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: |                         |
| Salbutamol                                | R03AC02, R03CC02        |
| Terbutaline                               | R03AC03, R03CC03        |
| Salmeterol                                | R03AC12                 |
| Formoterol                                | R03AC13                 |
| Indacaterol                               | R03AC18                 |
| Olodaterol                                | R03AC19                 |
| Beta blocking agents, non-selective       |                         |
| 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     |                         |
| 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                 |
| Drug                                      | ATC Code(s)          |
|-------------------------------------------|----------------------|
| 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].

| Referent drug                                      | 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 βAR Antagonists   | 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) |
|                                                    | (C07AB)                     |                             |                             |                             |
| Not using                                          | Non-selective βAR Antagonists (C07AA) |                             |                             |                             |
|                                                    | Beta-Blocking agents (C07)   |                             |                             |                             |
|                                                    | Adrenergics (inhaled or for systemic use) (R03A & R03C) |                             |                             |                             |
### Supplementary Table 3. β2-adrenoreceptor agonists included in the analysis and the number of older adults exposed.

| β2-adrenoreceptor drug | Exposed cohort 2A (n=314)\(^{b}\) (N), (%) | Exposed cohort 2B (n=593) (N), (%) |
|------------------------|---------------------------------------------|-----------------------------------|
| **β2-Agonists\(^a\)**  |                                             |                                   |
| Short acting β-agonists|                                             |                                   |
| Salbutamol             | 250, (79.6%)                                | 476, (80.3%)                      |
| Terbutaline            | 236, (75.2%)                                | 455, (76.7%)                      |
| Long acting β-agonists |                                             |                                   |
| Salmeterol             | 14, (4.46%)                                 | 20, (3.37%)                       |
| Formoterol             | 62, (19.7%)                                 | 121, (20.4%)                      |
| Ultra-long acting β-agonists |                                             |                                   |
| Indacaterol            | 31, (9.87%)                                 | 62, (10.5%)                       |
| Olodaterol             | 31, (9.87%)                                 | 58, (9.78%)                       |

\(^{a}\)One patient can be exposed to multiple non-selective β-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 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 |
|                     | Number withdrawing during interval | Proportion still at risk | Number withdrawing during interval | Proportion still at risk |
| 0                   | 0                  | 1.00                  | 0                 | 1.00                  |
| 365                 | 47                 | 1.00                  | 111               | 1.00                  |
| 730                 | 37                 | 1.00                  | 106               | 1.00                  |
| 1,095               | 21                 | 1.00                  | 100               | 1.00                  |
| 1,460               | 37                 | 1.00                  | 135               | 1.00                  |
| 1,825               | 40                 | 1.00                  | 148               | 1.00                  |
| 2,190               | 45                 | 1.00                  | 98                | 1.00                  |
| 2,555               | 35                 | 0.99                  | 100               | 1.00                  |
| 2,920               | 24                 | 0.99                  | 80                | 1.00                  |
| 3,285               | 32                 | 0.99                  | 105               | 1.00                  |
| 3,650               | 23                 | 0.99                  | 97                | 1.00                  |
| 4,015               | 22                 | 0.99                  | 70                | 1.00                  |
| 4,380               | 22                 | 0.98                  | 51                | 0.99                  |
| 4,745               | 17                 | 0.98                  | 60                | 0.99                  |
| 5,110               | 34                 | 0.98                  | 80                | 0.99                  |
| 5,475               | 336                | 0.98                  | 991               | 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 |