

Supplementary Material

Targeting the Beta-2-Adrenergic Receptor and the Risk of Developing Alzheimer's Disease: A Retrospective Inception Cohort Study

Supplementary Table 1. List of ATC codes [1].

Drug	ATC codes
Exposure Drug	
Selective Beta-2-adrenoreceptor agonists:	R03AC, R03CC
Salbutamol	R03AC02, R03CC02
Terbutaline	R03AC03, R03CC03
Salmeterol	R03AC12
Formoterol	R03AC13
Indacaterol	R03AC18
Olodaterol	R03AC19
Beta blocking agents, non-selective	C07AA
Pindolol	C07AA03
Propranolol	C07AA05
Sotalol	C07AA07
Reference Drug	
Drugs for the cardiovascular system	C
Cardiac therapy	C01
Antihypertensives	C02
Diuretics	C03
Peripheral Vasodilators	C04
Vasoprotectives	C05
Beta Blocking agents	C07
Selective beta-blocking agents	C07AB
Calcium channel blockers	C08
Agents acting on RAAS	C09
Drugs for obstructive airway diseases	R03
Adrenergics, Inhalants	R03A
Other drugs for obstructive airway diseases, inhalants	R03B
Adrenergics for systemic use	R03C
Other systemic drugs for obstructive airway diseases	R03D
Drugs proxy for AD	
Cholinesterase inhibitors	N06DA
Rivastigmine	N06DA02
Galantamine	N06DA03
Donepezil	N06DA04
Other anti-dementia drugs	N06DX
Memantine	N06DX01

Drugs proxy for Comorbidity

Diabetes	A10
High cholesterol levels	C10
Depression	N06A
High blood pressure	C02, C03, C07, C08, C09
Respiratory disease	R01, R02, R03, R05, R06, R07
Anti-Parkinson	N04
Beta-blocking agents, sensory organs	S01ED

REFERENCE

- [1] WHO Collaborating Centre for Drug Statistics Methodology (2020) ATC/DD index. https://www.whocc.no/atc_ddd_index/ Last updated December 14, Accessed November 17, 2020.

Supplementary Table 2. Overview of the referent drugs included in the analysis [1].

Exposed group 1 Matched to:		Exposed group 2 Matched to:		
Non-exposed group 1A	Non-exposed group 1B	Non-exposed group 2A	Non-exposed group 2B	
Referent drug	Selective β AR Antagonists (C07AB)	Drugs for the cardiovascular system (C01 C02, C03, C04, C05, C08, C09)	Drugs for obstructive airway diseases (R03B and/or R03D)	Drugs for the cardiovascular system (C01 C02, C03, C04, C05, C08, C09)
Not using	Non-selective β AR Antagonists (C07AA)	Beta-Blocking agents (C07)		
Adrenergics (inhalants or for systemic use) (R03A & R03C)				

Supplementary Table 3. β 2-adrenoreceptor agonists included in the analysis and the number of older adults exposed.

β -adrenoreceptor drug	Exposed cohort 2A (n=314) ^b (N), (%)	Exposed cohort 2B (n=593) (N), (%)
β 2-Agonists ^a		
Short acting β -agonists	250, (79.6%)	476, (80.3%)
Salbutamol	236, (75.2%)	455, (76.7%)
Terbutaline	14, (4.46%)	20, (3.37%)
Long acting β -agonists	62, (19.7%)	121, (20.4%)
Salmeterol	31, (9.87%)	62, (10.5%)
Formoterol	31, (9.87%)	58, (9.78%)
Ultra-long acting β -agonists	0, (0.00%)	1, (0.17%)
Indacaterol	0, (0.00%)	0, (0.00%)
Olodaterol	0, (0.00%)	1, (0.17%)

^aOne patient can be exposed to multiple non-selective β -agonists.

^bTwo individuals did not meet the exposure criteria to assign them to a specific drug (Exposure was defined as three or more prescriptions of the specific drug within the first year after the index date). Therefore, the sum of exposed cohort 2A sums up to n=312 instead of n=314.

Supplementary Table 4. Life tables of subjects exposed to non-selective β -antagonists and matched controls.

Interval start time	Exposed cohort 1A		Non-exposed cohort 1A		Exposed cohort 1B		Non-exposed cohort 1B	
	Number withdrawing during interval	Proportion still at risk	Number withdrawing during interval	Proportion still at risk	Number withdrawing during interval	Proportion still at risk	Number withdrawing during interval	Proportion still at risk
0	0	1.00	0	1.00	0	1.00	0	1.00
365	47	1.00	111	1.00	47	1.00	160	1.00
730	37	1.00	106	1.00	37	1.00	121	1.00
1,095	21	1.00	100	1.00	21	1.00	102	1.00
1,460	37	1.00	135	1.00	37	1.00	102	1.00
1,825	40	1.00	148	1.00	40	1.00	109	1.00
2,190	45	1.00	98	1.00	45	1.00	93	1.00
2,555	35	0.99	100	1.00	35	0.99	81	1.00
2,920	24	0.99	80	1.00	24	0.99	48	1.00
3,285	32	0.99	105	1.00	32	0.99	76	1.00
3,650	23	0.99	97	1.00	23	0.99	66	0.99
4,015	22	0.99	70	1.00	22	0.99	36	0.99
4,380	22	0.98	51	0.99	22	0.98	35	0.99
4,745	17	0.98	60	0.99	17	0.98	35	0.99
5,110	34	0.98	80	0.99	34	0.98	47	0.99
5,475	336	0.98	991	0.99	335	0.98	439	0.99

Supplementary Table 5. Life tables of subjects exposed to selective β -agonists and matched controls.

Interval start time	Exposed cohort 2A		Non-exposed cohort 2A		Exposed cohort 2B		Non-exposed cohort 2B	
	Number withdrawing during interval	Proportion still at risk	Number withdrawing during interval	Proportion still at risk	Number withdrawing during interval	Proportion still at risk	Number withdrawing during interval	Proportion still at risk
0	0	1.00	0	1.00	0	1.00	0	1.00
365	26	1.00	46	1.00	52	1.00	291	1.00
730	19	1.00	30	1.00	32	1.00	212	1.00
1,095	19	1.00	29	1.00	37	1.00	189	1.00
1,460	23	1.00	30	1.00	50	1.00	233	1.00
1,825	28	1.00	39	1.00	53	1.00	185	1.00
2,190	27	1.00	25	1.00	48	1.00	144	1.00
2,555	19	1.00	23	1.00	34	1.00	110	1.00
2,920	8	1.00	9	1.00	11	1.00	89	0.99
3,285	30	1.00	14	0.99	36	1.00	166	0.99
3,650	15	1.00	9	0.99	23	1.00	84	0.99
4,015	9	1.00	11	0.99	16	1.00	65	0.99
4,380	10	1.00	7	0.96	16	1.00	51	0.99
4,745	3	1.00	1	0.96	11	1.00	40	0.99
5,110	6	1.00	6	0.96	14	1.00	69	0.98
5,475	11	1.00	4	0.93	20	0.99	56	0.98
5,840	11	1.00	2	0.93	19	0.99	45	0.98
6,205	2	1.00	4	0.93	12	0.99	33	0.98
6,570	10	0.98	6	0.93	26	0.98	100	0.98
6,935	37	0.98	16	0.93	81	0.98	194	0.98