

## Supplementary Online Content

Kurth T, Rist PM, Ridker PM, Kotler G, Bubes V, Buring JE. Association of migraine with aura and other risk factors with incident cardiovascular disease in women. *JAMA*. doi:10.1001/jama.2020.7172

### **Supplement.** eAppendix

This supplementary material has been provided by the authors to give readers additional information about their work.

## Supplemental Material

### eAppendix

#### Sensitivity analysis: Multiple imputations

The Monotone Propensity method for missing continuous, the Fully Conditional Specification Logistic method for missing ordinal variables, and the Discriminant Function method for missing nominal variables (SAS Institute Inc. 2018. SAS/STAT® 15.1 User's Guide. Cary, NC: SAS Institute Inc. Chapters 79, 80. The MI and MIANALIZE Procedures) were applied to evaluate whether handling of missing information had an influence on our results. The imputation was sufficient: the Relative Efficiency  $\geq 0.99$ . The results of 25 multiple imputation runs are summarized in **eTable 2**. The results are similar to the results of the main analyses in which we used a missing variable indicator to account for missing information.

**eTable 1.** Crude and adjusted\* incidence rates per 1000 person-years of major cardiovascular disease according to vascular risk factors in the Women’s Health Study (N=27,858).

Vascular risk factor	N	N Events	Person Years	Crude Rate	Adjusted* Rate (95% CI)	P value**
Migraine with aura	1435	110	29,956	3.67	3.36 (2.72-3.99)	<.001
No migraine with aura***	26,423	1556	550,656	2.83	2.11 (1.98-2.24)	
Diabetes	682	134	11,387	11.77	5.76 (4.68-6.84)	<.001
No diabetes	27176	1532	569,225	2.69	2.11 (1.98-2.24)	
Current smoking	3241	313	60,511	5.17	4.29 (3.79-4.79)	<.001
Not currently smoking	24,617	1353	520,101	2.60	1.97 (1.85-2.10)	
Systolic blood pressure ≥160 mmHg	318	58	5,636	10.29	3.78 (2.76-4.81)	.002
Systolic blood pressure <160 mmHg	27,540	1608	574,976	2.80	2.15 (2.02-2.28)	
Total cholesterol ≥280 mg/dL	1645	163	33,094	4.93	2.85 (2.38-3.32)	.002
Total cholesterol <280 mg/dL	26,213	1503	547,518	2.75	2.12 (1.99-2.25)	
HDL-C <40 mg/dL	4822	413	95,299	4.33	2.63 (2.33-2.94)	<.001
HDL-C ≥40 mg/dL	23,036	1253	485,313	2.58	2.07 (1.94-2.21)	
Triglycerides ≥194 mg/dL	5546	517	110,583	4.68	2.67 (2.38-2.95)	<.001
Triglycerides <194 mg/dL	22,312	1149	470,029	2.45	2.05 (1.92-2.19)	
Family history of myocardial infarction prior to age 60	3945	267	82,544	3.24	2.71 (2.38-3.05)	<.001
No family history of myocardial infarction prior to age 60	23,913	1399	498,068	2.81	2.08 (1.95-2.22)	
Body mass index ≥30 kg/m <sup>2</sup>	4939	360	100,284	3.59	2.29 (2.02-2.56)	.29
Body mass index <30 kg/m <sup>2</sup>	22,919	1306	480,328	2.72	2.13 (2.00-2.27)	

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol.

\* Adjusted for all vascular risk factors shown in the table, plus age, alcohol use, exercise, hypertensive treatment, ever hormone use, and pre-menopausal status.

\*\* P value shows contrast of the dichotomized vascular risk factors categories.

\*\*\* Includes women reporting migraine without aura and women not reporting migraine in the year prior to baseline.

**eTable 2.** Crude and adjusted\* incidence rates per 1000 person-years for total stroke according to vascular risk factors in the Women’s Health Study (N=27,858).

Vascular risk factor	N	N Events	Person Years	Crude Rate	Adjusted* Rate (95% CI)	P value**
Migraine with aura	1435	57	30,329	1.88	1.78 (1.31-2.24)	.01
No migraine with aura***	26,423	830	555,289	1.50	1.17 (1.07-1.26)	
Diabetes	682	55	11,934	4.61	2.50 (1.79-3.21)	<.001
No diabetes	27,176	832	573,684	1.45	1.17 (1.07-1.26)	
Current smoking	3241	138	61,724	2.24	1.92 (1.58-2.25)	<.001
Not currently smoking	24,617	749	523,894	1.43	1.12 (1.02-1.21)	
Systolic blood pressure ≥160 mmHg	318	28	5,796	4.83	1.94 (1.19-2.69)	.047
Systolic blood pressure <160 mmHg	27,540	859	579,822	1.48	1.18 (1.09-1.28)	
Total cholesterol ≥280 mg/dL	1645	81	33,650	2.41	1.53 (1.17-1.88)	.051
Total cholesterol <280 mg/dL	26,213	806	551,968	1.46	1.17 (1.08-1.27)	
HDL-C <40 mg/dL	4822	193	97,013	1.99	1.37 (1.14-1.59)	.08
HDL-C ≥40 mg/dL	23,036	694	488,605	1.42	1.16 (1.06-1.26)	
Triglycerides ≥194 mg/dL	5546	239	112,615	2.12	1.30 (1.10-1.49)	.21
Triglycerides <194 mg/dL	22,312	648	473,003	1.37	1.17 (1.06-1.27)	
Family history of myocardial infarction prior to age 60	3945	136	83,507	1.63	1.42 (1.18-1.67)	.04
No family history of myocardial infarction prior to age 60	23,913	751	502,111	1.50	1.16 (1.06-1.26)	
Body mass index ≥30 kg/m <sup>2</sup>	4939	178	101,445	1.76	1.24 (1.04-1.44)	.59
Body mass index <30 kg/m <sup>2</sup>	22,919	709	484,173	1.46	1.18 (1.08-1.28)	

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol.

\* Adjusted for all vascular risk factors shown in the table, plus age, alcohol use, exercise, hypertensive treatment, ever hormone use, and pre-menopausal status.

\*\* P value shows contrast of the dichotomized vascular risk factors categories.

\*\*\* Includes women reporting migraine without aura and those not reporting migraine in the year prior to baseline.

**eTable 3.** Crude and adjusted\* incidence rates per 1000 person-years for myocardial infarction according to vascular risk factors in the Women’s Health Study (N=27,858).

Vascular risk factor	N	N Events	Person Years	Crude Rate	Adjusted* Rate (95% CI)	P value**
Migraine with aura	1435	43	30,387	1.42	1.21 (0.84-1.58)	.02
No migraine with aura	26,423	586	555,777	1.05	0.77 (0.69-0.85)	
Diabetes	682	65	11,674	5.57	2.58 (1.86-3.29)	<.001
No diabetes	27176	564	574,489	0.98	0.77 (0.69-0.84)	
Current smoking	3241	150	61,325	2.45	1.92 (1.58-2.25)	<.001
Not currently smoking	24,617	479	524,838	0.91	0.70 (0.63-0.78)	
Systolic blood pressure ≥160 mmHg	318	20	5,787	3.46	1.23 (0.66-1.79)	.12
Systolic blood pressure <160 mmHg	27,540	609	580377	1.05	0.79 (0.71-0.86)	
Total cholesterol ≥280 mg/dL	1645	68	33,563	2.03	1.10 (0.81-1.38)	.02
Total cholesterol <280 mg/dL	26,213	561	552,601	1.02	0.77 (0.70-0.85)	
HDL-C <40 mg/dL	4822	191	96,484	1.98	1.10 (0.90-1.30)	<.001
HDL-C ≥40 mg/dL	23,036	438	489,680	0.89	0.74 (0.66-0.82)	
Triglycerides ≥194 mg/dL	5546	233	112,134	2.08	1.14 (0.95-1.33)	<.001
Triglycerides <194 mg/dL	22,312	396	474,030	0.84	0.72 (0.64-0.80)	
Family history of myocardial infarction prior to age 60	3945	114	83,403	1.37	1.08 (0.88-1.29)	.002
No family history of myocardial infarction prior to age 60	23,913	515	502,761	1.02	0.75 (0.67-0.83)	
Body mass index ≥30 kg/m <sup>2</sup>	4939	135	101,398	1.33	0.73 (0.58-0.87)	.33
Body mass index <30 kg/m <sup>2</sup>	22,919	494	484,766	1.02	0.80 (0.72-0.89)	

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol.

\* Adjusted for all vascular risk factors shown in the table, plus age, alcohol use, exercise, hypertensive treatment, ever hormone use, and pre-menopausal status.

\*\* P value shows contrast of the dichotomized vascular risk factors categories. \*\*\* Includes women reporting migraine without aura and those not reporting migraine in the year prior to baseline.

**eTable 4.** Crude and adjusted\* incidence rates per 1000 person-years for death due to cardiovascular disease according to vascular risk factors in the Women’s Health Study (N=27,858).

Vascular risk factor	N	N Events	Person Years	Crude Rate	Adjusted* Rate (95% CI)	P value**
Migraine with aura	1435	22	32,695	0.67	0.46 (0.26-0.65)	.07
No migraine with aura***	26,423	369	596,658	0.62	0.28 (0.23-0.33)	
Diabetes	682	40	13,431	2.98	0.85 (0.54-1.16)	<.001
No diabetes	27176	351	615,922	0.57	0.28 (0.23-0.33)	
Current smoking	3241	77	68,457	1.13	0.69 (0.52-0.87)	<.001
Not currently smoking	24,617	314	560,896	0.56	0.25 (0.21-0.30)	
Systolic blood pressure ≥160 mmHg	318	20	6,542	3.06	0.54 (0.28-0.79)	.048
Systolic blood pressure <160 mmHg	27,540	371	622,811	0.60	0.28 (0.24-0.33)	
Total cholesterol ≥280 mg/dL	1645	40	36,762	1.09	0.36 (0.23-0.49)	.21
Total cholesterol <280 mg/dL	26,213	351	592,591	0.59	0.28 (0.23-0.33)	
HDL-C <40 mg/dL	4822	93	106,409	0.87	0.31 (0.22-0.39)	.57
HDL-C ≥40 mg/dL	23,036	298	522,944	0.57	0.28 (0.23-0.33)	
Triglycerides ≥194 mg/dL	5546	124	123,244	1.01	0.34 (0.26-0.42)	.09
Triglycerides <194 mg/dL	22,312	267	506,109	0.53	0.27 (0.23-0.32)	
Family history of myocardial infarction prior to age 60	3945	54	89,926	0.60	0.35 (0.25-0.46)	.13
No family history of myocardial infarction prior to age 60	23,913	337	539,427	0.63	0.28 (0.23-0.32)	
Body mass index ≥30 kg/m <sup>2</sup>	4939	96	110,248	0.87	0.38 (0.28-0.48)	.02
Body mass index <30 kg/m <sup>2</sup>	22,919	295	519,105	0.57	0.27 (0.22-0.32)	

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol.

\* Adjusted for all vascular risk factors shown in the table, plus age, alcohol use, exercise, hypertensive treatment, ever hormone use, and pre-menopausal status.

\*\* P value shows contrast of the dichotomized vascular risk factors categories. \*\*\* Includes women reporting migraine without aura and those not reporting migraine in the year prior to baseline.

**eTable 5.** Adjusted\* incidence rate per 1000 person-years for major cardiovascular disease according to vascular risk factors in the Women’s Health Study (N=27,858) using 25 multiple imputations runs to account for missing information.

<b>Vascular risk factor</b>	<b>Mean (95% CI)</b>	<b>Minimum</b>	<b>Maximum</b>	<b>CV</b>
Migraine with aura	3.360 (3.359-3.361)	3.334	3.366	0.086
Diabetes	5.749 (5.745-5.753)	5.728	5.761	0.162
Current smoking	4.304 (4.300-4.308)	4.291	4.322	0.232
Systolic blood pressure $\geq$ 160 mmHg	3.765 (3.752-3.778)	3.718	3.836	0.831
Total cholesterol $\geq$ 280 mg/dL	2.848 (2.847-2.850)	2.842	2.854	0.112
HDL-C <40 mg/dL	2.636 (2.635-2.637)	2.630	2.639	0.092
Triglycerides $\geq$ 194 mg/dL	2.670 (2.669-2.671)	2.668	2.674	0.067
Family history of myocardial infarction prior to age 60	2.705 (2.696-2.714)	2.670	2.749	0.829
Body mass index $\geq$ 30 kg/m <sup>2</sup>	2.291 (2.289-2.293)	2.285	2.301	0.198

CV = coefficient of variation.

\* Adjusted for all vascular risk factors (dichotomous) shown in the table, plus age, alcohol use, exercise, hypertensive treatment, ever hormone use, and pre-menopausal status.

**eTable 6.** Adjusted\* incidence rates per 1000 person-years for major cardiovascular disease according to vascular risk factors in the Women’s Health Study (N=27,858), using different reference groups.

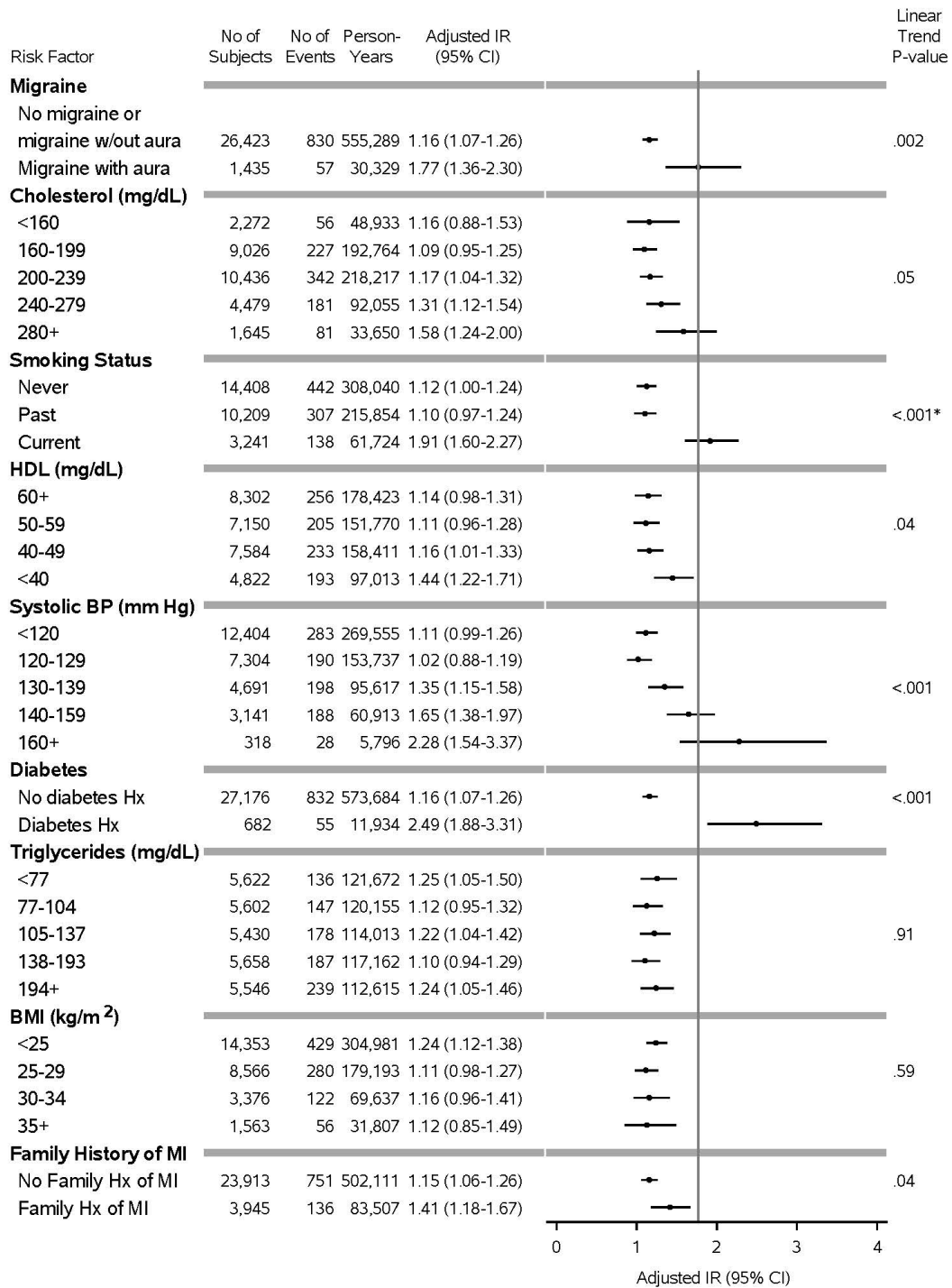
Vascular risk factor	Reference group includes migraine without aura, those with no history of migraine, and those never reported migraine (N=27,858)		Reference group includes only women who never reported migraine (N=24,163)	
	Adjusted* Rate (95% CI)	P value**	Adjusted* Rate (95% CI)	P value**
Migraine with aura	3.36 (2.72-3.99)	-	3.38 (2.74-4.02)	--
Diabetes	5.76 (4.68-6.84)	<.001	5.68 (4.55-6.82)	<.001
Current smoking	4.29 (3.79-4.79)	.02	4.23 (3.70-4.77)	.04
Systolic blood pressure ≥160 mmHg	3.78 (2.76-4.81)	.48	3.73 (2.64-4.82)	.58
Total cholesterol ≥280 mg/dL	2.85 (2.38-3.32)	.19	3.04 (2.51-3.56)	.40
HDL-C <40 mg/dL	2.63 (2.33-2.94)	.04	2.52 (2.20-2.84)	.01
Triglycerides ≥194 mg/dL	2.67 (2.38-2.95)	.043	2.70 (2.39-3.00)	.048
Family history of myocardial infarction prior to age 60	2.71 (2.38-3.05)	.07	2.62 (2.26-2.97)	.03
Body mass index ≥30 kg/m <sup>2</sup>	2.29 (2.02-2.56)	.001	2.34 (2.04-2.63)	.002

\* Adjusted for all vascular risk factors (dichotomous) listed in the table, plus age, alcohol use, exercise, hypertensive treatment, ever hormone use, and pre-menopausal status.

\*\* P value from a t-test examines whether the adjusted incidence rate among those with migraine with aura differs statistically from the adjusted incidence rate of the other vascular risk factor.

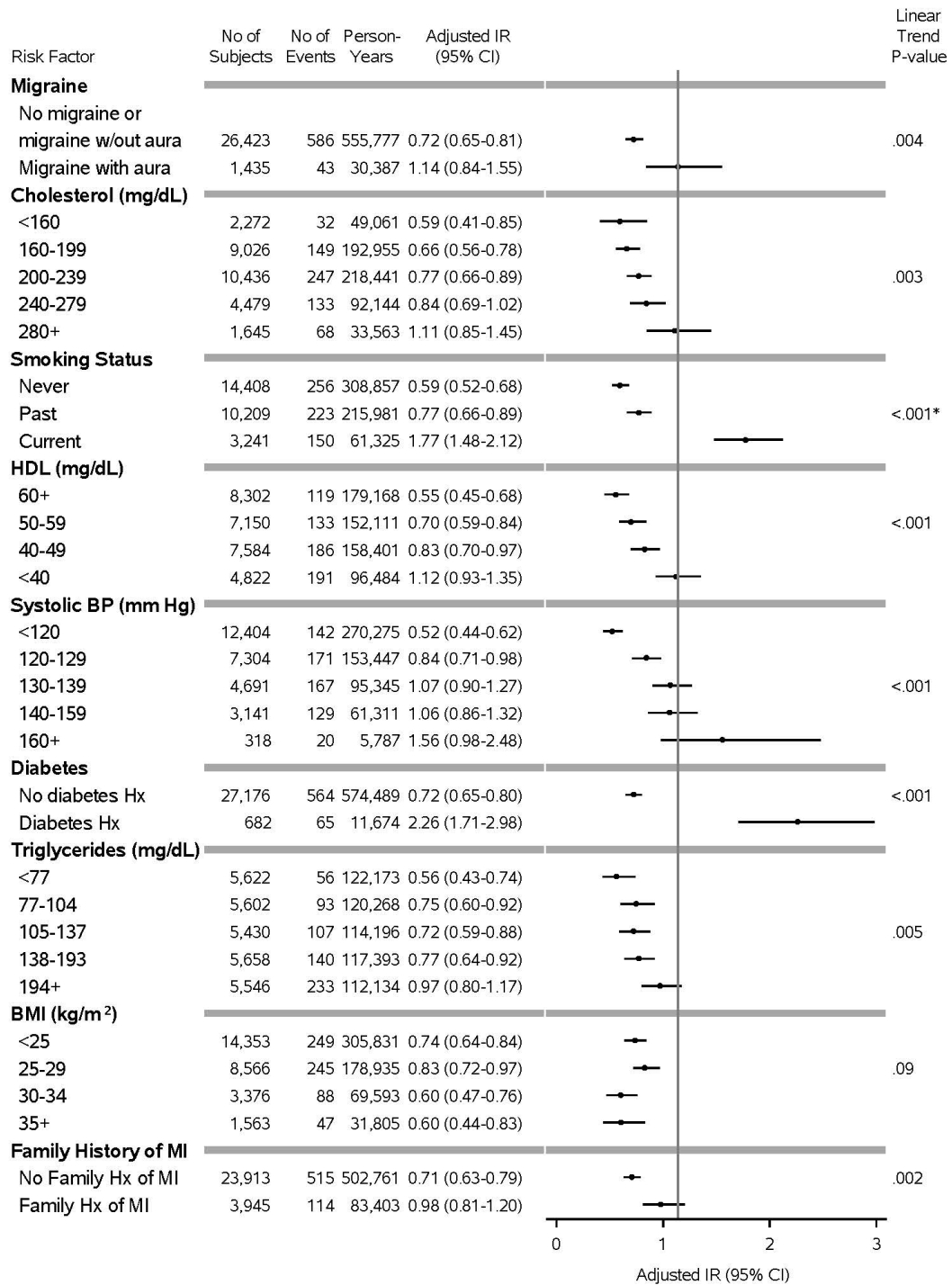


**Adjusted Incidence Rate for Total Stroke per 1000 Person-Years**

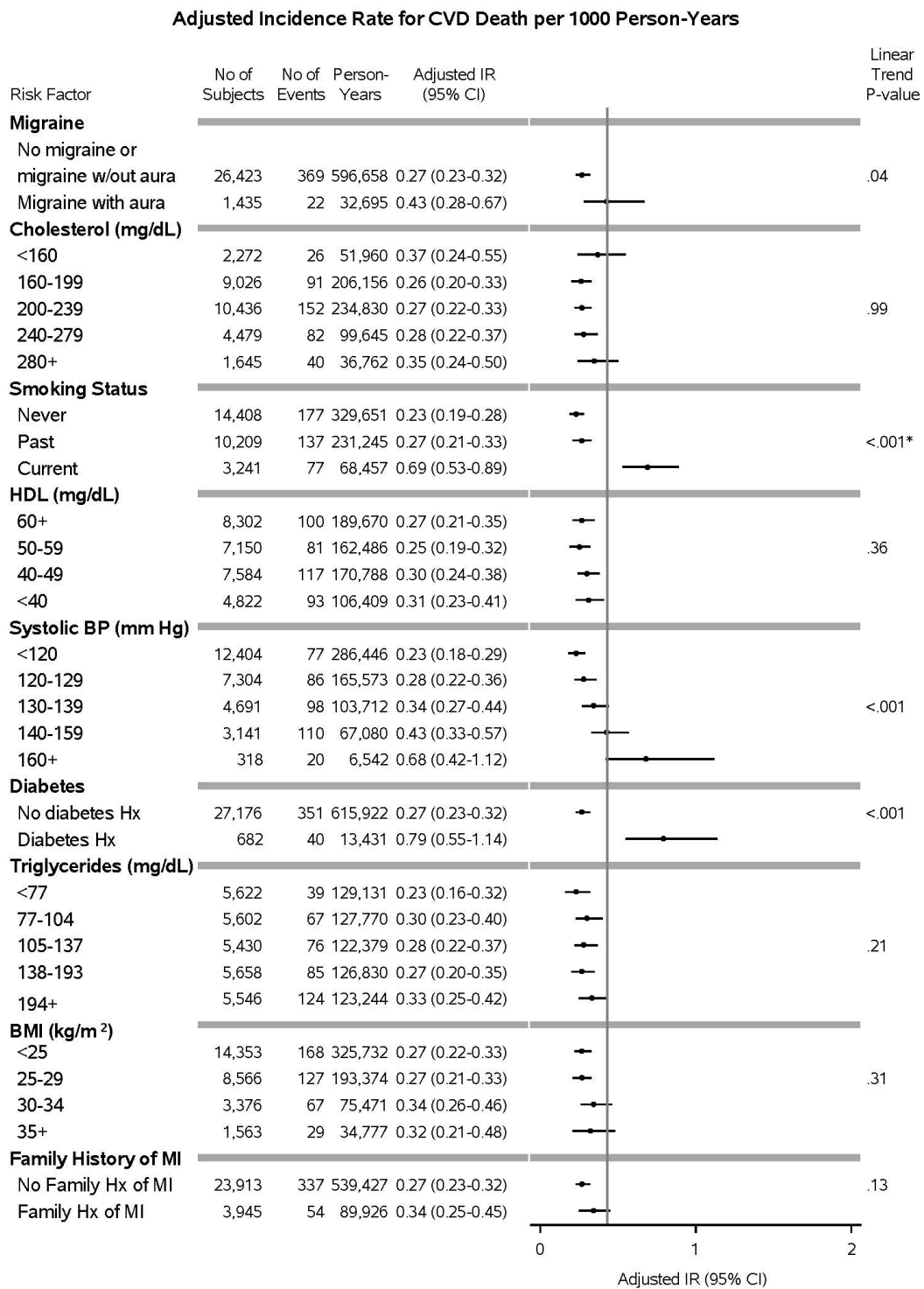


**eFigure 1.** The vertical line indicates the adjusted incidence rate for migraine with aura. Values to the left of the vertical line indicate lower and values to the right higher adjusted incident rates of total stroke compared to the incidence rate of migraine with aura. IR = incidence rate; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; BP = blood pressure; MI= myocardial infarction. Adjusted all vascular risk factors shown in the figure and age, alcohol use, exercise, hypertensive treatment, ever hormone use, and pre-menopausal status. Because two different approaches were used for categorizing covariates in the multivariable models, the estimated adjusted incidence rates differ slightly in eFigure 1 (in which some covariates were categorized as polychotomous) and Table 2 (in which all covariates were categorized as dichotomous). P values for trend across risk marker categories.  
\*P value was calculated using a chi-square test.

**Adjusted Incidence Rate for Myocardial Infarction per 1000 Person-Years**



**eFigure 2.** The vertical line indicates the adjusted incidence rate for migraine with aura. Values to the left of the vertical line indicate lower and values to the right higher adjusted incident rates of myocardial infarction compared to the incidence rate of migraine with aura. IR = incidence rate; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; BP = blood pressure; MI= myocardial infarction. Adjusted for all vascular risk factors shown in the figure and age, alcohol use, exercise, hypertensive treatment, ever hormone use, and pre-menopausal status. Because two different approaches were used for categorizing covariates in the multivariable models, the estimated adjusted incidence rates differ slightly in eFigure 2 (in which some covariates were categorized as polychotomous) and Table 2 (in which all covariates were categorized as dichotomous). P values for trend across risk marker categories. \*P value was calculated using a chi-square test.



**eFigure 3.** The vertical line indicates the adjusted incidence rate for migraine with aura. Values to the left of the vertical line indicate lower and values to the right higher adjusted incident rates of CVD death compared to the incidence rate of migraine with aura. CVD = cardiovascular disease; IR = incidence rate; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; BP = blood pressure; MI= myocardial infarction. Adjusted for all vascular risk factors shown in the figure and age, alcohol use, exercise, hypertensive treatment, ever hormone use, and pre-menopausal status. Because two different approaches were used for categorizing covariates in the multivariable models, the estimated adjusted incidence rates differ slightly in eFigure 3 (in which some covariates were categorized as polychotomous) and Table 2 (in which all covariates were categorized as dichotomous). P values for trend across risk marker categories.

\*P value was calculated using a chi-square test.