



Supplementary Material

Article Title: Risk of First Onset Stroke in SSRI-Exposed Adult Subjects: Survival Analysis and Examination of Age and Time Effects

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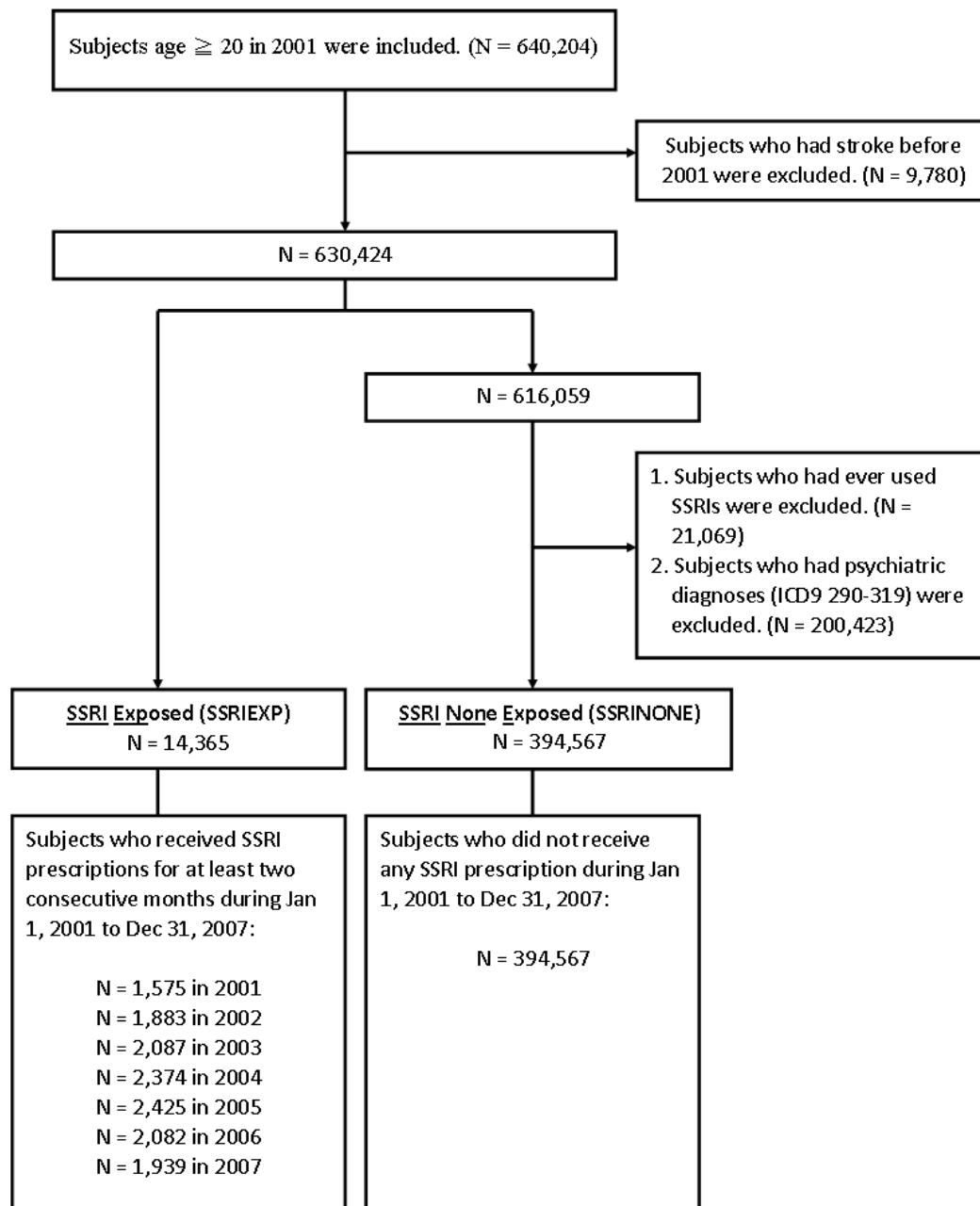
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eFigure 1

Sampling Procedures



eTable 1. Proportion of stroke event between SSRIEXP and SSRINONE subjects, as compared by age, sex, medication and diseases contributing to the risk of all stroke events. P values for the χ^2 tests are shown at right column. Significant values are in bold.

Variable	Total		SSRINONE		SSRIEXP		P value
	n = 408,932		n=394,567		n = 14,365		
	n	%	n	%	n	%	
Age (year)							
20-29	116,851	28.6	114,880	29.1	1,971	13.7	<0.001
30-39	111,457	27.3	107,943	27.4	3,514	24.5	
40-49	91,066	22.3	87,710	22.2	3,356	23.4	
50-59	44,312	10.8	41,856	10.6	2,456	17.1	
60-69	27,536	6.7	26,020	6.6	1,516	10.6	
70+	17,710	4.3	16,158	4.1	1,552	10.8	
Sex							
Female	190,078	46.5	181,018	45.9	9,060	63.1	<0.001
Male	218,854	53.5	213,549	54.1	5,305	36.9	
Stroke							
No	396,784	97.0	383,376	97.2	13,408	93.3	<0.001
Yes	12,148	3.0	11,191	2.8	957	6.7	
AF							
No	408,506	99.9	394,212	99.91	14,294	99.51	<0.001
Yes	426	0.1	355	0.09	71	0.49	
MI							
No	407,883	99.7	393,689	99.8	14,194	98.8	<0.001
Yes	1,049	0.3	878	0.2	171	1.2	
CHF							
No	407,355	99.6	393,228	99.7	14,127	98.3	<0.001
Yes	1,577	0.4	1,339	0.3	238	1.7	
AP							
No	400,774	98.0	387,695	98.3	13,079	91.1	<0.001
Yes	8,158	2.0	6,872	1.7	1,286	9.0	

PAD								
No		408,872	99.99	394,519	99.99	14,353	99.92	<0.001
Yes		60	0.01	48	0.01	12	0.08	
DM								
No		399,012	97.6	385,565	97.7	13,447	93.6	<0.001
Yes		9,920	2.4	9,002	2.3	918	6.4	
Hyperlipidemia								
No		394,781	96.5	382,027	96.8	12,754	88.8	<0.001
Yes		14,151	3.5	12,540	3.2	1,611	11.2	
Hypertension								
No		382,815	93.6	371,247	94.1	11,568	80.5	<0.001
Yes		26,117	6.4	23,320	5.9	2,797	19.5	
Renal diseases								
No		408,088	99.80	393,847	99.82	14,241	99.14	<0.001
Yes	CKD	422	0.10	359	0.09	63	0.44	
	ESRD	422	0.10	361	0.09	61	0.42	
Aspirin								
No		394,400	96.5	381,244	96.6	13,156	91.6	<0.001
Yes		14,532	3.6	13,323	3.4	1,209	8.4	
Heparin								
No		408,384	99.87	394,160	99.90	14,224	99.02	<0.001
Yes		548	0.13	407	0.10	141	0.98	
Warfarin								
No		408,526	99.9	394,216	99.91	14,310	99.62	<0.001
Yes		406	0.1	351	0.09	55	0.38	
NSAIDs								
No		182,808	44.7	179,258	45.4	3,550	24.7	<0.001
Yes		226,124	55.3	215,309	54.6	10,815	75.3	

Abbreviations: AF = atrial fibrillation, AP = angina pectoris, CHF = congestive heart failure, CKD = chronic kidney disease, DM = diabetes mellitus, ESRD = end-stage

renal disease, MI = myocardial infarction, NSAIDs = nonsteroidal anti-inflammatory drugs, PAD = peripheral artery disease, SSRI = selective serotonin reuptake inhibitor, SSRIEXP = SSRI exposed, SSRINONE = SSRI none exposed.

eTable 2. Ischemic stroke.

Variable	Total n = 409,819		SSRINONE n=395,164		SSRIEXP n = 14,655		P value
	N	%	n	%	n	%	
Age (year)							
20-29	116,872	28.52	114,896	29.08	1,976	13.48	<0.001
30-39	111,499	27.21	107,965	27.32	3,534	24.11	
40-49	91,177	22.25	87,785	22.21	3,392	23.15	
50-59	44,484	10.85	41,977	10.62	2,507	17.11	
60-69	27,783	6.78	26,201	6.63	1,582	10.79	
70+	18,004	4.39	16,340	4.13	1,664	11.35	
Sex							
Female	190,420	46.46	181,222	45.86	9,198	62.76	<0.001
Male	219,399	53.54	213,942	54.14	5,457	37.24	
Stroke							
No	399,347	97.44	385,554	97.57	13,793	94.12	<0.001
Yes	10,472	2.56	9,610	2.43	862	5.88	
AF							
No	409,380	99.89	394,801	99.91	14,579	99.48	<0.001
Yes	439	0.11	363	0.09	76	0.52	
MI							
No	408,745	99.74	394,268	99.77	14,477	98.79	<0.001
Yes	1,074	0.26	896	0.23	178	1.21	
CHF							
No	408,200	99.6	393,799	99.65	14,401	98.27	<0.001
Yes	1,619	0.4	1,365	0.35	254	1.73	
AP							
No	401,521	97.98	388,202	98.24	13,319	90.88	<0.001
Yes	8,298	2.02	6,962	1.76	1,336	9.12	
PAD							
No	409,755	99.98	395,114	99.99	14,641	99.9	<0.001

Yes	64	0.02	50	0.01	14	0.1	
DM							
No	399,733	97.54	386,050	97.69	13,683	93.37	<0.001
Yes	10,086	2.46	9,114	2.31	972	6.63	
Hyperlipidemia							
No	395,540	96.52	382,548	96.81	12,992	88.65	<0.001
Yes	14,279	3.48	12,616	3.19	1,663	11.35	
Hypertension							
No	383,154	93.49	371,444	94	11,710	79.9	<0.001
Yes	26,665	6.51	23,720	6	2,945	20.1	
Renal disease							
No	408,960	99.79	394,436	99.82	14,524	99.11	<0.001
Yes	CKD	431	0.11	365	0.09	66	0.45
	ESRD	428	0.1	363	0.09	65	0.44
Aspirin							
No	395,030	96.39	381,656	96.58	13,374	91.26	<0.001
Yes	14,789	3.61	13,508	3.42	1,281	8.74	
Heparin							
No	409,246	99.86	394,745	99.89	14,501	98.95	<0.001
Yes	573	0.14	419	0.11	154	1.05	
Warfarin							
No	409,393	99.9	394,797	99.91	14,596	99.6	<0.001
Yes	426	0.1	367	0.09	59	0.4	
NSAIDs							
No	183,113	44.68	179,487	45.42	3,626	24.74	<0.001
Yes	226,706	55.32	215,677	54.58	11,029	75.26	

Abbreviations: AF = atrial fibrillation, AP = angina pectoris, CHF = congestive heart failure, CKD = chronic kidney disease, DM = diabetes mellitus, ESRD = end-stage renal disease, MI = myocardial infarction, NSAIDs = nonsteroidal anti-inflammatory

drugs, PAD = peripheral artery disease, SSRIEXP = selective serotonin reuptake inhibitor exposed, SSRINONE = selective serotonin reuptake inhibitor none exposed.

eTable 3. Hemorrhagic stroke.

Variable	Total n = 413,485		SSRINONE n=395,164		SSRIEXP n = 16,543		P value
	N	%	n	%	n	%	
Age (year)							
20-29	116879	28.27	114892	28.94	1987	12.01	<0.001
30-39	111541	26.98	107984	27.2	3557	21.5	
40-49	91403	22.11	87890	22.14	3513	21.24	
50-59	45057	10.9	42268	10.65	2789	16.86	
60-69	28818	6.97	26779	6.75	2039	12.33	
70+	19787	4.79	17129	4.32	2658	16.07	
Sex							
Female	192154	46.47	181942	45.84	10212	61.73	<0.001
Male	221331	53.53	215000	54.16	6331	38.27	
Stroke							
No	411284	99.47	394903	99.49	16381	99.02	<0.001
Yes	2201	0.53	2039	0.51	162	0.98	
AF							
No	412921	99.86	396536	99.9	16385	99.04	<0.001
Yes	564	0.14	406	0.1	158	0.96	
MI							
No	412277	99.71	395998	99.76	16279	98.4	<0.001
Yes	1208	0.29	944	0.24	264	1.6	
CHF							
No	411620	99.55	395495	99.64	16125	97.47	<0.001
Yes	1865	0.45	1447	0.36	418	2.53	
AP							
No	404221	97.76	389591	98.15	14630	88.44	<0.001
Yes	9264	2.24	7351	1.85	1913	11.56	
PAD							
No	413399	99.98	396882	99.98	16517	99.84	<0.001

Yes		86	0.02	60	0.02	26	0.16	
DM								
No		402417	97.32	387328	97.58	15089	91.21	<0.001
Yes		11068	2.68	9614	2.42	1454	8.79	
Hyperlipidemia								
No		398267	96.32	383896	96.71	14371	86.87	<0.001
Yes		15218	3.68	13046	3.29	2172	13.13	
Hypertension								
No		384269	92.93	371922	93.7	12347	74.64	<0.001
Yes		29216	7.07	25020	6.3	4196	25.36	
Renal disease								
No		412537	99.77	396195	99.81	16342	98.78	<0.001
Yes	CKD	481	0.12	379	0.10	102	0.62	
	ESRD	467	0.11	368	0.09	99	0.60	
Aspirin								
No		396797	95.96	382381	96.33	14416	87.14	<0.001
Yes		16688	4.04	14561	3.67	2127	12.86	
Heparin								
No		412790	99.83	396485	99.88	16305	98.56	<0.001
Yes		695	0.17	457	0.12	238	1.44	
Warfarin								
No		412909	99.86	396494	99.89	16415	99.23	<0.001
Yes		576	0.14	448	0.11	128	0.77	
NSAID								
No		184079	44.52	180079	45.37	4000	24.18	<0.001
Yes		229406	55.48	216863	54.63	12543	75.82	

Abbreviations: AF = atrial fibrillation, AP = angina pectoris, CHF = congestive heart failure, CKD = chronic kidney disease, DM = diabetes mellitus, ESRD = end-stage renal disease, MI = myocardial infarction, NSAIDs = nonsteroidal anti-inflammatory

drugs, PAD = peripheral artery disease, SSRIEXP = selective serotonin reuptake inhibitor exposed, SSRINONE = selective serotonin reuptake inhibitor none exposed.

eTable 4. Cox proportion hazard regression model of stroke controlling for major depression and other variables (n = 609,355).

variable	Hazard Ratio	95% CI		P value
		Lower	Upper	
SSRIs (Use/ Non-use)	1.48	1.38	1.60	<0.001
Age (10 years)	1.08	1.07	1.08	<0.001
Sex (Male/ Female)	1.24	1.21	1.26	<0.001
Major depression (Yes/ No)	1.13	1.00	1.29	0.0589
Diabetes (Yes/ No)	1.77	1.72	1.83	<0.001
Hypertension (Yes/ No)	1.81	1.77	1.86	<0.001
Hyperlipidemia (Yes/ No)	1.19	1.15	1.23	<0.001
Renal disease				
CKD (Yes/ No)	1.23	1.08	1.40	0.0022
ESRD (Yes/ No)	2.04	1.73	2.41	<0.001

This dataset included patients with major depression before January 1, 2001 to account its effect from the beginning of the follow-up period so that a possible bias by indication of selective serotonin reuptake inhibitors can be examined.

Abbreviations: SSRIs = selective serotonin reuptake inhibitors, CKD = chronic kidney disease, ESRD = end-stage renal disease.