

[APPENDICES]

Appendix 1. Association between propulsives exposure within 1 year and parkinsonism

| Propulsives | n (%) | | OR (95% CI) | |
|-------------------|--------------------|-----------------------|------------------------|--------------------------------------|
| | Cases (n=5,496) | Controls (n=5,496) | Matched | Matched and adjusted ^a |
| Any propulsives | | | | |
| Never use | 1,792 (32.61) | 2,290 (41.67) | 1.000 (reference) | 1.000 (reference) |
| Use within 1 year | 3,704 (67.39) | 3,206 (58.33) | 1.600 (1.467–1.745) | 1.663 (1.519–1.820) |
| Levosulpiride | | | | |
| Never use | 3,536 (64.34) | 3,981 (72.43) | 1.000 (reference) | 1.000 (reference) |
| Use within 1 year | 1,960 (35.66) | 1,515 (27.57) | 1.504 (1.381–1.638) | 1.555 (1.421–1.701) |
| Mosapride | | | | |
| Never use | 3,944 (71.76) | 4,295 (78.15) | 1.000 (reference) | 1.000 (reference) |
| Use within 1 year | 1,552 | 1,201 | 1.492 (1.357–1.640) | 1.476 |

| | | | | |
|-----------------------|---------|---------|---------------|---------------|
| | (28.24) | (21.85) | | (1.336–1.630) |
| Metoclopramide | | | | |
| Never use | 4,227 | 4,474 | 1.000 | 1.000 |
| | (76.91) | (81.40) | (reference) | (reference) |
| Use within 1 year | 1,269 | 1,022 | 1.345 | 1.368 |
| | (23.09) | (18.60) | (1.221–1.482) | (1.234–1.516) |
| Domperidone | | | | |
| Never use | 4,280 | 4,489 | 1.000 | 1.000 |
| | (77.87) | (81.68) | (reference) | (reference) |
| Use within 1 year | 1,216 | 1,007 | 1.279 | 1.310 |
| | (22.13) | (18.32) | (1.162–1.407) | (1.185–1.448) |
| Itopride | | | | |
| Never use | 4,435 | 4,566 | 1.000 | 1.000 |
| | (80.70) | (83.08) | (reference) | (reference) |
| Use within 1 year | 1,061 | 930 | 1.189 | 1.211 |
| | (19.30) | (16.92) | (1.075–1.315) | (1.089–1.347) |
| Clebopride | | | | |
| Never use | 5,385 | 5,428 | 1.000 | 1.000 |
| | (97.98) | (98.76) | (reference) | (reference) |

| | | | | |
|-------------------|--------|--------|---------------|---------------|
| Use within 1 year | 111 | 68 | 1.662 | 1.810 |
| | (2.02) | (1.24) | (1.221–2.260) | (1.308–2.506) |

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted for Charlson comorbidity index score and comorbidities (peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, hemiplegia/paraplegia, any malignancy and metastatic solid tumor).

Appendix 2. Association between antipsychotics exposure within 1 year and parkinsonism

| Antipsychotics | n (%) | | OR (95% CI) | |
|--------------------------------|--------------------|-----------------------|------------------------|--------------------------------------|
| | Cases (n=5,496) | Controls (n=5,496) | Matched | Matched and adjusted ^a |
| Any antipsychotics | | | | |
| Never use | 5,293 (96.31) | 5,421 (98.64) | 1.000 (reference) | 1.000 (reference) |
| Use within 1 year | 203 (3.69) | 75 (1.36) | 2.910 (2.205–3.841) | 2.155 (1.596–2.909) |
| Typical antipsychotics | | | | |
| Never use | 5,397 (98.20) | 5,453 (99.22) | 1.000 (reference) | 1.000 (reference) |
| Use within 1 year | 99 (1.80) | 43 (0.78) | 2.366 (1.642–3.408) | 1.940 (1.312–2.870) |
| Atypical antipsychotics | | | | |
| Never use | 5,352 (97.38) | 5,453 (99.22) | 1.000 (reference) | 1.000 (reference) |
| Use within 1 year | 144 | 43 | 3.658 (2.555–5.237) | 2.441 |

| | | | | |
|---------------------------|---------|---------|---------------|---------------|
| | (2.62) | (0.78) | | (1.659–3.592) |
| Haloperidol | | | | |
| (typical antipsychotics) | | | | |
| Never use | 5,427 | 5,468 | 1.000 | 1.000 |
| | (98.74) | (99.49) | (reference) | (reference) |
| Use within 1 year | 69 | 28 | 2.464 | 1.723 |
| | (1.26) | (0.51) | (1.588–3.823) | (1.073–2.766) |
| Quetiapine | | | | |
| (atypical antipsychotics) | | | | |
| Never use | 5,419 | 5,466 | 1.000 | 1.000 |
| | (98.60) | (99.45) | (reference) | (reference) |
| Use within 1 year | 77 | 30 | 2.741 | 1.689 |
| | (1.40) | (0.55) | (1.764–4.258) | (1.047–2.724) |
| Risperidone | | | | |
| (atypical antipsychotics) | | | | |
| Never use | 5,431 | 5,483 | 1.000 | 1.000 |
| | (98.82) | (99.76) | (reference) | (reference) |
| Use within 1 year | 65 | 13 | 5.333 | 3.510 |
| | (1.18) | (0.24) | (2.879–9.880) | (1.839–6.701) |

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted for Charlson comorbidity index score and comorbidities (peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, hemiplegia/paraplegia, any malignancy and metastatic solid tumor).

Appendix 3. Association between flunarizine exposure within 1 year and parkinsonism

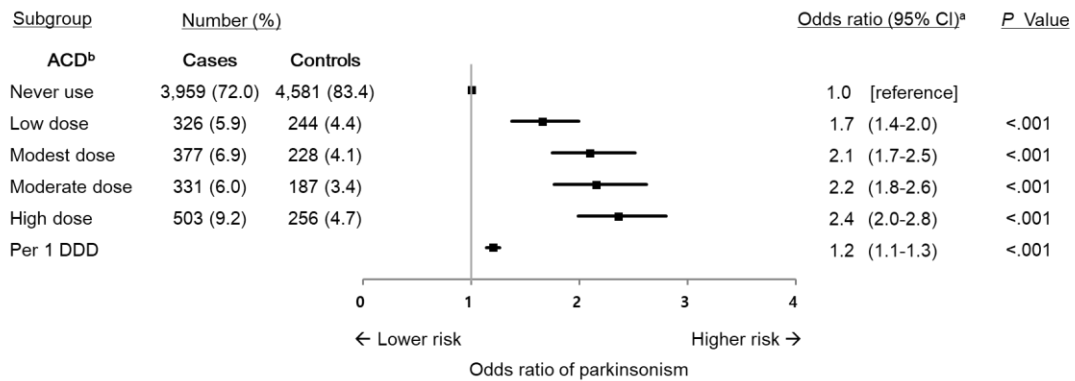
| Flunarizine | n (%) | | OR (95% CI) | |
|--------------------|----------------------------|-------------------------------|------------------------|---|
| | Cases (n=5,496) | Controls (n=5,496) | Matched | Matched and adjusted^a |
| <hr/> | | | | |
| Flunarizine | | | | |
| Never use | 5,280 (96.07) | 5,392 (98.11) | 1.000 (reference) | 1.000 (reference) |
| Use within 1 year | 216 (3.93) | 104 (1.89) | 2.155 (1.694–2.741) | 1.877 (1.460–2.411) |

Abbreviations: CI, confidence interval; OR, odds ratio.

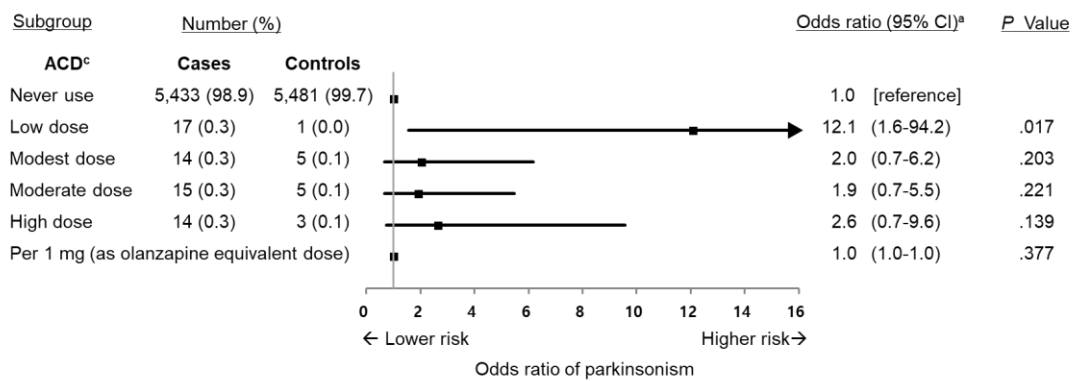
^aAdjusted for Charlson comorbidity index score and comorbidities (peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, hemiplegia/paraplegia, any malignancy and metastatic solid tumor).

Appendix 4. Association between drug exposure and parkinsonism stratified by acute cumulative dose

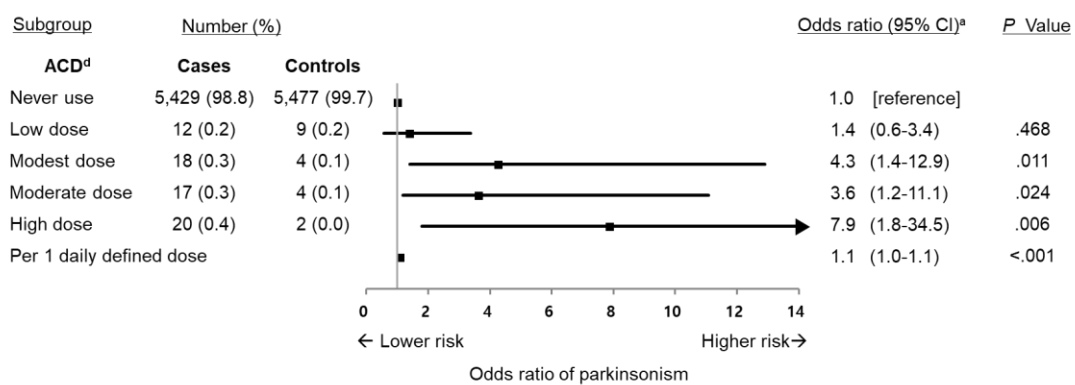
(a)



(b)



(c)



Abbreviations: ACD, acute cumulative dose; CI, confidence interval; DDD, daily defined dose.

^aAdjusted for Charlson comorbidity index score and comorbidities (peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, hemiplegia/paraplegia, any malignancy and metastatic solid tumor).

^bLow dose: $0 \text{ DDD} < \text{ACD} < 4 \text{ DDD}$; modest dose: $4 \text{ DDD} \leq \text{ACD} < 10 \text{ DDD}$; moderate dose: $10 \text{ DDD} \leq \text{ACD} < 20 \text{ DDD}$; high dose: $\text{ACD} \geq 20 \text{ DDD}$.

^cLow dose: $0 \text{ mg as olanzapine equivalent dose} < \text{ACD} < 18.666 \text{ mg as olanzapine equivalent dose}$; modest dose: $18.666 \text{ mg as olanzapine equivalent dose} \leq \text{ACD} < 47.916 \text{ mg as olanzapine equivalent dose}$; moderate dose: $47.916 \text{ mg as olanzapine equivalent dose} \leq \text{ACD} < 100.000 \text{ mg as olanzapine equivalent dose}$; high dose: $\text{ACD} \geq 100.000 \text{ mg as olanzapine equivalent dose}$.

^dLow dose: $0 \text{ DDD} < \text{ACD} < 4.5 \text{ DDD}$; modest dose: $4.5 \text{ DDD} \leq \text{ACD} < 12.75 \text{ DDD}$; moderate dose: $12.75 \text{ DDD} \leq \text{ACD} < 21 \text{ DDD}$; high dose: $\text{ACD} \geq 21 \text{ DDD}$.

Appendix 5. Association between drug exposure and parkinsonism stratified by age

| Age group | n (%) | | OR (use within 1 year vs. never use) (95% CI) | |
|-----------------------|--------------------|-----------------------|--|--------------------------------------|
| | Cases (n=5,496) | Controls (n=5,496) | Matched | Matched and adjusted ^a |
| Propulsives | | | | |
| <45 years | 359 (9.69) | 283 (8.83) | 1.673 (1.325–2.112) | 1.691 (1.332–2.147) |
| 45-54 years | 407 (10.99) | 334 (10.42) | 1.760 (1.370–2.262) | 1.862 (1.433–2.419) |
| 55-64 years | 609 (16.44) | 527 (16.44) | 1.603 (1.294–1.986) | 1.694 (1.347–2.131) |
| 65-74 years | 1,132 (30.56) | 989 (30.85) | 1.627 (1.380–1.919) | 1.707 (1.433–2.034) |
| 75-84 years | 999 (26.97) | 901 (28.10) | 1.488 (1.244–1.779) | 1.554 (1.288–1.876) |
| ≥85 years | 198 (5.35) | 172 (5.36) | 1.464 (1.042–2.057) | 1.466 (1.023–2.101) |
| Antipsychotics | | | | |

| | | | | |
|-------------|---------|---------|----------------|----------------|
| <45 years | 16 | 2 | 8.000 | 9.192 |
| | (7.88) | (2.67) | (1.839–34.793) | (1.698–49.759) |
| 45-54 years | 9 | 2 | 4.500 | 3.303 |
| | (4.43) | (2.67) | (0.972–20.827) | (0.637–17.120) |
| 55-64 years | 19 | 4 | 4.750 | 3.196 |
| | (9.36) | (5.33) | (1.616–13.962) | (0.941–10.855) |
| 65-74 years | 68 | 17 | 4.643 | 3.418 |
| | (33.50) | (22.67) | (2.606–8.271) | (1.851–6.315) |
| 75-84 years | 69 | 32 | 2.276 | 1.652 |
| | (33.99) | (42.67) | (1.471–3.522) | (1.019–2.679) |
| ≥85 years | 22 | 18 | 1.250 | 1.013 |
| | (10.84) | (24.00) | (0.648–2.412) | (0.493–2.081) |
| Flunarizine | | | | |
| <45 years | 15 | 9 | 1.667 | 1.342 |
| | (6.94) | (8.65) | (0.729–3.808) | (0.535–3.369) |
| 45-54 years | 28 | 12 | 2.333 | 1.901 |
| | (12.96) | (11.54) | (1.187–4.588) | (0.939–3.849) |
| 55-64 years | 35 | 12 | 2.917 | 2.609 |
| | (16.20) | (11.54) | (1.514–5.619) | (1.306–5.212) |

| | | | | |
|-------------|---------|---------|---------------|---------------|
| 65-74 years | 72 | 31 | 2.414 | 2.132 |
| | (33.33) | (29.81) | (1.566–3.721) | (1.358–3.347) |
| 75-84 years | 57 | 35 | 1.710 | 1.464 |
| | (26.39) | (33.65) | (1.098–2.663) | (0.918–2.333) |
| ≥85 years | 9 | 5 | 2.000 | 1.763 |
| | (4.17) | (4.81) | (0.602–6.642) | (0.511–6.081) |

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted for Charlson comorbidity index score and comorbidities (peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, hemiplegia/paraplegia, any malignancy and metastatic solid tumor).

Appendix 6. Association between drug exposure and parkinsonism stratified by sex

| Sex | n (%) | | OR (use within 1 year vs. never use) (95% CI) | |
|-----------------------|--------------------|-----------------------|--|--------------------------------------|
| | Cases (n=5,496) | Controls (n=5,496) | Matched | Matched and adjusted ^a |
| Propulsives | | | | |
| Male | 1,446 (39.04) | 1,257 (39.21) | 1.483 (1.305–1.686) | 1.564 (1.364–1.793) |
| Female | 2,258 (60.96) | 1,949 (60.79) | 1.704 (1.514–1.917) | 1.756 (1.555–1.984) |
| Antipsychotics | | | | |
| Male | 106 (52.22) | 32 (42.67) | 3.643 (2.398–5.534) | 2.645 (1.670–4.189) |
| Female | 97 (47.78) | 43 (57.33) | 2.385 (1.641–3.466) | 1.865 (1.246–2.792) |
| Flunarizine | | | | |
| Male | 73 (33.80) | 31 (29.81) | 2.448 (1.590–3.771) | 2.012 (1.266–3.197) |
| Female | 143 | 73 | 2.029 (1.518–2.713) | 1.806 (1.339–2.435) |

(66.20) (70.19)

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted for Charlson comorbidity index score and comorbidities (peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, hemiplegia/paraplegia, any malignancy and metastatic solid tumor).

Appendix 7. Result of sensitivity analyses: Association between drug exposure within 1 year and parkinsonism

| Age group | n (%) | | OR (95% CI) | |
|-----------------------|------------------|---------------------|--------------------------|--------------------------------------|
| | Cases (n=111) | Controls (n=444) | Matched | Matched and adjusted ^a |
| Propulsives | | | | |
| Never use | 28 (25.23) | 164 (36.94) | 1.000 (reference) | 1.000 (reference) |
| Use within 1 year | 83 (74.77) | 280 (63.06) | 1.946 (1.158–3.271) | 1.871 (1.107–3.161) |
| Antipsychotics | | | | |
| Never use | 96 (86.49) | 438 (98.65) | 1.000 (reference) | 1.000 (reference) |
| Use within 1 year | 15 (13.51) | 6 (1.35) | 11.557 (4.190–31.882) | 11.184 (4.035–30.997) |
| Flunarizine | | | | |
| Never use | 109 (98.20) | 435 (97.97) | 1.000 (reference) | 1.000 (reference) |
| Use within 1 year | 2 | 9 | 0.879 (0.177–4.355) | 0.909 |

(1.80)

(2.03)

(0.182–4.547)

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted for Charlson comorbidity index score .

Appendix 8. Association between typical and atypical antipsychotics exposure and parkinsonism stratified by chronic cumulative dose

| Antipsychotics | n (%) | | OR (95% CI) | |
|------------------------|--------------------|-----------------------|------------------------|--------------------------------------|
| | Cases (n=5,496) | Controls (n=5,496) | Matched | Matched and adjusted ^a |
| Any antipsychotics | | | | |
| Never use | 5,293 (96.31) | 5,421 (98.64) | 1.000 (reference) | 1.000 (reference) |
| Low dose | 45 (0.82) | 19 (0.35) | 2.553 (1.470–4.433) | 1.879 (1.035–3.409) |
| Modest dose | 48 (0.87) | 17 (0.31) | 2.939 (1.685–5.125) | 2.596 (1.423–4.737) |
| Moderate dose | 51 (0.93) | 14 (0.25) | 4.083 (2.172–7.677) | 2.575 (1.336–4.964) |
| High dose | 50 (0.91) | 15 (0.27) | 3.463 (1.939–6.183) | 2.580 (1.403–4.745) |
| Per 1 mg ^b | | | 1.000 (1.000–1.001) | 1.000 (1.000–1.000) |
| Typical antipsychotics | | | | |

| | | | | |
|-------------------------|--------|--------|----------------|----------------|
| Low dose | 16 | 10 | 1.707 | 1.396 |
| | (0.29) | (0.18) | (0.769–3.786) | (0.599–3.256) |
| Modest dose | 17 | 6 | 2.833 | 3.671 |
| | (0.31) | (0.11) | (1.117–7.186) | (1.345–10.018) |
| Moderate dose | 18 | 6 | 3.203 | 2.369 |
| | (0.33) | (0.11) | (1.260–8.139) | (0.915–6.129) |
| High dose | 24 | 9 | 2.667 | 1.987 |
| | (0.44) | (0.16) | (1.240–5.737) | (0.879–4.487) |
| Per 1 mg ^b | | | 1.000 | 1.000 |
| | | | (1.000–1.000) | (1.000–1.000) |
| Atypical antipsychotics | | | | |
| Low dose | 52 | 17 | 3.224 | 2.129 |
| | (0.95) | (0.31) | (1.833–5.672) | (1.162–3.899) |
| Modest dose | 35 | 13 | 2.892 | 2.082 |
| | (0.64) | (0.24) | (1.518–5.511) | (1.037–4.179) |
| Moderate dose | 43 | 9 | 5.491 | 3.451 |
| | (0.78) | (0.16) | (2.570–11.732) | (1.558–7.646) |
| High dose | 14 | 3 | 4.667 | 3.145 |
| | (0.25) | (0.05) | (1.341–16.239) | (0.877–11.279) |
| Per 1 mg ^b | | | 1.002 | 1.001 |
| | | | (1.001–1.003) | (1.000–1.002) |

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted for Charlson comorbidity index score and comorbidities (peripheral vascular disease,

cerebrovascular disease, dementia, chronic pulmonary disease, hemiplegia/paraplegia, any malignancy and metastatic solid tumor).

^bAs olanzapine equivalent dose.