports are also based on limited case-control designs and address associations with coronary atherosclerosis. One report from the Framingham Study found that 61 men with coronary heart disease had significantly higher estradiol levels than 61 matched controls.[2] It could not be determined, however, if the hyperestrogenemia preceded or followed the coronary event or its treatment. In another study from the Honolulu Heart Program, estradiol levels were measured retrospectively in 96 men with a myocardial infarction and compared to 96 controls.[5] In the latter report, there was no significant relationship between estradiol concentrations and case-control status, although deterioration of blood samples may have been a factor. In another case-control study of coronary thrombosis, blood samples were taken at the time of angiography.[3] While the timing of the hyperestrogenemia was again uncertain, estrogen was elevated in the cases of thrombosis, and it was the only risk factor significantly related to a thrombotic event.

Less is known about the relationship of stroke

Table 3 *Estimated relative hazard of stroke in elderly men in the top vs the bottom four quintiles of total and bioavailable estradiol*

	Total estradiol		Bioavailable estradiol	
Type of stroke	Relative hazard (95% CI)*	*p* Value	Relative hazard (95% CI)*	*p* Value
Total	2.2 (1.5,3.4)	<0.001	2.2 (1.4,3.3)	<0.001
Thromboembolic	2.1 (1.2,3.5)	0.006	2.0 (1.2,3.4)	0.009
Hemorrhagic	2.2 (1.1,4.4)	0.025	2.2 (1.1,4.4)	0.030

* Relative hazards are adjusted for age, testosterone, hypertension, diabetes, body mass index, total and high-density lipoprotein cholesterol, peripheral vascular disease, physical activity index, alcohol intake, atrial fibrillation, and dementia.

with endogenous estrogen. In two case-control studies, stroke was unrelated to levels of estradiol.[29,30] In both instances, estradiol concentrations were determined after the stroke event. In a sample of 1,009 Caucasian men aged 40 to 79 in the Rancho Bernardo Study, there was no apparent relationship between estrogen and death from cardiovascular and ischemic heart disease after 12 years of follow-up.[6] While the sample in the latter study was smaller than in the current report, the younger age of the Rancho Bernardo sample could have further limited statistical power.

In contrast, in 575 elderly men who underwent MRI in the Honolulu-Asia Aging Study, those with elevated concentrations of estradiol had a higher frequency of lacunar infarcts than men with lower concentrations.[7] In the latter study, however, it could not be determined if the lacunar event occurred before or after the collection of sera for the measurement of estradiol. There exists the possibility that findings may reflect injury in regions of the brain that regulate hormone levels. In the current report, all strokes followed blood collection in men who were without evidence of prevalent cerebrovascular and coronary heart disease. The strongest corroborating evidence comes from the Rotterdam Study, where elevated estrogen was associated with an increased risk of dementia with a contributing cerebrovascular cause.[8]

While the latter findings support the possibility that elevated estrogen levels in elderly men may be associated with an increased risk of stroke, explanations for a causal pathway are unclear. In the current report, the relationship between estradiol and stroke was unexplained by several coexisting factors, including adiposity, atrial fibrillation, and dementia. While there is a potential role for risk factors that were not measured, effects of estradiol could be more direct than through a cascade of intervening events that involve common stroke risk factors. Biologic effects of estradiol could be modulated by estrogen receptor subtypes.[31] It has also been proposed that estrogen can promote stroke and ischemia through the overproduction of nitric oxide and oxidative stress.[32]

Relationships between estrogen and stroke risk factors are also not clear. Some evidence suggests that elevated estrogen levels are associated with low concentrations of homocysteine, fibrinogen, and PAI-1, and to favorable lipid profiles.[31] Others describe adverse relationships with diabetes, hypertension, and obesity.[33] In the current report, total cholesterol declined with increasing estradiol levels. Low cholesterol in this elderly sample, however, has been associated with increased mortality and coronary heart disease, possibly through subclinical frailty.[34,35]

The possibility that elevated levels of endogenous estrogen are associated with adverse risk factor profiles is consistent with findings of an association between exogenous estrogen in men with a prior myocardial infarction and an increased risk of secondary events, pulmonary embolism, and thrombophlebitis.[36] Thromboembolic outcomes have also been attributed to exogenous estrogen in women.[37-40]

Whether estradiol acts as a causal agent is equivocal. Estradiol could be a marker for other unmeasured factors that contribute to stroke that are more prevalent in the higher estradiol ranges. As a source of embolism, it seems interesting that the prevalence of atrial fibrillation rose significantly from 1.0 to 4.4% from the bottom to top estradiol quintiles. Although the relationship between estradiol and stroke was unchanged after accounting for atrial fibrillation, there remains the possibility that elevated estradiol could be a part of a causal chain through relationships with paroxysmal or transient conduction disturbances that are difficult to detect, leading to chronic dysrhythmias later in life and a higher susceptibility to stroke. Elevated estradiol, however, also had an effect on hemorrhagic events which would not include an atrial fibrillation link. A number of other intervening conditions could still develop in the course of follow-up. Conditions such as dementia, often characterized by a complex mixture of vascular derangements and risk factor relationships, may be important. In the current study, dementia prevalence rose from 2.3 to 7.4% from the bottom to top estradiol quintiles. There also exists the possibility that reports of an association between elevated estradiol and vascular dementia[8-10] are explained by a heightened risk for stroke.

It is not clear if findings in the current report apply to other population segments. In general, however, risk factor associations in the sample from Hawaii are comparable to those that have been described elsewhere.[41,42] In a comparison with the Framingham Study, similar risk factor effects on the incidence of stroke were observed.[42] Although there is consistency in relationships between stroke and its risk factors, the possibility that associations include serum estradiol in elderly men is in need of confirmation and further study.

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