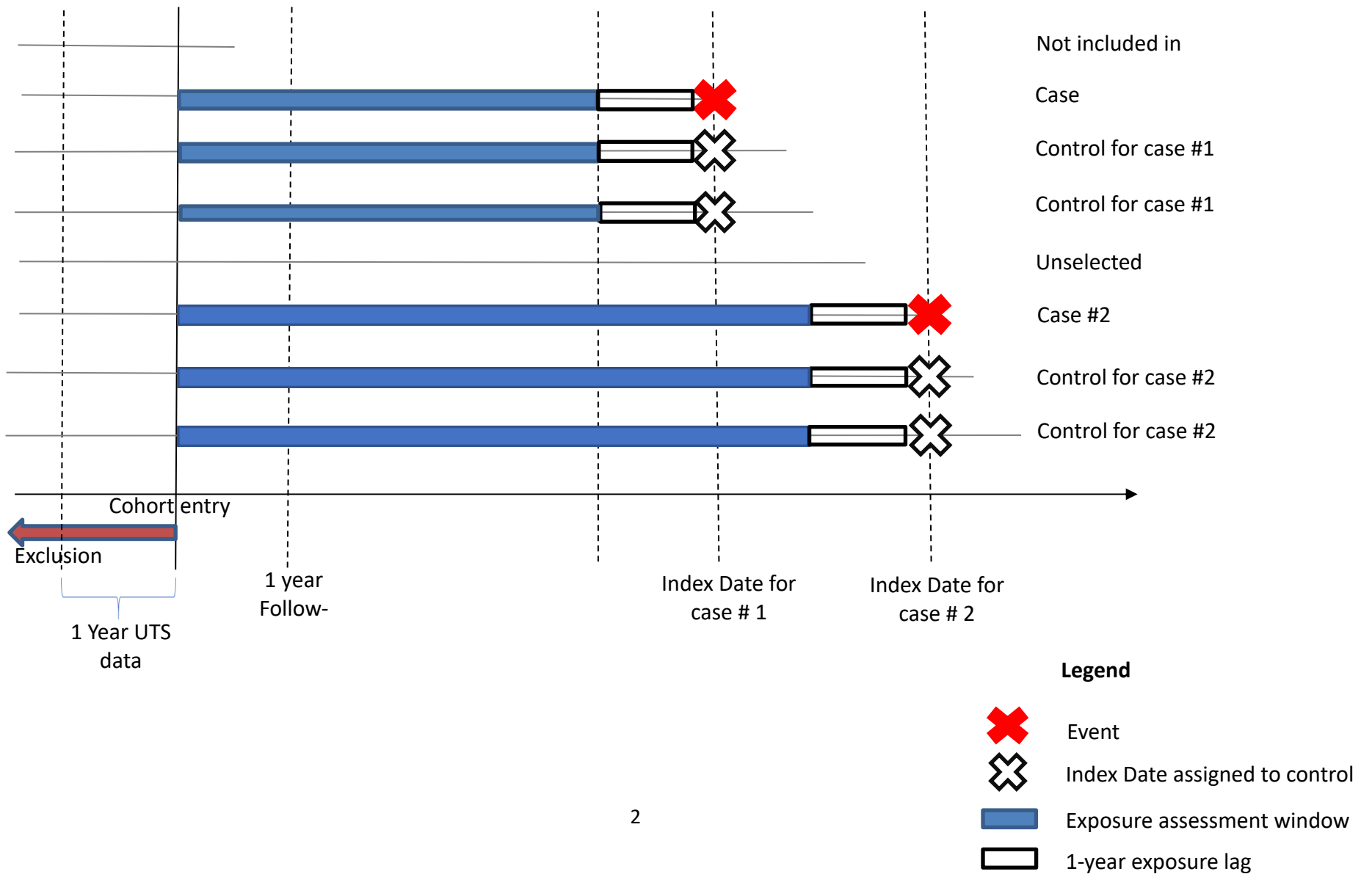Web Material

# β2-agonists and the incidence of Parkinson disease

Francesco Giorgianni, Pierre Ernst, Sophie Dell'Aniello, Samy Suissa, and Christel Renoux

**Web Figure 1. Cohort formation and case control selection**



Not included in

Case

Control for case #1

Control for case #1

Unselected

Case #2

Control for case #2

Control for case #2

Cohort entry

Exclusion

1 Year UTS data

1 year Follow-

Index Date for case # 1

Index Date for case # 2

**Legend**

✖ Event

✖ Index Date assigned to control

▬ Exposure assessment window

☐ 1-year exposure lag

2

**Web Table 1. Crude and adjusted rate ratios of Parkinson's disease associated with ever use of beta 2 agonists, stratified by short- and long-acting and by route of administration, United Kingdom, 1995-2016**

| Exposure | Cases n (%) | Controls[a] n (%) | Crude RR | Adjusted RR (95% CI)[b] |
|---|---|---|---|---|
| No use | 7,972 (92.7) | 78,646 (91.4) | 1.00 | 1.00 (Reference) |
| **Short acting beta 2 agonists** | 620 (7.2) | 7,195 (8.4) | 0.85 | 0.83 (0.76 - 0.92) |
| | | | | |
| Cumulative duration of use | | | | |
|    < 3 months | 254 (3.0) | 2,933 (3.4) | 0.85 | 0.81 (0.71 - 0.92) |
|    3 - 24 months | 237 (2.8) | 2,816 (3.3) | 0.83 | 0.82 (0.71 - 0.94) |
|    > 24 months | 129 (1.5) | 1,446 (1.7) | 0.87 | 0.97 (0.79 - 1.19) |
| | | | | |
| No use | 7,972 (92.7) | 78,646 (91.4) | 1.00 | 1.00 (Reference) |
| **Long acting beta2 agonists** | 157 (1.8) | 1,865 (2.3) | 0.82 | 0.89 (0.74 - 1.08) |
| | | | | |
| Cumulative duration of use | | | | |
|    < 3 months | 25 (0.3) | 349 (0.4) | 0.70 | 0.70 (0.46 - 1.05) |
|    3 months - 24 months | 60 (0.7) | 737 (0.9) | 0.80 | 0.86 (0.65 - 1.14) |
|    > 24 months | 72 (0.8) | 779 (1.0) | 0.90 | 1.05 (0.80 - 1.38 |
| | | | | |
| No use | 7,972 (92.7) | 78,646 (91.4) | 1.00 | 1.00 (Reference) |
| **Inhaled beta 2 agonists** | 588 (6.8) | 6,887 (8.0) | 0.84 | 0.83 (0.75 - 0.91) |
| | | | | |
| Cumulative duration of use | | | | |
|    < 3 months | 224 (2.6) | 2,505 (2.9) | 0.88 | 0.83 (0.73 - 0.96) |
|    3 - 24 months | 209 (2.4) | 2,653 (3.1) | 0.77 | 0.76 (0.66 - 0.89) |
|    > 24 months | 155 (1.8) | 1,729 (2.0) | 0.88 | 0.97 (0.80 - 1.17) |
| | | | | |
| No use | 7,972 (92.7) | 78,646 (91.4) | 1.00 | 1.00 (Reference) |
| **Oral beta 2 agonists** | 62 (0.7) | 773 (0.9) | 0.79 | 0.75 (0.58 – 0.98) |
| | | | | |
| Cumulative duration of use | | | | |
|    < 3 months | 47 (0.5) | 541 (0.6) | 0.85 | 0.81 (0.60 - 1.09) |
|    > 3 months | 15 (0.2) | 232 (0.3) | 0.64 | 0.62 (0.36 - 1.04) |

Abbreviations: RR, rate ratio; CI, confidence interval.

[a] Cases and controls were matched on age, sex, date of cohort entry, and duration of follow-up.

[b] Adjusted for variables listed in table 1, and use of beta blockers, respiratory antimuscarinic drugs and use of other beta 2 agonists.

**Web Table 2. Crude and adjusted rate ratios of Parkinson's disease associated with ever use of beta 2 agonists compared with no use using a 60-day grace period, United Kingdom, 1995-2016**

| Exposure | Cases n (%) | Controls[a] n (%) | Crude RR | Adjusted RR (95% CI)[b] |
|---|---|---|---|---|
| **Cumulative duration of use** | | | | |
| < 3 months | 82 (1.0) | 822 (1.0) | 0.98 | 0.93 (0.74 - 1.17) |
| 3 - 24 months | 380 (4.4) | 4678 (5.4) | 0.80 | 0.77 (0.69 - 0.86) |
| > 24 months | 170 (2.0) | 1894 (2.2) | 0.88 | 0.96 (0.80 - 1.15) |

Abbreviations: RR, rate ratio; CI, confidence interval.

[a] Cases and controls were matched on age, sex, date of cohort entry, and duration of follow-up.

[b] Adjusted for variables listed in table 1, and use of beta blockers and respiratory antimuscarinic drugs.

**Web Table 3. Crude and adjusted rate ratios of Parkinson's disease associated with ever use of beta 2 agonists compared with no-use with exposure defined as at least 4 prescriptions within 1 year, United Kingdom, 1995-2016**

| Exposure | Cases n (%) | Controls[a] n (%) | Crude RR | Adjusted RR (95% CI)[b] |
|---|---|---|---|---|
| No use | 8,378 (97.4) | 83,300 (96.8) | 1.00 | 1.00 (Reference) |
| At least 4 beta 2 agonist prescriptions within one year | 226 (2.6) | 2,740 (3.2) | 0.82 | 0.89 (0.76 - 1.05) |

Abbreviations: RR, rate ratio; CI, confidence interval.

[a] Cases and controls were matched on age, sex, date of cohort entry, and duration of follow-up.

[b] Adjusted for variables listed in table 1, and use of beta blockers and respiratory antimuscarinic drugs.

**Web Table 4. Crude and adjusted rate ratios of Parkinson's disease associated with ever use of beta 2 agonists compared with no-use, varying the duration of SABA prescriptions with unknown duration, United Kingdom, 1995-2016**

| Exposure | Cases n (%) | Controls[a] n (%) | Crude RR | Adjusted RR (95% CI)[b] |
|---|---|---|---|---|
| **Cumulative duration of use, assuming as-needed SABA prescriptions to last 1 month** | | | | |
| Beta 2 agonists | | | | |
| < 3 months | 273 (3.2) | 3020 (3.5) | 0.89 | 0.84 (0.74 - 0.96) |
| 3 - 24 months | 214 (2.5) | 2812 (3.3) | 0.75 | 0.74 (0.64 - 0.86) |
| > 24 months | 145 (1.7) | 1562 (1.8) | 0.91 | 1.01 (0.83 - 1.23) |
| | | | | |
| SABA[c] | | | | |
| < 3 months | 269 (3.1) | 3065 (3.6) | 0.86 | 0.82 (0.72 - 0.93) |
| 3 -24 months | 242 (2.8) | 2899 (3.4) | 0.82 | 0.82 (0.72 - 0.94) |
| > 24 months | 109 (1.3) | 1231 (1.4) | 0.87 | 0.97 (0.78 - 1.21) |
| | | | | |
| **Cumulative duration of use, assuming as-needed SABA prescriptions to last 6 months** | | | | |
| Beta 2 agonists | | | | |
| < 3 months | 93 (1.1) | 960 (1.1) | 0.95 | 0.90 (0.73 - 1.12) |
| 3 - 24 months | 353 (4.1) | 4,258 (4.9) | 0.81 | 0.78 (0.70 - 0.88) |
| > 24 months | 186 (2.2) | 2,176 (2.5) | 0.84 | 0.90 (0.76 - 1.07) |
| | | | | |
| SABA[c] | | | | |
| < 3 months | 85 (1.0) | 905 (1.1) | 0.92 | 0.88 (0.70 - 1.10) |
| 3 -24 months | 361 (4.2) | 4,313 (5.0) | 0.82 | 0.80 (0.71 - 0.89) |
| > 24 months | 174 (2.0) | 1,977 (2.3) | 0.86 | 0.93 (0.78 - 1.10) |

Abbreviations: SABA, short-acting beta2 agonist; RR, rate ratio; CI, confidence interval.
[a] Cases and controls were matched on age, sex, date of cohort entry, and duration of follow-up.
[b] Adjusted for variables listed in table 1, and use of beta blockers and respiratory antimuscarinic drugs.
[c] Adjusted for other beta 2 agonists.

**Web Table 5. Crude and adjusted rate ratios of Parkinson's disease associated with ever use of beta 2 agonists compared with no-use using a stricter case definition[a], United Kingdom, 1995-2016**

| Exposure | Cases n (%) | Controls[b] n (%) | Crude RR | Adjusted RR (95% CI)[c] |
|---|---|---|---|---|
| No use | 6,954 (92.6) | 68,359 (91.0) | 1.00 | 1.00 (Reference) |
| Beta 2 agonists | 558 (7.4) | 6,761 (9.0) | 0.81 | 0.80 (0.73 - 0.89) |
| | | | | |
| Cumulative duration of use | | | | |
| < 3 months | 230 (3.1) | 2,647 (3.5) | 0.85 | 0.81 (0.70 - 0.93) |
| 3 -24 months | 194 (2.6) | 2,449 (3.3) | 0.77 | 0.77 (0.66 - 0.89) |
| > 24 months | 134 (1.8) | 1,665 (2.2) | 0.78 | 0.87 (0.71 - 1.07) |

Abbreviations: RR, rate ratio; CI, confidence interval.
[a] Cases of Parkinson's disease restricted to those with at least 2 prescriptions for antiparkinson drugs along with PD diagnosis within one year.
[b] Cases and controls were matched on age, sex, date of cohort entry, and duration of follow-up.
[c] Adjusted for variables listed in table 1, and use of beta blockers and respiratory antimuscarinic drugs.

**Web Table 6. Crude and adjusted rate ratios of Parkinson's disease associated with ever use of beta 2 agonists compared with no use using multiple imputation for missing values for BMI and smoking, United Kingdom, 1995-2016**

| Exposure | Cases n (%) | Controls[a] n (%) | Crude RR | Adjusted RR (95% CI)[b] |
|---|---|---|---|---|
| No use | 7,972 (92.7) | 78,646 (91.4) | 1.00 | 1.00 (Reference) |
| Beta 2 agonists | 632 (7.3) | 7,394 (8.6) | 0.84 | 0.83 (0.76 - 0.91) |
| | | | | |
| Cumulative duration of use | | | | |
| < 3 months | 257 (3.0) | 2,896 (3.4) | 0.87 | 0.83 (0.73 - 0.95) |
| 3 – 24 months | 219 (2.5) | 2,762 (3.2) | 0.78 | 0.77 (0.66 - 0.89) |
| > 24 months | 156 (1.8) | 1,736 (2.0) | 0.88 | 0.98 (0.81 - 1.18) |

Abbreviations: BMI, body mass index; RR, rate ratio; CI, confidence interval.

[a] Cases and controls were matched on age, sex, date of cohort entry, and duration of follow-up.

[b] Adjusted for variables listed in table 1, and use of beta blockers and respiratory antimuscarinic drugs.

**Web Table 7. Crude and adjusted rate ratios of Parkinson's disease associated with ever use of salbutamol compared with no use, United Kingdom, 1995-2016**

| Exposure | Cases n (%) | Controls[a] n (%) | Crude RR | Adjusted RR (95% CI)[b] |
|---|---|---|---|---|
| No use | 7,972 (92.7) | 78,646 (91.4) | 1.00 | 1.00 (Reference) |
| Salbutamol | 569 (6.6) | 6,597 (7.7) | 0.85 | 0.84 (0.76 - 0.92) |
| | | | | |
| Cumulative duration of use | | | | |
| < 3 months | 226 (2.6) | 2,610 (3.0) | 0.85 | 0.81 (0.71 - 0.93) |
| 3 - 24 months | 220 (2.6) | 2,628 (3.1) | 0.82 | 0.82 (0.71 - 0.95) |
| > 24 months | 123 (1.4) | 1,359 (1.6) | 0.89 | 0.99 (0.80 - 1.22) |
| | | | | |
| No use | 8,378 (97.4) | 83,300 (96.8) | 1.00 | 1.00 (Reference) |
| At least 4 prescriptions of salbutamol in one year | 181 (2.1) | 2,214 (2.6) | 0.85 | 0.89 (0.75 - 1.06) |

Abbreviations: RR, rate ratio; CI, confidence interval.

[a] Cases and controls were matched on age, sex, date of cohort entry, and duration of follow-up.

[b] Adjusted for variables listed in table 1, and use of beta blockers, respiratory antimuscarinic drugs, and other beta 2 agonists.

**Web Table 8. Crude and adjusted rate ratios of Parkinson's disease associated with ever use of respiratory antimuscarinic drugs compared with no use, United Kingdom, 1995-2016**

| Exposure | Cases n (%) | Controls[a] n (%) | Crude RR | Adjusted RR (95% CI)[b] |
|---|---|---|---|---|
| No use | 8,492 (98.7) | 84,513 (98.2) | 1.00 | 1.00 (Reference) |
| Antimuscarinics | 112 (1.3) | 1,527 (1.8) | 0.73 | 0.88 (0.71 - 1.08) |
| | | | | |
| Cumulative duration of use | | | | |
| &lt; 3 months | 29 (0.3) | 380 (0.4) | 0.76 | 0.83 (0.57 - 1.23) |
| 3 - 24 months | 49 (0.6) | 610 (0.7) | 0.80 | 0.98 (0.72 - 1.32) |
| &gt; 24 months | 34 (0.4) | 537 (0.6) | 0.63 | 0.79 (0.55 - 1.13) |
| | | | | |
| No use | 8,535 (99.2) | 85,079 (98.9) | 1.00 | 1.00 (Reference) |
| At least 4 antimuscarinic prescriptions in one year | 69 (0.8) | 961 (1.1) | 0.71 | 0.90 (0.70 - 1.17) |

Abbreviations: RR, rate ratio; CI, confidence interval.

[a] Cases and controls were matched on age, sex, date of cohort entry, and duration of follow-up.

[b] Adjusted for variables listed in table 1, and use of beta blockers and beta 2 agonists.

**Web Table 9. Crude and adjusted rate ratios of Parkinson's disease associated with ever use of beta-blockers compared with no use using different lag times, United Kingdom, 1995-2016**

| Exposure | Cases n (%)) | Controls[a] n (%) | Crude RR | Adjusted RR (95% CI)[b] |
|---|---|---|---|---|
| **With a 2-year exposure lag** | | | | |
| Non use | 6,257 (80.9) | 65,703 (85.0) | 1.00 | 1.00 (Reference) |
| Beta-blockers | 1,475 (19.1) | 11,617 (15.0) | 1.37 | 1.34 (1.25 - 1.43) |
| | | | | |
| Cumulative duration of use | | | | |
| < 1 year | 616 (8.0) | 4,258 (5.5) | 1.54 | 1.49 (1.36 - 1.63) |
| 1 - 5 years | 587 (7.6) | 4,700 (6.1) | 1.34 | 1.31 (1.20 - 1.44) |
| > 5 years | 272 (3.5) | 2,659 (3.4) | 1.11 | 1.09 (0.95 - 1.25) |
| **With a 3-year exposure lag** | | | | |
| Non use | 5,708 (82.4) | 59,383 (85.7) | 1.00 | 1.00 (Reference) |
| Beta-blockers | 1,220 (17.6) | 9,897 (14.3) | 1.31 | 1.28 (1.19 - 1.37) |
| | | | | |
| Cumulative duration of use | | | | |
| < 1 year | 514 (7.4) | 3,671 (5.3) | 1.47 | 1.43 (1.30 - 1.58) |
| 1 - 5 years | 490 (7.1) | 4,124 (6.0) | 1.26 | 1.23 (1.11 - 1.36) |
| > 5 years | 216 (3.1) | 2,102 (3.0) | 1.10 | 1.08 (0.93 - 1.25) |
| **With a 5-year exposure lag** | | | | |
| Non use | 6,891 (89.1) | 70,210 (90.1) | 1.00 | 1.00 (Reference) |
| Beta-blockers | 841 (10.9) | 7,110 (9.2) | 1.23 | 1.22 (1.12 - 1.32) |
| | | | | |
| Cumulative duration of use | | | | |
| <1 year | 369 (4.8) | 2,785 (3.6) | 1.37 | 1.35 (1.20 - 1.51) |
| 1 - 5 years | 349 (4.5) | 3,118 (4.0) | 1.16 | 1.15 (1.02 - 1.29) |
| > 5 years | 123 (1.6) | 1,207 (1.6) | 1.07 | 1.06 (0.87 - 1.29) |

RR, rate ratio; CI, confidence interval.

[a] Cases and controls were matched on age, sex, date of cohort entry, and duration of follow-up.

[b] Adjusted for variables listed in table 1, and use of beta 2 agonists and respiratory antimuscarinic drugs.