## **Supplementary Material**

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

<b>Supplementary Tal</b>	le 1. List of ATC codes [	1]	
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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     C       Drugs for the cardiovascular system     C       Cardiac therapy     C01       Antihypertensives     C02       Diurectics     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     R03C       Other systemic drugs for obstructive airway diseases     R03C       Other systemic drugs for obstructive airway diseases     R03C       Other systemic dr	<b>Supplementary Table 1.</b> List of ATC codes [1].	
Selective Beta-2-adrenoreceptor agonists:  Salbutamol R03ACQ2, R03CCQ2 Terbutaline R03AC012 Formoterol R03AC12 Formoterol R03AC13 Indacaterol R03AC18 Olodaterol R03AC19 Beta blocking agents, non-selective Pindolol Propranolol C07AA Pindolol Propranolol Sotalol  Reference Drug  Drugs for the cardiovascular system Cardiac therapy Antihypertensives C03 Peripheral Vasodilators Vasoprotectives C05 Beta Blocking agents C07 Selective beta-blocking agents C07 Selective beta-blocking agents C07 Selective beta-blocking agents C09 Drugs for obstructive airway diseases Adrenergics, Inhalants Adrenergics for systemic use Other systemic drugs for obstructive airway diseases C06 Drugs proxy for AD Cholinesterase inhibitors Rivastigmine R06DA03 Donepezil R03ACQ2 R03ACQ3 R03ACQ3 R03ACQ3 R03ACQ2 R03ACQ2 R03ACQ2 R03ACQ2 R03ACQ3 R03ACQ3 R03ACQ3 R03ACQ3 R04DA02 R04DA03 R06DA03 R06DA04	Drug	ATC codes
Salbutamol R03AC02, R03CC02 Terbutaline R03AC03, R03CC03 Salmeterol R03AC12 Formoterol R03AC13 Indacaterol R03AC13 Indacaterol R03AC18 Olodaterol R03AC19 Beta blocking agents, non-selective C07AA Pindolol C07AA03 Propranolol C07AA07  Reference Drug  Drugs for the cardiovascular system C Cardiac therapy C01 Antihypertensives C02 Diurectics C03 Peripheral Vasodilators C07 Selective beta-blocking agents C07 Selective beta-blocking agents C07 Selective beta-blocking agents C07 Agents acting on RAAS C09 Drugs for obstructive airway diseases R03 Adrenergics, Inhalants R03A Other drugs for obstructive airway diseases R03 Other systemic drugs for obstructive airway diseases Drugs proxy for AD Cholinesterase inhibitors N06DA0 Rivastigmine N06DA03 Donepezil N06DA04	Exposure Drug	
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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 Diurectics C03 Peripheral Vasodilators C05 Beta Blocking agents C07 Selective beta-blocking agents C07 Selective beta-blocking agents C07 Calcium channel blockers C08 Agents acting on RAAS C09 Drugs for obstructive airway diseases R03 Adrenergics, Inhalants Adrenergics for systemic use R03C Other systemic drugs for obstructive airway diseases R03D  Drugs proxy for AD Cholinesterase inhibitors N06DA02 Galantamine N06DA03 Donepezil N06DA04	Salbutamol	R03AC02, R03CC02
Formoterol R03AC13 Indacaterol R03AC18 Olodaterol R03AC19 Beta blocking agents, non-selective C07AA Pindolol C07AA05 Sotalol C07AA07  Reference Drug  Drugs for the cardiovascular system C Cardiac therapy C01 Antihypertensives C02 Diurectics C03 Peripheral Vasodilators C05 Beta Blocking agents C07 Selective beta-blocking agents C07 Calcium channel blockers C08 Agents acting on RAAS C09 Drugs for obstructive airway diseases R03 Adrenergics, Inhalants Adrenergics for systemic use R03C Other systemic drugs for obstructive airway diseases R03D  Drugs proxy for AD Cholinesterase inhibitors N06DA02 Galantamine N06DA03 Donepezil N06DA04	Terbutaline	R03AC03, R03CC03
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 Diurectics C03 Peripheral Vasodilators C05 Beta Blocking agents C07 Selective beta-blocking agents C07 Selective beta-blocking agents C07 Selective beta-blocking agents C08 Agents acting on RAAS C09 Drugs for obstructive airway diseases R03 Adrenergics, Inhalants R03B Adrenergics for systemic use R03C Other systemic drugs for obstructive airway diseases R03D  Drugs proxy for AD Cholinesterase inhibitors N06DA02 Galantamine N06DA03 Donepezil N06DA04	Salmeterol	R03AC12
Olodaterol Beta blocking agents, non-selective Pindolol Propranolol CO7AA05 Sotalol CO7AA07  Reference Drug  Drugs for the cardiovascular system Cardiac therapy Antihypertensives Co2 Diurectics Co3 Peripheral Vasodilators Vasoprotectives Co4 Vasoprotectives Co5 Beta Blocking agents Co7 Selective beta-blocking agents Calcium channel blockers Agents acting on RAAS Co9 Drugs for obstructive airway diseases, inhalants Adrenergics, Inhalants Adrenergics for systemic use Other systemic drugs for obstructive airway diseases Ro3  Drugs proxy for AD Cholinesterase inhibitors Rivastigmine Ro4 Rivastigmine No6DA03 Ro5 Ro5 Ro5 Ro5 RO7AA07  CO7AA07  CO1 CO1 CO2 CO2 CO3 CO2 CO3 CO3 CO4 CO4 CO4 CO5 CO5 CO5 CO6 CO7 CO7 CO7 CO7 CO8 CO8 CO9	Formoterol	R03AC13
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Propranolol Sotalol C07AA07  Reference Drug  Drugs for the cardiovascular system Cardiac therapy C01 Antihypertensives C02 Diurectics C03 Peripheral Vasodilators Vasoprotectives C05 Beta Blocking agents C107 Selective beta-blocking agents C107 Selective beta-blocking agents C107 Selective beta-blocking agents C108 Agents acting on RAAS C109  Drugs for obstructive airway diseases Adrenergics, Inhalants Other drugs for obstructive airway diseases, inhalants Adrenergics for systemic use Other systemic drugs for obstructive airway diseases  Drugs proxy for AD  Cholinesterase inhibitors Rivastigmine N06DA02 Galantamine N06DA03 Donepezil N06DA04	Beta blocking agents, non-selective	C07AA
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Vasoprotectives Beta Blocking agents C07 Selective beta-blocking agents Calcium channel blockers Agents acting on RAAS Coppure for obstructive airway diseases Adrenergics, Inhalants Other drugs for obstructive airway diseases, inhalants Adrenergics for systemic use Other systemic drugs for obstructive airway diseases  Drugs proxy for AD Cholinesterase inhibitors Rivastigmine N06DA02 Galantamine N06DA03 Donepezil N06DA04	* -	C03
Beta Blocking agents  Selective beta-blocking agents  Calcium channel blockers  Agents acting on RAAS  Cross  Drugs for obstructive airway diseases  Adrenergics, Inhalants  Other drugs for obstructive airway diseases, inhalants  Adrenergics for systemic use  Other systemic drugs for obstructive airway diseases  Proceedings  Ross  Ross  Ross  Ross  Ross  Ross  Ross  Ross  Condense for systemic use  Ross  Ross  Ross  Condense for systemic use  Ross  Ross	Peripheral Vasodilators	C04
Selective beta-blocking agents Calcium channel blockers Agents acting on RAAS Crop Drugs for obstructive airway diseases Adrenergics, Inhalants Other drugs for obstructive airway diseases, inhalants Adrenergics for systemic use Other systemic drugs for obstructive airway diseases Ro3C Other systemic drugs for obstructive airway diseases  Crop  Ro3A  Ro3B  Ro3B  Ro3C  Other systemic drugs for obstructive airway diseases Ro3D  Cholinesterase inhibitors Rivastigmine No6DA  Rivastigmine No6DA02  Galantamine No6DA03  Donepezil No6DA04	Vasoprotectives	C05
Calcium channel blockers Agents acting on RAAS C09 Drugs for obstructive airway diseases R03 Adrenergics, Inhalants R03A Other drugs for obstructive airway diseases, inhalants Adrenergics for systemic use R03C Other systemic drugs for obstructive airway diseases R03D  Drugs proxy for AD Cholinesterase inhibitors Rivastigmine N06DA02 Galantamine N06DA03 Donepezil N06DA04	Beta Blocking agents	C07
Agents acting on RAAS  Drugs for obstructive airway diseases  Adrenergics, Inhalants  Other drugs for obstructive airway diseases, inhalants  Adrenergics for systemic use  Other systemic drugs for obstructive airway diseases  Other systemic drugs for obstructive airway diseases  Prugs proxy for AD  Cholinesterase inhibitors  Rivastigmine  N06DA0  Rivastigmine  N06DA03  Donepezil  N06DA04	Selective beta-blocking agents	C07AB
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Adrenergics, Inhalants Other drugs for obstructive airway diseases, inhalants Adrenergics for systemic use R03C Other systemic drugs for obstructive airway diseases R03D  Prugs proxy for AD Cholinesterase inhibitors Rivastigmine N06DA02 Galantamine N06DA03 Donepezil N06DA04	Agents acting on RAAS	C09
Other drugs for obstructive airway diseases, inhalants Adrenergics for systemic use Other systemic drugs for obstructive airway diseases  R03C Other systemic drugs for obstructive airway diseases  R03D  Drugs proxy for AD Cholinesterase inhibitors N06DA Rivastigmine N06DA02 Galantamine N06DA03 Donepezil N06DA04	Drugs for obstructive airway diseases	R03
Adrenergics for systemic use Other systemic drugs for obstructive airway diseases  Prugs proxy for AD Cholinesterase inhibitors Rivastigmine Rivastigmine N06DA02 Galantamine N06DA03 Donepezil N06DA04	Adrenergics, Inhalants	R03A
Other systemic drugs for obstructive airway diseases R03D  Drugs proxy for AD Cholinesterase inhibitors N06DA Rivastigmine N06DA02 Galantamine N06DA03 Donepezil N06DA04	Other drugs for obstructive airway diseases, inhalants	R03B
Drugs proxy for ADCholinesterase inhibitorsN06DARivastigmineN06DA02GalantamineN06DA03DonepezilN06DA04	Adrenergics for systemic use	R03C
Cholinesterase inhibitors  Rivastigmine  Galantamine  Donepezil  N06DA  N06DA02  N06DA03  N06DA03	Other systemic drugs for obstructive airway diseases	R03D
Cholinesterase inhibitors  Rivastigmine  Galantamine  Donepezil  N06DA  N06DA02  N06DA03  N06DA03	Drugs proxy for AD	
Galantamine N06DA03 Donepezil N06DA04		N06DA
Galantamine N06DA03 Donepezil N06DA04	Rivastigmine	N06DA02
1		N06DA03
Other anti-dementia drugs N06DY	Donepezil	N06DA04
Office affir-definentia drugs	Other anti-dementia drugs	N06DX
Memantine N06DX01	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 <b>9</b> Matche	- ·	Exposed group 2  Matched to:				
	Non-exposed group 1A	Non-exposed group 1B	Non-exposed group 2A	Non-exposed group 2B			
Referent drug	Selective βAR 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 βAR Antagonists (C07AA)	Be	eta-Blocking agents (C	707)			
	Adrenergics (inhalants or for systemic use) (R03A & R03C)						

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

β-adrenoreceptor drug	Exposed cohort 2A	Exposed cohort 2B		
	$(n=314)^b (N), (\%)$	(n=593) (N), (%)		
β2-Agonists <sup>a</sup>				
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%)		

 $<sup>{}^{</sup>a}\text{One}$  patient can be exposed to multiple non-selective  $\beta$ -agonists.

b Two 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  $\beta$ -antagonists and matched controls.

	Exposed col	nort 1A N	on-exposed coh	ort 1A	Exposed coho	rt 1B	Non-exposed	cohort 1B
Interval	Number	Proportion	Number	Proportion	Number	Proportion	Number	Proportion
start	withdrawing	still at risk	withdrawing	still at risk	withdrawing	still at risk	withdrawing	still at risk
time	during		during		during		during	
	interval		interval		interval		interval	
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  $\beta$ -agonists and matched controls.

	Exposed co	hort 2A	Non-exposed	cohort 2A	Exposed c	ohort 2B	Non-exposed	l cohort 2B
Interval	Number	Proportion	Number	Proportion	Number	Proportion	Number	Proportion
start	withdrawing	still at risk						
time	during		during		during		during	
	interval		interval		interval		interval	
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