

# Aspirin Use Reduces Risk of Stroke in Women with a History of Hypertensive Disorders of Pregnancy: The California Teachers Study

## APPENDIX

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**Table e-1. International Classification of Diseases, Ninth Revision (ICD-9) codes used in analysis**

Code description	ICD-9 code
<i>Acute cerebrovascular events</i>	
Ischemic stroke <sup>a</sup>	433.01, 433.10, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.11, 434.91, 436
Intracerebral hemorrhage <sup>a</sup>	431
Subarachnoid hemorrhage <sup>a</sup>	430
Transient ischemic attack <sup>a</sup>	435
Cerebral venous thrombosis <sup>1</sup>	325
Cervical artery dissection <sup>2,3</sup>	443.21, 443.24
Cerebrovascular diseases in the puerperium <sup>4,5</sup>	671.5, 674, 674.01, 674.02, 674.03, 674.04
<i>Hypertensive disorders of pregnancy</i>	
Gestational hypertension <sup>6</sup>	642.3, 642.30, 642.31, 642.32, 642.34, 642.9, 642.90, 642.91, 642.92, 642.93, 642.94
Mild/unspecified preeclampsia <sup>7</sup>	642.4, 642.40, 642.41, 642.42, 642.43, 642.44, 642.7, 642.70, 642.71, 642.72, 642.73, 642.74
Severe preeclampsia <sup>7</sup>	642.5, 642.50, 642.51, 642.52, 642.53, 642.54
Eclampsia <sup>7</sup>	642.6, 642.60, 642.61, 642.62, 642.63, 642.64
<i>Cardiac outcomes</i>	
Myocardial infarction <sup>8,9</sup>	410.0, 410.00, 410.01, 410.02, 410.1, 410.10, 410.11, 410.12, 410.2, 410.20, 410.21, 410.22, 410.3, 410.30, 410.31, 410.32, 410.4, 410.40, 410.41, 410.42, 410.5, 410.50, 410.51, 410.52, 410.6, 410.60, 410.61, 410.62, 410.7, 410.70, 410.71, 410.72, 410.8, 410.80, 410.81, 410.82, 410.9, 410.90, 410.91, 410.92, 411.0, 411.1, 411.8, 411.81, 411.89
<sup>a</sup> Diagnostic codes internally validated (see Appendix 1)	

**Table e-2. Positive predictive values for stroke and TIA admissions/events identified by California hospital discharge records, compared to medical record review.**

Events, defined by ICD-9 codes	First Admission N=212 PPV % (95% CI)	First Admission, First Position N=198 PPV % (95% CI)	First Admission, Second Position N=14 PPV % (95% CI)
<b>All Stroke</b> <i>All Stroke excluding 432.1 and 437</i>	83 (77-89) 87 (81-92)	87 (81-93) 90 (84-95)	36 (8-65) 44 (12-77)
<b>Hemorrhagic Stroke</b> <i>Hemorrhagic Stroke excluding 432.1</i> Subarachnoid (430) Intraparenchymal (431) Other intracranial (432)	74 (82-86) 82 (71-93) 81 (64-98) 81 (64-98) 13 (0-35)	80 (69-92) 86 (76-96) 85 (69-100) 88 (69-100) 17 (0-46)	0 (0-100) 0 (0-100) 0 (0-100) 0 (0-100) 0 (0-100)
<b>Ischemic Stroke (433, 434)</b>	<b>85 (76-92)</b>	<b>88 (80-95)</b>	<b>57 (20-94)</b>
<b>Other Stroke (437)</b>	0 (0-100)	0 (0-100)	N/A
<b>TIA (435)</b>	<b>55 (43-67)</b>	<b>56 (44-68)</b>	<b>33 (0-87)</b>

**Table e-3. Agreement of confirmed stroke and TIA events between two independent neurologists.**

Events, defined by ICD-9 codes	First Admission N=212 Kappa (95% CI)	First Admission, First Position N=198 Kappa (95% CI)	First Admission, Second Position N=14 Kappa (95% CI)
<b>All Stroke</b>	0.81 (0.74-0.89)	0.82 (0.73-0.90)	0.66 (0.25-1.00)
<i>All Stroke excluding 432.1 and 437</i>	<i>0.81 (0.72-0.89)</i>	<i>0.81 (0.72-0.90)</i>	<i>0.64 (0.21-1.00)</i>
<b>Hemorrhagic Stroke</b>	0.94 (0.88-1.00)	0.94 (0.88-1.00)	1.00
<i>Hemorrhagic Stroke excluding 432.1</i>	<i>0.94 (0.88-1.00)</i>	<i>0.94 (0.88-1.00)</i>	<i>1.00</i>
Subarachnoid (430)	0.91 (0.80-1.00)	0.91 (0.80-1.00)	1.00
Intraparenchymal (431)	0.88 (0.77-0.98)	0.87 (0.76-0.98)	1.00
Other intracranial (432)	0.50 (NA*)	0.50 (NA*)	1.00
<b>Ischemic Stroke (433, 434)</b>	0.85 (0.78-0.92)	0.86 (0.79-0.93)	0.66 (0.25-1.00)
<b>Other Stroke (437)</b>	0.75 (0.41-1.00)	0.75 (0.41-1.00)	1.00
<b>TIA (435)</b>	0.73 (0.61-0.84)	0.74 (0.63-0.85)	0.42 (NA*)
<i>*not applicable: numbers too small to reliably calculate</i>			

**Table e-4. Baseline characteristics of women 60 and under at time of enrollment (n=83,749), stratified by reported aspirin use**

	<b>Reported regular aspirin use (n=17,652)</b>	<b>Did not report regular aspirin use (n=66,097)</b>
History of preeclampsia*	940 (5.3%)	3130 (4.7%)
Median age at start of study (IQR)*	49.6 (44.4-54.1)	46.3 (38.5-52.0)
Mean age at first pregnancy (SD)*	25.3 (4.9)	25.9 (4.9)
Mean number of pregnancies at time of questionnaire 2, 1997-1998 (SD)	2.0 (1.6)	2.0 (1.5)
Self-identified race/ethnicity*		
<i>White</i>	15,736 (89.2%)	55,333 (83.7%)
<i>Black</i>	388 (2.2%)	1810 (2.7%)
<i>Hispanic</i>	650 (3.7%)	3972 (6.0%)
<i>Native American</i>	153 (0.9%)	374 (0.6%)
<i>Asian/Pacific Islander</i>	394 (2.2%)	3074 (4.7%)
<i>Other/Mixed</i>	206 (1.2%)	1094 (1.7%)
<i>Unknown</i>	125 (0.7%)	440 (0.7%)
Obesity (BMI $\geq$ 30 at baseline)*	2927 (16.6%)	8604 (13.0%)
Median baseline BMI (IQR)*	24.0 (21.5-27.9)	23.2 (21.0-26.7)
Median BMI at questionnaire 4, 2005-2006 (IQR)*	25.6 (22.6-29.7)	24.7 (22.0-28.4)
Tobacco use (former or current, on any questionnaire)*	5858 (33.2%)	17,227 (26.1%)
Migraine*	5983 (33.9%)	12,140 (18.4%)
Diabetes*	1411 (8.0%)	3525 (5.3%)
Hypertension*	2736 (15.5%)	5705 (8.6%)
Chronic kidney disease*	292 (2.7%)	673 (1.9%)
Reported regular statin use on questionnaire 4 or 5*	4761 (27.0%)	11,033 (16.7%)
<p><i>Aspirin use was reported on questionnaires 1 (1995-1996), 4 (2005-2006) and 5 (2012-2013). Women were considered to be regular aspirin users if they reported taking aspirin or an aspirin-containing medication 3 or more times per week for at least 1 year.</i></p> <p>PEC: preeclampsia. SD: standard deviation. BMI: body mass index. IQR: interquartile range. All characteristics reported at baseline unless otherwise noted. *p-value&lt;0.001</p>		

**Table e-5. Baseline characteristics of women 60 and under at time of enrollment (n=83,749), stratified by regular statin use**

	<b>Reported regular statin use (n=15,794)</b>	<b>Did not report statin use (n=67,955)</b>
History of preeclampsia*	1001 (6.3%)	3069 (4.5%)
Median age at start of study (IQR)*	51.0 (46.5-55.1)	45.9 (38.1-51.7)
Mean age at first pregnancy (SD)*	25.7 (4.8)	25.8 (4.9)
Mean number of pregnancies at time of questionnaire 2, 1997-1998 (SD)	2.1 (1.5)	2.0 (1.5)
Self-identified race/ethnicity*		
<i>White</i>	13,641 (86.4%)	57,428 (84.5%)
<i>Black</i>	393 (2.5%)	1805 (2.6%)
<i>Hispanic</i>	639 (4.1%)	3983 (5.9%)
<i>Native American</i>	109 (0.7%)	418 (0.6%)
<i>Asian/Pacific Islander</i>	753 (4.8%)	2715 (4.0%)
<i>Other/Mixed</i>	171 (1.1%)	1129 (1.7%)
<i>Unknown</i>	88 (0.6%)	477 (0.7%)
Obesity (BMI≥30 at baseline)*	2998 (19.0%)	8533 (12.6%)
Median baseline BMI (IQR)*	24.9 (22.2-28.4)	23.1 (21.0-26.6)
Median BMI at questionnaire 4, 2005-2006 (IQR)*	26.7 (23.7-30.7)	24.3 (21.8-27.9)
Tobacco use (former or current, on any questionnaire)*	5139 (32.5%)	17,946 (26.4%)
Migraine*	3850 (24.4%)	14,273 (21%)
Diabetes*	2807 (17.8%)	2129 (3.1%)
Hypertension*	2907 (18.4%)	5534 (8.1%)
Chronic kidney disease*	483 (3.6%)	482 (1.4%)
Reported regular aspirin use on questionnaires 1, 4 or 5*	4761 (30.1%)	12,891 (19.0%)
<p><i>Statin use was reported on questionnaires 4 (2005-2006) and 5 (2012-2013).</i>            PEC: preeclampsia. SD: standard deviation. BMI: body mass index. IQR: interquartile range. All characteristics reported at baseline unless otherwise noted. *p-value&lt;0.001</p>		

**Table e-6: Subgroup analysis, parous women only (n=67,185)**

<b>Risk of stroke in parous women with history of PEC compared to those without history of PEC</b>	<b>Overall stroke (HR, 95%CI)</b>	<b>Stroke before age 60 (HR, 95%CI)</b>
<b>All women</b>		
<i>Unadjusted</i>	1.4 (1.1-1.6)	1.6 (1.1-2.2)
<i>Adjusted*</i>	1.3 (1.1-1.6)	1.3 (0.9-1.8)
<b>Non aspirin users</b>		
<i>Unadjusted</i>	1.4 (1.1-1.7)	1.8 (1.2-2.6)
<i>Adjusted*</i>	1.4 (1.1-1.7)	1.4 (0.99-2.1)
<b>Aspirin users</b>		
<i>Unadjusted</i>	1.2 (0.9-1.7)	1.1 (0.5-2.4)
<i>Adjusted*</i>	1.1 (0.8-1.6)	0.9 (0.4-1.9)
<b>Non statin users</b>		
<i>Unadjusted</i>	1.3 (1.0-1.6)	1.6 (1.0-2.3)
<i>Adjusted*</i>	1.2 (0.99-1.6)	1.2 (0.8-1.8)
<b>Statin users</b>		
<i>Unadjusted</i>	1.4 (1.0-1.9)	1.8 (0.9-3.5)
<i>Adjusted*</i>	1.4 (1.0-2.0)	1.4 (0.7-2.8)
*adjusted for age, race/ethnicity, smoking, migraine, obesity, diabetes, hypertension HR: hazard ratio. PEC: preeclampsia. CI: confidence interval.		

**Table e-7. Sensitivity analysis excluding TIA, cervical artery dissections, cerebral venous thromboses, pregnancy-associated acute cerebrovascular disease**

HR and 95% CI for stroke in women aged 60 and under with history of PEC	Overall stroke	Stroke before age 60
All women		
<i>Unadjusted</i>	1.2 (0.9-1.5)	1.4 (0.96-2.1)
<i>Adjusted*</i>	1.1 (0.9-1.4)	1.1 (0.75-1.7)
Non aspirin users		
<i>Unadjusted</i>	1.3 (0.96-1.6)	1.7 (1.1-2.6)
<i>Adjusted*</i>	1.2 (0.9-1.6)	1.4 (0.9-2.1)
Aspirin users		
<i>Unadjusted</i>	1.0 (0.6-1.5)	0.8 (0.3-2.1)
<i>Adjusted*</i>	0.9 (0.6-1.4)	0.6 (0.2-1.6)
Non statin users		
<i>Unadjusted</i>	1.2 (0.9-1.5)	1.5 (1.0-2.4)
<i>Adjusted*</i>	1.1 (0.9-1.5)	1.2 (0.8-1.9)
Statin users		
<i>Unadjusted</i>	1.1 (0.7-1.7)	1.1 (0.4-2.7)
<i>Adjusted*</i>	1.1 (0.7-1.7)	0.9 (0.4-2.2)
*adjusted for age, race/ethnicity, smoking, migraine, obesity, diabetes, hypertension TIA: transient ischemic attack. HR: hazard ratio. PEC: preeclampsia. CI: confidence interval.		



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