Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
**eMethods: Description of case-control, sensitivity, and supplementary analyses**

**Case-control analysis**

The case-control analysis aimed to investigate the association between cumulative doses of quetiapine, used as low-dose treatment, and type 2 diabetes mellitus (T2DM). The case-control analysis was nested among low-dose quetiapine users and, thus, did not include a comparator group. Each T2DM case was matched on age and sex with ten controls, using risk set sampling. The observation period for each low-dose quetiapine user was similar to the follow-up period used in ITT-analyses, i.e., follow-up was confined to use of low-dose quetiapine alone and did not include time with use of SSRIs, other antipsychotics, or higher strengths of quetiapine tablets than equivalents of 25 mg or 50 mg per day.

We calculated odds ratios (ORs) for the association between cumulative quetiapine dose and T2DM, using conditional logistic regression in two ways:

1. Using cumulative quetiapine doses transformed by the binary logarithm as the independent variable. In this analysis, the OR represents the increase in risk for each doubling of the cumulative dose (pre-planned analysis).
2. Using predefined strata of cumulative dose (6.25–12.5/12.51–25/25.01–50/100.01–200/>200 DDD) as the independent variable.

Use of ≤6.25 DDD was used as reference in both approaches, as this amount is equivalent to 100 tablets of 25 mg quetiapine – the smallest package marketed in Denmark.

**Sensitivity analyses**

To test the impact of analytical choices on the observed association between use of low-dose quetiapine and T2DM, we conducted the following six sensitivity analyses (reported in eFigures 3-4 and eTables 8-9):

1. The grace period was varied from 90 to 60 and 120 days in as-treated analyses to test the impact of grace period definition on incidence rate estimates.
2. The washout window was extended from one to five years (applying to prior use of quetiapine, SSRIs, or other antipsychotics), to assess the impact of previous use of these drugs on T2DM risk.
3. The maximum follow-up period was extended from five to 10 years, to assess if a potential long-term risk existed beyond our initial follow-up window.
4. Exclusion of individuals with history of recurrent depression from cohort entry, to assess the impact of long-term depression on T2DM risk.
5. Using inverse probability of censoring weights (IPCW) in the main analysis, to explore the magnitude of selection bias due to potential informative censoring (e.g., using higher doses quetiapine or being diagnosed with a severe mental illness). To construct IPCWs, time was partitioned into 90-day periods, and the probability of being uncensored at the beginning of each period was estimated using logistic regression analysis. The regression model included treatment status, calendar time, and all covariates from the hdPS-model (as measured at baseline). Stabilized IPCWs were then calculated as the cumulative probability of remaining uncensored, conditional on treatment status and calendar time, divided by the cumulative probability of remaining uncensored on treatment status, calendar time and baseline covariates (in the hdPS-model). We then obtained IPCW-weighted hazard ratios using pooled logistic regression analyses.
6. Using standardized mortality ratio weights (SMRW) in a Cox proportional hazards regression model as an alternative to propensity score (PS) matching. Users of low-dose quetiapine were given a weight of 1, and SSRI-users were weighted according to their PS with a weight equal to PS/(1-PS).

**Supplementary analyses**

To test the impact of different exposures or comparator, and to test assay sensitivity, we conducted the following four supplementary analyses:

1. Extending the exposure definition to include 100 mg quetiapine tablets. This alternative exposure definition was tested in both AT- and ITT-analyses as well as the case-control analysis of the association with cumulative dose (eFigure 3 and eTable 7).
2. Extending the exposure definition to include all strengths of quetiapine tablets. This alternative exposure definition was tested in both AT- and ITT-analyses as well as the case-control analysis of the association with cumulative dose (eFigure 3 and eTable 7).
3. Using Z-drugs as active comparator to assess the appropriateness of choosing SSRIs as the comparator in the main analyses (eFigure 5).
4. Using olanzapine as alternative exposure to test assay sensitivity of the main analyses (eFigure 6).
eFigure 1: Graphical representation of baseline assessment and follow-up

- **Exclusion Assessment Window (Register coverage)**
  Days [-365; -1]
- **Exclusion Assessment Window (No Diabetes or SM)**
  Days [∞; -1]
- **Washout Window (exposure)**
  (No Rx of other study drug or other AP)
  Days [-365; -1]
- **Exclusion Assessment Window (Age < 18y, initiate both QUE and SSRI, filling of high-dose QUE)**
  Day 0
- **Covariate Assessment Window (Age, sex)**
  Day 0
- **Covariate Assessment Window (Baseline conditions and drug use)**
  Days [-365; -1]
- **Follow up window**
  (day 0; censor)

Study start: 01-01-1998
Study end: 31-12-2018
Notes: a) History of diabetes was assessed as prescriptions for antidiabetic medications, hospital diagnoses of diabetes, or blood levels of glycosylated hemoglobin above reference values, b) History of severe mental illness was defined as hospital diagnoses of schizophrenia, schizoaffective disorder, or bipolar affective disorder, c) High-dose quetiapine was defined as filling of prescriptions with tablet strengths >50mg, d) Baseline covariates for the propensity score model included prescriptions and hospital diagnoses from the prior 365 days, e) Follow-up ended at the earliest of diabetes, death, emigration, end of study, five years of follow-up, or censoring for meeting baseline exclusion criteria (i.e., diagnosis of SMI, use of high-dose QUE, use of other study drug, use of other AP, or new diagnosis of type 1 diabetes mellitus).

Abbreviations: AP: Antipsychotic, Rx: Prescription, SMI: Serious Mental Illness, SSRI: Selective Serotonin Reuptake-inhibitor, QUE: Quetiapine.
eTable 1: ICD and ATC codes for exposure and outcome variables

| Study drugs | ATC: N05AH04 |
|-------------|--------------|
| Quetiapine   |              |
| SSRIs        | ATC: N06AB   |

**Outcome**

| Diabetes (T2DM) | ATC: A10 |
|-----------------|----------|
| ICD-10: E10-14, G590, G632, G990, H280, H360, M142, N083, O240-243. HbA1c ≥ 6.4% or ≥ 48mmol/mol |

**Exclusion criteria**

| Severe mental illness | ICD-10: F20, 25, 30-31 |
|-----------------------|-------------------------|
| Other antipsychotics  | ATC: N05A (excl. N05AH04 and N05AN01) |
| History of diabetes   | Defined as above        |

**Comorbidities**

| Hypertension       | ICD-10: I10-13,15 |
|--------------------|------------------|
| ATC: C02, C08-09   |                  |
| COPD               | ICD-10: J40-44   |
| ATC: R03           |                  |
| Heart failure      | ICD-10: I098-99, I110, I130, I132, I255, I420, I425-29, I43, I50 |
| Obesity            | ICD-10: E65-66   |
| Alcohol-related disorders | ICD-10: I426, F10, K292, K70, K852, K860, T51, Y911-913, Z502, Z721 |
| ATC: N07BB         |                  |
| Major depression   | ICD-10: F32-33   |
| Recurrent depression| ICD-10: F33      |

**Other medications**

| Digoxin           | ATC: C01AA        |
|                  |                   |
| Thiazide diuretics| ATC: C03A         |
| Beta-blockers     | ATC: C07          |
| Statins           | ATC: C10          |
| Oral glucocorticoids | ATC: H02AB    |
| Other antipsychotics | ATC: N05A (excl. N05AH04 and N05AN01) |
| Mirtazapine       | ATC: N06AX11      |
| Antihistamines    | ATC: R06A         |

**Hemoglobin A1c (HbA1c)**

| Prediabetes (covariate) | HbA1c: 5.7-6.3% or 39-47 mmol/mol |

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a) Individuals with new diagnosis type 1 diabetes mellitus (T1DM) during follow-up were censored and were not classified as having the outcome of interest - if they had solely E10-diagnoses and prescriptions for insulin in registers, as this was considered incident T1DM. Occurrences of both E10 and other E1x-diagnoses or use of other antidiabetic medications than insulin was classified as T2DM due to the potential low validity of the T1DM-diagnosis. ATC: World Health Organization Anatomical Therapeutic Chemical classification, HbA1c: Glycosylated Hemoglobin A1c, ICD-10: World Health Organization International Classification of diseases, 10th revision.

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**eTable 2: Covariates included in high-dimensional propensity score model**

The 50 most common prescriptions and hospital diagnoses among the included low-dose quetiapine or SSRI-users within 12 months before cohort entry. Use of drugs or occurrence of hospital diagnoses are divided into three groups: At least one occurrence, sporadic use (i.e., more than the median number of prescriptions/hospital contacts in the cohort), and frequent use (i.e., more than the 75th percentile of prescriptions/hospital contacts in the cohort).

| ATC-group or ICD-10 diagnosis                      | Frequency           | Low-dose Quetiapine, N (%) | SSRI, N (%) | RR (cd) | RR (ce) | Multiplicative bias |
|---------------------------------------------------|---------------------|-----------------------------|-------------|---------|---------|---------------------|
| Statins (C10AA)                                   | One or more         | 5852 (10)                   | 68270 (8)   | 2.37    | 0.73    | 1.025               |
| Other special examinations and investigations (Z01, outpatient) | One or more         | 16242 (28)                  | 158853 (19) | 1.25    | 1.13    | 1.022               |
| Proton pump inhibitors (A02BC)                    | One or more         | 11224 (19)                  | 119379 (14) | 1.43    | 1.11    | 1.021               |
| Proton pump inhibitors (A02BC)                    | Median or more      | 5474 (9)                    | 53234 (6)   | 1.52    | 1.23    | 1.016               |
| Obesity (E66, outpatient)                          | One or more         | 442 (1)                     | 3403 (0)    | 4.51    | 1.35    | 1.012               |
| Other antiepileptics (N03AX)                      | One or more         | 5637 (10)                   | 16697 (2)   | 1.15    | 3.02    | 1.012               |
| Other opioids (N02AX)                             | One or more         | 8092 (14)                   | 87408 (10)  | 1.33    | 1.42    | 1.012               |
| NSAIDs (M01AE)                                    | One or more         | 11797 (20)                  | 142569 (17) | 1.36    | 1.14    | 1.012               |
| Paracetamol (N02BE)                               | One or more         | 15885 (28)                  | 133001 (16) | 1.09    | 1.30    | 1.011               |
| Statins (C10AA)                                   | Median or more      | 2278 (4)                    | 25816 (3)   | 2.21    | 0.86    | 1.010               |
| Inhaled adrenergics with corticosteroids (R03AK)   | One or more         | 2364 (4)                    | 23276 (3)   | 1.63    | 1.01    | 1.008               |
| Non-selective monoamine reuptake inhibitors (N06AA) | One or more         | 3271 (6)                    | 21024 (3)   | 1.26    | 3.28    | 1.008               |
| Sleep disorders (G47, outpatient)                  | One or more         | 423 (1)                     | 2258 (0)    | 2.62    | 1.32    | 1.007               |
| Other opioids (N02AX)                             | Median or more      | 3686 (6)                    | 34916 (4)   | 1.31    | 1.64    | 1.007               |
| Medical observation (Z03, outpatient)              | One or more         | 6459 (11)                   | 64957 (8)   | 1.20    | 1.02    | 1.007               |
| Non-selective monoamine reuptake inhibitors (N06AA) | Median or more      | 1959 (3)                    | 9875 (1)    | 1.30    | 4.87    | 1.007               |
| Penicillin with beta-lactamase inhibitor (J01CR)   | One or more         | 1778 (3)                    | 9435 (1)    | 1.34    | 1.03    | 1.007               |
| Other antidepressants (N06AX)                      | Third quartile or more | 7536 (13)              | 10053 (1)   | 1.05    | 13.76   | 1.006               |
| Proton pump inhibitors (A02BC)                    | Third quartile or more | 2690 (5)                  | 28312 (3)   | 1.50    | 1.40    | 1.006               |
| Other antiepileptics (N03AX)                      | Median or more      | 2887 (5)                    | 7467 (1)    | 1.15    | 3.49    | 1.006               |
| Medical observation (Z03, inpatient)               | One or more         | 6829 (12)                   | 64946 (8)   | 1.14    | 1.42    | 1.006               |
| Drugs used in erectile dysfunction (G04BE)         | One or more         | 1452 (3)                    | 10703 (1)   | 1.45    | 1.20    | 1.006               |
| Obesity (E66, inpatient)                           | One or more         | 325 (1)                     | 3295 (0)    | 4.00    | 1.25    | 1.005               |
| Other opioids (N02AX)                             | Third quartile or more | 2414 (4)                  | 21397 (3)   | 1.29    | 1.75    | 1.005               |
| Beta-lactamase resistant penicillins (J01CF)       | One or more         | 2930 (5)                    | 29595 (4)   | 1.29    | 1.25    | 1.004               |
| NSAIDs (M01AE)                                    | Third quartile or more | 2591 (4)                  | 30257 (4)   | 1.52    | 1.27    | 1.004               |
| ATC-group or ICD-10 diagnosis                              | Frequency | Low-dose Quetiapine, N (%) | SSRI, N (%) | RR (cd) | RR (ce) | Multiplicative bias |
|-----------------------------------------------------------|-----------|----------------------------|-------------|---------|---------|---------------------|
| Dihydropyridine derivatives (C08CA)                       | One or more | 4256 (7)                   | 58068 (7)   | 1.78    | 0.79    | 1.003               |
| Persons encountering health services (Z71, outpatient)     | One or more | 652 (1)                    | 5250 (1)    | 1.65    | 1.15    | 1.003               |
| Paracetamol (N02BE)                                        | Median or more | 7111 (12)                | 61083 (7)   | 1.06    | 1.38    | 1.003               |
| Other antidepressants (N06AX)                              | Median or more | 11224 (19)               | 19674 (2)   | 1.02    | 9.65    | 1.003               |
| Natural opium alkaloids (N02AA)                           | One or more | 3757 (7)                   | 32659 (4)   | 1.11    | 1.28    | 1.003               |
| Drugs used in opioid dependence (N07BC)                   | One or more | 775 (1)                    | 2875 (0)    | 1.30    | 4.10    | 1.003               |
| Other antiepileptics (N03AX)                              | Third quartile or more | 1558 (3)                | 3862 (0)    | 1.13    | 3.77    | 1.003               |
| Benzodiazepine related drugs (N05CF)                      | Third quartile or more | 2849 (5)                | 24687 (3)   | 1.14    | 2.44    | 1.003               |
| Angiotensin II antagonists and diuretics (C09DA)           | One or more | 1251 (2)                   | 15834 (2)   | 2.03    | 0.77    | 1.003               |
| Inhaled adrenergics with corticosteroids (R03AK)           | Median or more | 995 (2)                   | 10246 (1)   | 1.56    | 0.93    | 1.003               |
| Statins (C10AA)                                           | Third quartile or more | 792 (1)                  | 9247 (1)    | 2.04    | 1.09    | 1.003               |
| Natural opium alkaloids (N02AA)                           | Third quartile or more | 1062 (2)                 | 7728 (1)    | 1.30    | 1.71    | 1.003               |
| Beta blocking agents, selective (C07AB)                   | Median or more | 2139 (4)                 | 28583 (3)   | 1.88    | 0.90    | 1.003               |
| Benzodiazepine related drugs (N05CF)                      | Median or more | 4747 (8)                 | 46010 (5)   | 1.09    | 2.20    | 1.003               |
| Beta blocking agents, selective (C07AB)                   | Third quartile or more | 1182 (2)                | 14452 (2)   | 1.72    | 0.96    | 1.002               |
| Imidazole and triazole derivatives (D01AC)                | One or more | 3944 (7)                   | 49061 (6)   | 1.23    | 1.12    | 1.002               |
| Hormonal contraceptives (G03AB)                           | One or more | 223 (0)                    | 8766 (1)    | 0.69    | 0.89    | 1.002               |
| Use of tobacco (F17, inpatient)                           | One or more | 213 (0)                    | 1271 (0)    | 1.91    | 1.58    | 1.002               |
| Muscle relaxants (M03BB)                                  | One or more | 1184 (2)                   | 12217 (1)   | 1.33    | 1.16    | 1.002               |
| Anticholinergics (R03BB)                                  | One or more | 1137 (2)                   | 12992 (2)   | 1.46    | 0.88    | 1.002               |

ATC: Anatomical Therapeutic Chemical Classification, ICD-10: World Health Organization International Classification of diseases, 10th revision, RR(cd): Association between confounder and outcome as relative risk, RR(ce): Association between confounder and exposure as relative risk, SSRI: Selective Serotonin Reuptake-inhibitors.
**eFigure 2: Propensity score distribution before and after matching**

A: Before propensity score matching, B: After propensity score matching (without trimming).
## eTable 3: Characteristics of unmatched individuals

|                                | Individuals not included in the hdPS-matched cohort |                  |                  |
|--------------------------------|---------------------------------------------------|-----------------|-----------------|
|                                | Low-dose Quetiapine | SSRI            | SMD             |
| **All**                        | 3,085                | 783,968         | .               |
| **Sex, N (%)**                 |                      |                 |                 |
| Female                         | 1,758 (57.0)         | 482,786 (61.6)  | 0.09            |
| **Age, N (%)**                 |                      |                 |                 |
| Median (IQR)                   | 47 (36-60)           | 47 (33-67)      | <0.01           |
| 18-64 years                    | 2,451 (79.4)         | 571,011 (72.8)  | 0.16            |
| 65-79 years                    | 400 (13.0)           | 127,140 (16.2)  | 0.09            |
| 80+ years                      | 234 (7.6)            | 85,817 (10.9)   | 0.12            |
| **Year of cohort entry, N (%)**|                      |                 |                 |
| 1998-2002                      | 0                    | 227,759 (29.1)  | 0.90            |
| 2003-2007                      | 6 (0.2)              | 245,651 (31.3)  | 0.95            |
| 2008-2012                      | 198 (6.4)            | 207,102 (26.4)  | 0.56            |
| 2013-2017                      | 2,135 (69.2)         | 89,531 (11.4)   | 1.46            |
| **Comorbidities, N (%)**       |                      |                 |                 |
| Hypertension                   | 736 (23.9)           | 151,562 (19.3)  | 0.11            |
| COPD                           | 516 (16.7)           | 93,853 (12.0)   | 0.14            |
| Heart failure                  | 69 (2.2)             | 20,972 (2.7)    | 0.03            |
| Obesity                        | 307 (10.0)           | 21,878 (2.8)    | 0.30            |
| Alcohol-related disorders      | 836 (27.1)           | 106,441 (13.6)  | 0.34            |
| Major depression               | 1,467 (47.6)         | 41,996 (5.4)    | 1.09            |
| Recurrent depression           | 941 (30.5)           | 10,342 (1.3)    | 0.87            |
| **Drugs used in the past year, N (%)** |                      |                 |                 |
| Digoxin                        | 36 (1.2)             | 21,271 (2.7)    | 0.11            |
| Thiazide diuretics             | 226 (7.3)            | 77,530 (9.9)    | 0.09            |
| Beta-blockers                  | 402 (13.0)           | 86,500 (11.0)   | 0.06            |
| Statins                        | 396 (12.8)           | 69,573 (8.9)    | 0.13            |
| Oral glucocorticoids           | 270 (8.8)            | 54,261 (6.9)    | 0.07            |
| Mirtazapine                    | 1,251 (40.6)         | 36,097 (4.6)    | 0.95            |
| Antihistamines                 | 488 (15.8)           | 55,787 (7.1)    | 0.28            |
| **Hemoglobin A1c at baseline** |                      |                 |                 |
| Normal                         | 554 (18.0)           | 20,565 (2.6)    | 0.52            |
| Prediabetes                    | 217 (7.0)            | 7,119 (0.9)     | 0.32            |
| Missing                        | 2,314 (75.0)         | 756,284 (96.5)  | 0.64            |

COPD: Chronic obstructive pulmonary disease, hdPS: High-dimensional propensity score, IQR: Interquartile range, SMD: Standardized mean difference, SSRI: selective serotonin reuptake inhibitor.

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**eTable 4: Characteristics of follow-up in full and hdPS-matched cohort**

|                                | Full cohort             | hdPS-matched cohort         |
|--------------------------------|------------------------|----------------------------|
|                                | Low-dose Quetiapine    | SSRI                       |
| N                              | 57,701                 | 838,584                    |
|                                | 54,616                 | N = 54,616                 |
| **As-treated analysis**        |                        |                            |
| Median follow-up, years (IQR)  | 0.5 (0.3-0.8)          | 0.7 (0.4-1.5)              |
|                                | 0.5 (0.3-0.7)          | 0.6 (0.4-1.3)              |
| Number of prescriptions, N (%) |                        |                            |
| Median (IQR)                   | 1.0 (1.0-3.0)          | 3.0 (1.0-8.0)              |
| Range                          | 1-240                  | 1-259                      |
| 1 prescription                 | 31,147 (54)            | 244,649 (29)               |
|                                | 29,791 (55)            | 18,570 (34)                |
| 2-4 prescriptions              | 15,176 (26)            | 249,805 (30)               |
|                                | 14,244 (26)            | 17,941 (33)                |
| 5-9 prescriptions              | 5,308 (9)              | 158,321 (19)               |
|                                | 4,937 (9)              | 9,682 (18)                 |
| 10+ prescriptions             | 6,070 (11)             | 185,809 (22)               |
|                                | 5,644 (10)             | 8,423 (15)                 |
| **Average daily dose, DDD/day**|                        |                            |
| Median (IQR)                   | 0.04 (0.03-0.07)       | 0.62 (0.38-0.94)           |
| <0.25, N (%)                   | 57,001 (99)            | 120,522 (14)               |
|                                | 53,976 (99)            | 3,447 (6)                  |
| 0.25-0.49, N (%)               | 671 (1)                | 171,168 (20)               |
|                                | 616 (1)                | 9,671 (18)                 |
| 0.50-0.99, N (%)               | 27 (0)                 | 369,823 (44)               |
|                                | 22 (0)                 | 27,156 (50)                |
| 1.00+, N (%)                   | (n<5)                  | 176,130 (21)               |
|                                | (n<5)                  | 14,283 (26)                |
| **Intention-to-treat analysis**|                        |                            |
| Median follow-up, years (IQR)  | 1.3 (0.3-3.3)          | 5.0 (2.4-5.0)              |
|                                | 1.3 (0.3-3.4)          | 2.3 (0.8-4.8)              |

Abbreviations: DDD: WHO Defined Daily Dose, hdPS: High-dimensional propensity score, IQR: Interquartile range, N: Number, SSRI: Selective serotonin reuptake-inhibitor.
### eTable 5: Reasons for censoring in full and hdPS-matched cohort

|                    | Full cohort |             | hdPS-matched cohort |             |
|--------------------|-------------|-------------|---------------------|-------------|
|                    | Low-dose Quetiapine | SSRI | Low-dose Quetiapine | SSRI |
| As-treated analysis| N = 57,701 | N = 838,584 | N = 54,616 | N = 54,616 |
| Death              | 3,422 (6)  | 59,603 (7) | 3,302 (6)          | 3,511 (6)  |
| Emigration         | 112 (0)    | 3,508 (0)  | 107 (0)            | 241 (0)    |
| New diagnosis of T1DM | (n<5)      | 69 (0)     | (n<5)              | (n<5)      |
| New diagnosis of SMI| 752 (1)    | 3,119 (0)  | 703 (1)            | 233 (0)    |
| Use of high-dose quetiapine | 4,373 (8)  | 1,135 (0)  | 4,015 (7)          | 148 (0)    |
| Switching to other study drug | 6,540 (11) | 12,625 (2) | 6,322 (12)        | 2,261 (4)  |
| Prescription of another AP | 4,653 (8)  | 40,370 (5) | 4,399 (8)          | 2,336 (4)  |
| End of follow-up   | 860 (1)    | 50,165 (6) | 831 (2)            | 1,371 (3)  |
| End of study (31dec2018) | 7,080 (12) | 31,861 (4) | 6,333 (12)        | 10,745 (20) |
| End of first treatment episode | 29,484 (51) | 627,736 (75) | 28,207 (52) | 33,217 (61) |
| Intention-to-treat analysis |             |             |                     |             |
| Death              | 4,906 (9)  | 98,489 (12)| 4,745 (9)          | 5,064 (9)  |
| Emigration         | 420 (1)    | 12,780 (2) | 406 (1)            | 741 (1)    |
| New diagnosis of T1DM | 7 (0)      | 170 (0)    | 7 (0)              | 9 (0)      |
| New diagnosis of SMI | 1,082 (2)  | 6,536 (1)  | 1,013 (2)          | 413 (1)    |
| Use of high-dose quetiapine | 4,898 (8)  | 2,442 (0)  | 4,515 (8)          | 257 (0)    |
| Switching to other study drug | 9,863 (17)| 24,615 (3) | 9,568 (18)        | 3,564 (7)  |
| Prescription of another AP | 6,764 (12) | 78,364 (9) | 6,418 (12)        | 3,707 (7)  |
| End of follow-up   | 7,293 (13) | 502,546 (60)| 7,154 (13)       | 13,064 (24) |
| End of study (31dec2018) | 21,573 (37)| 89,924 (11)| 19,953 (37)      | 26,574 (49) |

Abbreviations: AP: Antipsychotic drug, hdPS: High-dimensional propensity score, T1DM: Type 1 Diabetes mellitus, SMI: Severe mental illness (i.e., schizophrenia, schizoaffective disorder, and bipolar disorder), SSRI: Selective serotonin reuptake-inhibitor.
### eTable 6: Outcome distribution for full and hdPS-matched cohort

|                  | As-treated analysis | Intention-to-treat analysis |
|------------------|---------------------|----------------------------|
|                  | Full cohort         | hdPS-matched cohort        |
|                  | Low-dose Quetiapine | SSRI                       | Low-dose Quetiapine | SSRI |
|                  | N = 57,701          | N = 838,584                | N = 54,616         | N = 54,616 |
| Incident T2DM    | 425                 | 8,462                      | 397                | 553  |
| New diagnosis of DM | 84 (20)            | 2,743 (32)                | 82 (21)           | 109 (20) |
| First prescription of antidiabetic medication | 134 (32) | 4,347 (51) | 125 (31) | 191 (35) |
| First measurement of elevated HbA1c | 207 (49) | 1,372 (16) | 190 (48) | 253 (46) |
| Incident T2DM    | 895                 | 22,718                     | 837               | 1,223 |
| New diagnosis of DM | 147 (16)           | 6,503 (29)                | 144 (17)          | 207 (17) |
| First prescription of antidiabetic medication | 316 (35) | 12,345 (54) | 296 (35) | 476 (39) |
| First measurement of elevated HbA1c | 432 (48) | 3,870 (17) | 397 (47) | 540 (44) |

Abbreviations: DM: Diabetes mellitus, HbA1c: Glycosylated hemoglobin A1c, hdPS: High-dimensional propensity score, SSRI: Selective serotonin reuptake-inhibitor, T2DM: Type 2 diabetes mellitus.
eFigure 3: Supplementary analysis including higher tablet strengths in the exposure definition for quetiapine

eFigure 3-1: Including higher tablet strengths in as-treated analyses

|                      | Quetiapine | SSRI | IRR (95%CI) |
|----------------------|------------|------|-------------|
|                      | Events     | IR   | Events      | IR          |          |
| **Full cohort**      |            |      |             |             |          |
| Main analysis        | 425        | 9.59 | 8462        | 8.13        | 1.18 (1.07-1.30) |
| Including 100mg tablets | 500        | 9.88 | 8462        | 8.13        | 1.22 (1.11-1.33) |
| Including 400mg tablets | 560        | 10.17| 8462        | 8.13        | 1.25 (1.15-1.36) |
| **hdPS-matched cohort** |            |      |             |             |          |
| Main analysis        | 397        | 9.49 | 553         | 9.58        | 0.99 (0.87-1.13) |
| Including 100mg tablets | 459        | 9.64 | 611         | 9.97        | 0.97 (0.86-1.09) |
| Including 400mg tablets | 521        | 9.97 | 562         | 8.89        | 1.12 (0.99-1.26) |

0.5 1 2

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eFigure 3-2: Including higher tablet strengths in the intention-to-treat analyses

|                      | Quetiapine | SSRI | IRR (95%CI) |
|----------------------|------------|------|-------------|
|                      | Events     | IR   | Events      | IR          |          |
| **Full cohort**      |            |      |             |             |          |
| Main analysis        | 895        | 8.16 | 22718       | 7.19        | 1.13 (1.06-1.21) |
| Including 100mg tablets | 1019       | 8.24 | 22718       | 7.19        | 1.14 (1.08-1.22) |
| Including 400mg tablets | 1111       | 8.39 | 22718       | 7.19        | 1.17 (1.10-1.24) |
| **hdPS-matched cohort** |            |      |             |             |          |
| Main analysis        | 837        | 7.97 | 1223        | 8.67        | 0.92 (0.84-1.00) |
| Including 100mg tablets | 948        | 8.02 | 1286        | 8.54        | 0.94 (0.86-1.02) |
| Including 400mg tablets | 1049       | 8.24 | 1277        | 8.07        | 1.02 (0.94-1.11) |

0.5 1 2
# eTable 7: Case-control analysis with different exposure definitions

| Exposure                  | Main analysis (25-50mg tablets) | Including 25-100mg tablets<sup>a</sup> | Including 25-400mg tablets<sup>a</sup> |
|---------------------------|----------------------------------|---------------------------------------|---------------------------------------|
|                           | Cases, No | Controls, No | Odds ratio (95%CI) | Cases, No | Controls, No | Odds ratio (95%CI) | Cases, No | Controls, No | Odds ratio (95%CI) |
| Doubling of dose          | 895       | 8831         | 1.02 (0.95 to 1.09) | 1019      | 10082        | 1.07 (1.01 to 1.12) | 1111      | 11009        | 1.08 (1.03 to 1.13) |
| Cumulative dose, DDD      | .         | .            | .                     | .         | .            | .                     | .         | .            | .                     |
| 0-6.25                    | 381       | 3796         | 1.00 (reference)     | 380       | 3925         | 1.00 (reference)     | 380       | 4009         | 1.00 (reference)     |
| 6.26-12.5                 | 138       | 1380         | 0.99 (0.80 to 1.23)  | 146       | 1525         | 0.92 (0.74 to 1.13)  | 150       | 1527         | 1.00 (0.81 to 1.23)  |
| 12.51-25                  | 114       | 1134         | 1.02 (0.81 to 1.29)  | 127       | 1325         | 0.99 (0.79 to 1.23)  | 129       | 1391         | 0.97 (0.78 to 1.22)  |
| 25.01-50                  | 109       | 1063         | 1.02 (0.80 to 1.29)  | 126       | 1224         | 0.99 (0.79 to 1.23)  | 133       | 1313         | 1.04 (0.83 to 1.30)  |
| 50.01-100                 | 81        | 798          | 0.95 (0.73 to 1.25)  | 105       | 981          | 1.00 (0.79 to 1.28)  | 116       | 1168         | 1.07 (0.85 to 1.36)  |
| 100.01-200                | 46        | 445          | 1.09 (0.77 to 1.55)  | 73        | 669          | 1.04 (0.78 to 1.38)  | 90        | 837          | 1.05 (0.80 to 1.36)  |
| >200                      | 26        | 215          | 1.28 (0.80 to 2.05)  | 62        | 433          | 1.53 (1.10 to 2.11)  | 113       | 764          | 1.44 (1.13 to 1.84)  |

Notes: a) Including quetiapine tablets up to 100/400mg, but excluding individuals with severe mental disorders as in the main analysis. Abbreviations: CI: confidence interval, DDD: daily defined dose

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eFigure 4: Sensitivity analysis varying grace period, washout period, maximum follow-up, and exclusion criteria

**eFigure 4-1: Varying analytical choices in as-treated analyses**

|                    | Quetiapine | SSRI | IR | IR | Favours QUE | Favours SSRI | IRR (95%CI) |
|--------------------|------------|------|----|----|-------------|--------------|-------------|
| **Full cohort**    |            |      |    |    |             |              |             |
| Main analysis      | 425        | 9.59 | 8462| 8.13|             |              | 1.18 (1.07-1.30) |
| Decreasing grace period from 90 to 60 days | 379        | 9.49 | 7356| 8.13|             |              | 1.17 (1.05-1.29) |
| Increasing grace period from 90 to 120 days | 449        | 9.35 | 9363| 8.14|             |              | 1.15 (1.04-1.26) |
| Extending washout from 1 to 5 years | 283        | 9.27 | 8256| 8.11|             |              | 1.14 (1.02-1.29) |
| Extending follow-up from 5 to 10 years | 435        | 9.49 | 10035| 8.51|             |              | 1.11 (1.01-1.23) |
| Excluding recurrent depression | 362        | 9.39 | 8242| 8.11|             |              | 1.16 (1.04-1.29) |
| **hdPS-matched cohort** |            |      |    |    |             |              |             |
| Main analysis      | 397        | 9.49 | 553 | 9.58|             |              | 0.99 (0.87-1.13) |
| Decreasing grace period from 90 to 60 days | 358        | 9.52 | 486 | 9.48|             |              | 1.00 (0.88-1.15) |
| Increasing grace period from 90 to 120 days | 418        | 9.22 | 601 | 9.54|             |              | 0.97 (0.85-1.09) |
| Extending washout from 1 to 5 years | 280        | 9.21 | 406 | 9.71|             |              | 0.95 (0.82-1.11) |
| Extending follow-up from 5 to 10 years | 435        | 9.50 | 621 | 9.83|             |              | 0.97 (0.86-1.09) |
| Excluding recurrent depression | 360        | 9.34 | 502 | 9.42|             |              | 0.99 (0.87-1.14) |

**eFigure 4-2: Varying analytical choices in intention-to-treat analyses**

|                    | Quetiapine | SSRI | IR | IR | Favours QUE | Favours SSRI | IRR (95%CI) |
|--------------------|------------|------|----|----|-------------|--------------|-------------|
| **Full cohort**    |            |      |    |    |             |              |             |
| Main analysis      | 895        | 8.16 | 22718| 7.19|             |              | 1.13 (1.06-1.21) |
| Extending washout from 1 to 5 years | 590        | 7.89 | 22156| 7.17|             |              | 1.10 (1.01-1.19) |
| Extending follow-up from 5 to 10 years | 1007       | 8.17 | 38376| 7.48|             |              | 1.09 (1.03-1.16) |
| Excluding recurrent depression | 745        | 7.81 | 22083| 7.18|             |              | 1.09 (1.01-1.17) |
| **hdPS-matched cohort** |            |      |    |    |             |              |             |
| Main analysis      | 837        | 7.97 | 1223 | 8.67|             |              | 0.92 (0.84-1.00) |
| Extending washout from 1 to 5 years | 585        | 7.84 | 838 | 8.34|             |              | 0.94 (0.85-1.04) |
| Extending follow-up from 5 to 10 years | 1006       | 8.17 | 1575 | 8.56|             |              | 0.95 (0.88-1.03) |
| Excluding recurrent depression | 743        | 7.79 | 1085| 8.23|             |              | 0.95 (0.86-1.04) |
### eTable 8: Supplementary analysis using inverse probability of censoring weights

|                     | Full cohort                      | hdPS-matched cohort             |
|---------------------|----------------------------------|---------------------------------|
|                     | Without IPCW                    | With IPCW                      | Without IPCW | With IPCW |
| As-treated analysis | HR (95%CI)                       | HR (95%CI)                     | HR (95%CI) | HR (95%CI) |
|                     | 1.22 (1.10-1.34)                 | 1.18 (1.07-1.31)               | 1.00 (0.88-1.14) | 0.98 (0.85-1.12) |
| Intention-to-treat  | 1.20 (1.12-1.28)                 | 1.27 (1.17-1.36)               | 0.94 (0.86-1.03) | 0.92 (0.84-1.01) |

Abbreviations: CI: Confidence interval, hdPS: High-dimensional propensity score, HR: Hazard ratio, IPCW: Inverse probability of censoring weights.

### eTable 9: Supplementary analysis using standardized mortality ratio-weights

|                     | Full cohort                      |
|---------------------|----------------------------------|
|                     | Without SMRW                    | With SMRW                      |
| As-treated analysis | HR (95%CI)                       | HR (95%CI)                     |
|                     | 1.21 (1.10-1.34)                 | 0.98 (0.86-1.11)               |
| Intention-to-treat  | 1.14 (1.06-1.22)                 | 0.94 (0.87-1.03)               |

Abbreviations: CI: Confidence interval, HR: Hazard ratio, SMRW: Standardized mortality ratio weights.
eFigure 5: Supplementary analysis using Z-drugs as comparator
A: On-treatment analysis on full cohort. B: On-treatment analysis on matched cohort. C: Intention-to-treat analysis on full cohort. D: Intention-to-treat analysis on matched cohort. Exposure was benzodiazepine-related drugs (Z-drugs, ATC: N05CF, any tablet strength) and SSRIs. All other inclusion, exclusion, and censoring criteria were identical to the main analysis.
eFigure 6: Control analysis using olanzapine as exposure
A: On-treatment analysis on full cohort. B: On-treatment analysis on matched cohort. C: Intention-to-treat analysis on full cohort. D: Intention-to-treat analysis on matched cohort. Exposure was olanzapine (N05AH03, any tablet strength) and SSRIs. All other inclusion, exclusion, and censoring criteria were identical to the main analysis.