**eAppendix 1.** STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Item No | Recommendation | Page No. | Relevant text from manuscript |
|  **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | 1,2 | Abstract |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 1,2 | Abstract |
| Introduction |  |  |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 | Introduction: paragraphs 1,2,3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 | Introduction: paragraphs 4 |
| Methods |  |  |
| Study design | 4 | Present key elements of study design early in the paper | 4 | Methods: data source and study design and participants |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 | Methods: data source and study design and participants |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 4 | Methods: study design and participants |
| (*b*)For matched studies, give matching criteria and number of exposed and unexposed | 4 | Methods: study design and participants |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4,5 | Methods: study design and participants outcomes |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4,5 | Methods: study design and participants outcomes |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5 | Methods: statistical analysis |
| Study size | 10 | Explain how the study size was arrived at | 4 | Methods: study design and participants |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 5 | Methods: statistical analysis |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 5 | Methods: statistical analysis |
| (*b*) Describe any methods used to examine subgroups and interactions |  | Not applicable  |
| (*c*) Explain how missing data were addressed |  | Not applicable |
| (*d*) If applicable, explain how loss to follow-up was addressed | 5 | Methods: statistical analysis |
| (*e*) Describe any sensitivity analyses | 5 | Methods: statistical analysis |
| Results |  |  |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 5 | Results: paragraph 1Table 1 |
| (b) Give reasons for non-participation at each stage |  | Not applicable |
| (c) Consider use of a flow diagram |  | Figure 1 |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 5 | Results: paragraph 1Table 1 |
| (b) Indicate number of participants with missing data for each variable of interest |  | Not applicable |
| (c) Summarise follow-up time (eg, average and total amount) | 5 | Results: paragraph 1 |
| Outcome data | 15\* | Report numbers of outcome events or summary measures over time | 6 | Results: paragraph 2Table 2 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 6,7 | Results: paragraph 3Table 3,4 |
| (*b*) Report category boundaries when continuous variables were categorized |  | Not applicable |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |  | Not applicable |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 6 | Results: paragraph 4eTable 5, 8, 9 |
| Discussion |  |  |
| Key results | 18 | Summarise key results with reference to study objectives | 7 | Discussion: paragraph 1 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 8,9 | Discussion: study strengths and limitations |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 7,8 | Discussion: paragraph 2,3,4 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 8 | Discussion: paragraph 4 |
| Other information |  |  |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 9 | Funding/Support |

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

**Supplementary Method**

*Detailed description of the propensity score matching*

The treated group is represented by clozapine users (ClozUs), while the control group consists of non-clozapine antipsychotic users (Non-ClozUs). The propensity score indicates the probability of receiving treatment (i.e., being a ClozU), estimated using logistic regression based on the following variables measured before or at the first antipsychotic prescription date, which serves as a proxy for illness onset: 1) Demographics: Age, sex, and education level; 2) Physical Comorbidities: Cardiovascular disease (CVD), hypertension, atrial fibrillation, diabetes, cancer, dyslipidemia, and chronic obstructive pulmonary disease (COPD); 3) Psychiatric Comorbidities: Depression, anxiety disorder, bipolar affective disorder, personality disorder, alcohol use disorder, and substance use disorder; and 4) Suicide Attempts: Only those occurring prior to the illness onset were included in the propensity score calculation. Nearest neighbor matching was employed to pair each treated individual (ClozU) with a control individual (Non-ClozU) who had the closest propensity score at a 1:2 ratio.

**eTable 1.** Supplementary information about the definition of variables and outcomes

|  |  |
| --- | --- |
|  | **ICD-9-CM codes** |
| **Physical comorbidities** |  |
|  Cardiovascular diseases (CVD) | CVD diagnostic categories included coronary heart disease (ICD-9-CM 410-414), stroke (362.3, 430.x, 431.x, 433.x1, 434.x1, 435.x, and 436), peripheral arterial disease (ICD-9-CM 443.8-443.9) and heart failure (428, 402.x1, 404.x1, 404.x3). |
|  Hypertension | 401-405 |
|  Atrial fibrillation | 427.3 |
|  Diabetes | 249.[0-3, 5-9]0, 249.5-249.9, 250, 366.41, 357.2, 362.0, 251.3 |
|  Cancer | 140-239 |
|  Dyslipidemia | 272.0-272.5, 272.8-272.9 |
|  Chronic obstructive pulmonary disease (COPD) | 491, 492, 494, 496 |
| **Psychiatric comorbidities** |  |
|  Depression | 296.2, 296.3, 300.4, 311 |
|  Substance use disorder | 292.0-292.2, 292.8, 292.9, 304, 305 |
|  Anxiety disorder | 293.84, 300.0-300.3, 300.5-300.9 |
|  Bipolar disorder | 296.0, 296.4-8 |
|  Personality disorder | 301 |
|  Alcohol use disorder | 291, 303.0, 303.9, 305.0 |
|  | **ICD-10-CM codes** |
| **Cause-specific mortality** |  |
| Suicide | X60-84, Y10-34 |
| CVD | I00-99 |
| Infection | A00-99, B00-99, G00-04, H30.0, H44.0, H44.1, H45, H60, H65, H66, H70, I30.0, I30.1, I31.1, I33.0, I33.9, I39, I40.0, I41, J00-J22, J36, J39.0, J85, J86, K65.0, K65.9, K67, K75.0, K75.3, K77.0, K81.0, L03, L08.0, M01-03, M72.6, M86, N39.0, N41, N45.9, N70-73, R02, R50, R57, R83, U07.1 |
| Cancer | C00-97 |

**eTable 2.** Incidence rates and IRRs of all-cause and cause-specific mortality stratified by clozapine prescription

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cause of death** | **Clozapine users**N=3,152 | **Non-clozapine antipsychotic users**N=6,304 | **IRR (95% CI)** | **P value** |
| **Events, n** | **Incidence per 100 person-years (95% CI)** | **Events, n** | **Incidence per 100 person-years (95% CI)** |
|  All-cause | 429 | 1.11 (1.01–1.21) | 865 | 1.13 (1.06–1.21) | 0.98 (0.87–1.10) | 0.74 |
|  Suicide | 62 | 0.16 (0.12–0.20) | 167 | 0.22 (0.19–0.25) | 0.73 (0.55–0.98) | 0.037 |
|  CVD | 33 | 0.09 (0.06–0.12) | 95 | 0.12 (0.10–0.15) | 0.69 (0.46–1.02) | 0.061 |
|  Infection | 113 | 0.29 (0.24–0.35) | 160 | 0.21 (0.18–0.24) | 1.40 (1.10–1.78) | 0.0064 |
|  Cancer | 50 | 0.13 (0.10–0.17) | 103 | 0.13 (0.11–0.16) | 0.96 (0.68–1.35) | 0.81 |

*Note.* CVD, cardiovascular disease; IRR, incidence rate ratio

**eTable 3.** Counts of other antipsychotics prescribed when clozapine was discontinued

|  |  |
| --- | --- |
|  | **Discontinuous clozapine users**N=1132 |
| **Other antipsychotics** | **No. of patients (%)** |
| Olanzapine | 791 (69.88) |
| Haloperidol | 621 (54.86) |
| Amisulpride | 530 (46.82) |
| Risperidone | 512 (45.23) |
| Quetiapine | 476 (42.05) |
| Aripiprazole | 402 (35.51) |
| Paliperidone | 363 (32.07) |
| Flupenthixol | 335 (29.59) |
| Sulpiride | 314 (27.74) |
| Zuclopenthixol | 260 (22.97) |
| Trifluoperazine | 221 (19.52) |
| Chlorpromazine | 209 (18.46) |
| Ziprasidone | 111 (9.81) |
| Perphenazine | 61 (5.39) |
| Lurasidone | 37 (3.27) |
| Deanxit | 24 (2.12) |
| Pericyazine | 19 (1.68) |
| Thiothixene | 13 (1.15) |
| Pimozide | 12 (1.06) |
| Brexpiprazole | 9 (0.80) |
| Sertindole | 8 (0.71) |
| Thioridazine | 6 (0.53) |

**eTable 4.** Counts of other antipsychotics co-prescribed with clozapine as polypharmacy

|  |  |
| --- | --- |
|  | **Clozapine polypharmacy** |
|  | **All**N=1,524 | **Discontinuous**N=429 | **Continuous**N=1,095 |
| **Other antipsychotics** | **No. of patients (%)** | **No. of patients (%)** | **No. of patients (%)** |
| Amisulpride | 606 (39.76) | 159 (37.06) | 447 (40.82) |
| Sulpiride | 510 (33.46) | 124 (28.90) | 386 (35.25) |
| Aripiprazole | 322 (21.13) | 78 (18.18) | 244 (22.28) |
| Risperidone | 248 (16.27) | 66 (15.38) | 182 (16.62) |
| Haloperidol | 169 (11.09) | 53 (12.35) | 116 (10.59) |
| Olanzapine | 162 (10.63) | 58 (13.52) | 104 (9.50) |
| Flupenthixol | 138 (9.06) | 38 (8.86) | 100 (9.13) |
| Quetiapine | 127 (8.33) | 35 (8.16) | 92 (8.40) |
| Paliperidone | 84 (5.51) | 23 (5.36) | 61 (5.57) |
| Zuclopenthixol | 81 (5.31) | 29 (6.76) | 52 (4.75) |
| Trifluoperazine | 52 (3.41) | 16 (3.73) | 36 (3.29) |
| Chlorpromazine | 47 (3.08) | 16 (3.73) | 31 (2.83) |
| Deanxit | 14 (0.92) | 2 (0.47) | 12 (1.10) |
| Perphenazine | 10 (0.66) | 5 (1.17) | 5 (0.46) |
| Lurasidone | 9 (0.59) | 3 (0.70) | 6 (0.55) |
| Ziprasidone | 6 (0.39) | 1 (0.23) | 5 (0.46) |
| Pericyazine | 1 (0.07) | 0 (0.00) | 1 (0.09) |
| Pimozide | 1 (0.07) | 1 (0.23) | 0 (0.00) |
| Thioridazine | 1 (0.07) | 0 (0.00) | 1 (0.09) |

**eTable 5.** Sample characteristics at the index date (i.e., the date of the first clozapine prescription) stratified by monotherapy and polypharmacy

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Clozapine users** | **Non-clozapine antipsychotic users** | **P value** | **Maximum Pairwise SMD** |
|  | **Monotherapy** | **Polypharmacy** |  |
|  | **Continuous** | **Discontinuous** | **Continuous** | **Discontinuous** | **Continuous** | **Discontinuous** |
| **Characteristics**  | N=925 | N=703 | N=1,095 | N=429 | N=4,326 | N=1,978 |
| **Age, mean(SD)** | 37.99 (13.34) | 41.50 (13.53) | 37.17 (11.59) | 39.31 (12.00) | 40.61 (12.76) | 36.64 (13.13) | <0.001 | 0.38 |
| **Sex, n (%)** |  |  |  |  |  |  | 0.0056 | 0.17 |
|  Female | 486 (52.54) | 391(55.62) | 516 (47.12) | 214 (49.88) | 2159 (49.91)  | 1031 (52.12)  |  |  |
|  Male | 439 (47.46) | 312 (44.38) | 579 (52.88) | 215 (50.12) | 2167 (50.09) | 947 (47.88) |  |  |
| **Educational level, n (%)** |  |  |  |  |  |  | <0.001 |  |
|  Less than primary | 14 (1.51) | 12 (1.71) | 13 (1.19) | 6 (1.40) | 61 (1.41) | 27 (1.37) |  | 0.04 |
|  Primary | 17 (1.84) | 9 (1.28) | 14 (1.28) | 5 (1.17) | 609 (14.08) | 195 (9.86) |  | 0.22 |
|  Secondary | 116 (12.54) | 118 (16.79) | 106 (9.68) | 50 (11.66) | 2976 (68.79) | 1367 (69.11) |  | 0.16 |
|  Tertiary or above | 614 (66.38) | 453 (64.44) | 785 (71.69) | 294 (68.53) | 615 (14.22) | 367 (18.55) |  | 0.12 |
|  Unknown | 164 (17.73) | 111 (15.79) | 177 (16.16) | 74 (17.25) | 65 (1.50) | 22 (1.11) |  | 0.06 |
| ***Conditions before or at the first antipsychotic date, n (%)*** |
|  **Suicidal attempt**  | 198 (21.41) | 155 (22.05) | 254 (23.20) | 98 (22.84) | 980 (22.65) | 463 (23.41) | 0.88 | 0.05 |
|  **Physical comorbidities** |  |  |  |  |  |  |  |  |
|  CVD | 7 (0.76) | 4 (0.57) | 2 (0.18) | 3 (0.70) | 15 (0.35) | 6 (0.30) | 0.25 | 0.08 |
|  Hypertension | 5 (0.54) | 9 (1.28) | 3 (0.27) | 2 (0.47) | 19 (0.44) | 5 (0.25) | 0.021 | 0.14 |
|  Atrial fibrillation | 1 (0.11) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 2 (0.05) | 0 (0.00) | 0.65 | 0.07 |
|  Diabetes | 16 (1.73) | 14 (1.99) | 12 (1.10) | 6 (1.40) | 59 (1.36) | 24 (1.21) | 0.58 | 0.07 |
|  Cancer | 20 (2.16) | 9 (1.28) | 17 (1.55) | 3 (0.70) | 53 (1.23) | 29 (1.47) | 0.24 | 0.12 |
|  Dyslipidemia | 1 (0.11) | 1 (0.14) | 2 (0.18) | 0 (0.00) | 4 (0.09) | 2 (0.10) | 0.94 | 0.06 |
|  COPD | 2 (0.22) | 1 (0.14) | 0 (0.00) | 0 (0.00) | 6 (0.14) | 2 (0.10) | 0.73 | 0.07 |
|  **Psychiatric comorbidities** |  |  |  |  |  |  |  |  |
|  Depression | 53 (5.73) | 41 (5.83) | 43 (3.93) | 23 (5.36) | 198 (4.58) | 109 (5.51) | 0.18 | 0.09 |
|  Anxiety disorder | 31 (3.35) | 22 (3.13) | 38 (3.47) | 15 (3.50) | 104 (2.40) | 99 (5.01) | <0.001 | 0.14 |
|  Bipolar affective disorder | 20 (2.16) | 26 (3.70) | 29 (2.65) | 11 (2.56) | 152 (3.51) | 85 (4.30) | 0.031 | 0.12 |
|  Personality disorder | 45 (4.86) | 27 (3.84) | 38 (3.47) | 14 (3.26) | 178 (4.11) | 65 (3.29) | 0.32 | 0.08 |
|  Alcohol use disorder | 14 (1.51) | 22 (3.13) | 16 (1.46) | 13 (3.03) | 56 (1.29) | 40 (2.02) | 0.0018 | 0.13 |
|  Substance use disorder | 5 (0.54) | 7 (1.00) | 17 (1.55) | 6 (1.40) | 27 (0.62) | 19 (0.96) | 0.035 | 0.10 |
| ***Conditions between the first antipsychotic date and the index date, n (%)*** |
|  **Suicidal attempt**  | 199 (21.51) | 163 (23.19) | 280 (25.57) | 98 (22.84) | 845 (19.53) | 381 (19.26) | <0.001 | 0.15 |
|  **Physical comorbidities** |  |  |  |  |  |  |  |  |
|  CVD | 17 (1.84) | 15 (2.13) | 8 (0.73) | 1 (0.23) | 77 (1.78) | 20 (1.01) | 0.0036 | 0.17 |
|  Hypertension | 33 (3.57) | 19 (2.70) | 24 (2.19) | 11 (2.56) | 127 (2.94) | 36 (1.82) | 0.060 | 0.11 |
|  Atrial fibrillation | 1 (0.11) | 1 (0.14) | 1 (0.09) | 0 (0.00) | 10 (0.23) | 1 (0.05) | 0.51 | 0.07 |
|  Diabetes | 38 (4.11) | 23 (3.27) | 37 (3.38) | 9 (2.10) | 159 (3.68) | 38 (1.92) | 0.0032 | 0.13 |
|  Cancer | 14 (1.51) | 14 (1.99) | 10 (0.91) | 6 (1.40) | 103 (2.38) | 33 (1.67) | 0.024 | 0.12 |
|  Dyslipidemia | 8 (0.86) | 10 (1.42) | 9 (0.82) | 0 (0.00) | 38 (0.88) | 4 (0.20) | 0.0043 | 0.17 |
|  COPD | 2 (0.22) | 3 (0.43) | 0 (0.00) | 1 (0.23) | 14 (0.32) | 2 (0.10) | 0.24 | 0.09 |
|  **Psychiatric comorbidities** |  |  |  |  |  |  |  |  |
|  Depression | 43 (4.65) | 45 (6.40) | 45 (4.11) | 12 (2.80) | 195 (4.51) | 112 (5.66) | 0.024 | 0.17 |
|  Anxiety disorder | 31 (3.35) | 25 (3.56) | 41 (3.74) | 15 (3.50) | 144 (3.33) | 158 (7.99) | <0.001 | 0.23 |
|  Bipolar affective disorder | 17 (1.84) | 18 (2.56) | 31 (2.83) | 12 (2.80) | 94 (2.17) | 49 (2.48) | 0.64 | 0.06 |
|  Personality disorder | 46 (4.97) | 35 (4.98) | 66 (6.03) | 11 (2.56) | 211 (4.88) | 85 (4.30) | 0.089 | 0.17 |
|  Alcohol use disorder | 36 (3.89) | 13 (1.85) | 37 (3.38) | 14 (3.26) | 80 (1.85) | 59 (2.98) | <0.001 | 0.12 |
|  Substance use disorder | 4 (0.43) | 8 (1.14) | 11 (1.00) | 3 (0.70) | 45 (1.04) | 39 (1.97) | 0.0042 | 0.15 |
| **Number of antipsychotics prescribed before the index date, mean (SD)** | 5.91 (2.30) | 5.91 (2.55) | 6.38 (2.34) | 6.15 (2.54) | 3.15 (1.90) | 2.64 (1.75) | <0.001 | 1.66 |
| **Duration of schizophrenia at the index date, mean (SD)** | 5.33 (3.47) | 4.95 (3.47) | 5.43 (3.35) | 4.95 (3.26) | 6.00 (3.32) | 4.94 (3.24) | <0.001 | 0.32 |

*Note.* CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease

**eTable 6.** Risk of mortality associated with continuous and discontinuous use of clozapine compared to other antipsychotics within samples recruited between 2003 and 2012

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All-cause** | **Suicide** | **CVD** |  | **Infection** |  | **Cancer** |  |
| **Factors**  | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** |
| **Antipsychotic use (Ref. Other antipsychotics)** |  |  |  |  |  |  |  |  |  |  |
|  Discontinuous clozapine | **1.32 (1.02–1.70)** | **0.025** | 2.18 (0.99–4.80) | 0.056 | 1.28 (0.62–2.63) | 1.00 | 0.87 (0.61–1.25) | 1.00 | 1.03 (0.59–1.78) | 1.00 |
|  Continuous clozapine | **1.26 (1.01–1.57)** | **0.040** | **3.33 (1.59–6.98)** | **<0.001** | 1.38 (0.71–2.69) | 1.00 | 0.74 (0.54–1.01) | 0.066 | 1.09 (0.66–1.80) | 1.00 |

*Note.* Accelerated failure time (AFT) models are controlled for 6 imbalanced covariates out of 33 covariates (standardized mean difference (SMD)>0.1; i.e., age, educational level, alcohol use disorder before or at the first antipsychotic date, suicidal attempt between the first antipsychotic date and the index date, schizophrenia duration, and count of previous antipsychotics)

Initial clozapine users between Jan.1, 2003, and Dec. 31, 2012,

N=3,107

Excluded those who had a clozapine prescription before Jan.1, 2005,

N=1,466

Schizophrenia patients had clozapine between Jan.1, 2005, and Dec. 31, 2014, N=4,573

Schizophrenia patients never had clozapine between Jan.1, 1999, and Mar. 31, 2021, N=63,151

Propensity score matching at a ratio of 1:2

Clozapine users (ClozUs)

 N=3,107

Non-clozapine antipsychotic users (Non-ClozUs)

 N=6,214

**eFigure 1.** Flowchart of the sample selection

**eTable 7.** Sample characteristics at the index date (i.e., the date of the first clozapine prescription) of samples recruited between 2005 and 2014

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Clozapine users** | **Non-clozapine antipsychotic users** |  | **Maximum Pairwise SMD** |
|  | **All** | **Continuous** | **Discontinuous** | **All** | **Continuous** | **Discontinuous** | **P value** |
| **Characteristics**  | N=3,107 | N=2,032 | N=1,075 | N=6,214 | N=4,296 | N=1,918 |  |
| **Age, mean(SD)** | 39.17 (13.05) | 37.98 (12.67) | 41.43 (13.46) | 40.25 (13.34) | 41.41 (13.05) | 37.63 (13.61) | <0.001 | 0.29 |
| **Sex, n (%)** |  |  |  |  |  |  | 0.23 | 0.06 |
|  Female | 1604 (51.63) | 1027 (50.54) | 577 (53.67)  | 3189 (51.32) | 2183 (50.81)  | 1006 (52.45)  |  |  |
|  Male | 1503 (48.37) | 1005 (49.46) | 498 (46.33) | 3025 (48.68) | 2113 (49.19) | 912 (47.55) |  |  |
| **Educational level, n (%)** |  |  |  |  |  |  | <0.001 |  |
|  Less than primary | 38 (1.22) | 23 (1.13) | 15 (1.40) | 64 (1.03) | 49 (1.14) | 15 (0.78) |   | 0.06 |
|  Primary | 354 (11.39) | 199 (9.79) | 155 (14.42) | 725 (11.67) | 553 (12.87) | 172 (8.97) |   | 0.17 |
|  Secondary | 2119 (68.20) | 1433 (70.52) | 686 (63.81) | 4276 (68.81) | 2953 (68.74) | 1323 (68.98) |   | 0.14 |
|  Tertiary or above | 552 (17.77) | 351 (17.27) | 201 (18.70) | 1065 (17.14) | 681 (15.85) | 384 (20.02) |  | 0.11 |
|  Unknown | 44 (1.42) | 26 (1.28) | 18 (1.67) | 84 (1.35) | 60 (1.40) | 24 (1.25) |  | 0.04 |
| ***Conditions before or at the first antipsychotic date, n (%)*** |
|  **Suicidal attempt**  | 672 (21.63) | 441 (21.70) | 231 (21.49) | 1358 (21.85) | 921 (21.44) | 437 (22.78) | 0.68 | 0.03 |
|  **Physical comorbidities** |  |  |  |  |  |  |  |  |
|  CVD | 19 (0.61) | 9 (0.44) | 10 (0.93) | 24 (0.39) | 12 (0.28) | 12 (0.63) | 0.025 | 0.09 |
|  Hypertension | 22 (0.71) | 10 (0.49) | 12 (1.12) | 39 (0.63) | 24 (0.56) | 15 (0.78) | 0.14 | 0.07 |
|  Atrial fibrillation | 1 (0.03) | 1 (0.05) | 0 (0.00) | 2 (0.03) | 2 (0.05) | 0 (0.00) | 0.70 | 0.03 |
|  Diabetes | 41 (1.32) | 24 (1.18) | 17 (1.58) | 72 (1.16) | 50 (1.16) | 22 (1.15) | 0.71 | 0.04 |
|  Cancer | 46 (1.48) | 33 (1.62) | 13 (1.21) | 78 (1.26) | 52 (1.21) | 26 (1.36) | 0.59 | 0.04 |
|  Dyslipidemia | 4 (0.13) | 2 (0.10) | 2 (0.19) | 4 (0.06) | 2 (0.05) | 2 (0.10) | 0.54 | 0.04 |
|  COPD | 4 (0.13) | 4 (0.20) | 0 (0.00) | 3 (0.05) | 1 (0.02) | 2 (0.10) | 0.087 | 0.07 |
|  **Psychiatric comorbidities** |  |  |  |  |  |  |  |  |
|  Depression | 177 (5.70) | 110 (5.41) | 67 (6.23) | 337 (5.42) | 220 (5.12) | 117 (6.10) | 0.30 | 0.05 |
|  Anxiety disorder | 95 (3.06) | 68 (3.35) | 27 (2.51) | 200 (3.22) | 95 (2.21) | 105 (5.47) | <0.001 | 0.18 |
|  Bipolar affective disorder | 102 (3.28) | 61 (3.00) | 41 (3.81) | 247 (3.97) | 168 (3.91) | 79 (4.12) | 0.24 | 0.06 |
|  Personality disorder | 120 (3.86) | 76 (3.74) | 44 (4.09) | 235 (3.78) | 164 (3.82) | 71 (3.70) | 0.96 | 0.02 |
|  Alcohol use disorder | 56 (1.80) | 31 (1.53) | 25 (2.33) | 70 (1.13) | 47 (1.09) | 23 (1.20) | 0.014 | 0.10 |
|  Substance use disorder | 36 (1.16) | 21 (1.03) | 15 (1.40) | 58 (0.93) | 34 (0.79) | 24 (1.25) | 0.19 | 0.06 |
| ***Conditions between the first antipsychotic date and the index date, n (%)*** |
|  **Suicidal attempt**  | 727 (23.40) | 480 (23.62) | 247 (22.98) | 1213 (19.52) | 838 (19.51) | 375 (19.55) | <0.001 | 0.10 |
|  **Physical comorbidities** |  |  |  |  |  |  |  |  |
|  CVD | 48 (1.54) | 28 (1.38) | 20 (1.86) | 110 (1.77) | 87 (2.03) | 23 (1.20) | 0.071 | 0.07 |
|  Hypertension | 102 (3.28) | 61 (3.00) | 41 (3.81) | 206 (3.32) | 161 (3.75) | 45 (2.35) | 0.022 | 0.08 |
|  Atrial fibrillation | 3 (0.10) | 2 (0.10) | 1 (0.09) | 10 (0.16) | 8 (0.19) | 2 (0.10) | 0.74 | 0.03 |
|  Diabetes | 120 (3.86) | 88 (4.33) | 32 (2.98) | 239 (3.85) | 192 (4.47) | 47 (2.45) | <0.001 | 0.11 |
|  Cancer | 54 (1.74) | 34 (1.67) | 20 (1.86) | 184 (2.96) | 138 (3.21) | 46 (2.40) | 0.0011 | 0.10 |
|  Dyslipidemia | 29 (0.93) | 19 (0.94) | 10 (0.93) | 63 (1.01) | 53 (1.23) | 10 (0.52) | 0.071 | 0.08 |
|  COPD | 6 (0.19) | 3 (0.15) | 3 (0.28) | 18 (0.29) | 13 (0.30) | 5 (0.26) | 0.73 | 0.03 |
|  **Psychiatric comorbidities** |  |  |  |  |  |  |  |  |
|  Depression | 167 (5.37) | 111 (5.46) | 56 (5.21) | 335 (5.39) | 209 (4.86) | 126 (6.57) | 0.054 | 0.07 |
|  Anxiety disorder | 138 (4.44) | 90 (4.43) | 48 (4.47) | 309 (4.97) | 160 (3.72) | 149 (7.77) | <0.001 | 0.18 |
|  Bipolar affective disorder | 102 (3.28) | 65 (3.20) | 37 (3.44) | 179 (2.88) | 113 (2.63) | 66 (3.44) | 0.23 | 0.05 |
|  Personality disorder | 160 (5.15) | 108 (5.31) | 52 (4.84) | 340 (5.47) | 243 (5.66) | 97 (5.06) | 0.64 | 0.04 |
|  Alcohol use disorder | 124 (3.99) | 91 (4.48) | 33 (3.07) | 157 (2.53) | 92 (2.14) | 65 (3.39) | <0.001 | 0.13 |
|  Substance use disorder | 29 (0.93) | 18 (0.89) | 11 (1.02) | 99 (1.59) | 53 (1.23) | 46 (2.40) | <0.001 | 0.13 |
| **Number of antipsychotics prescribed before the index date, mean (SD)** | 6.45 (2.49) | 6.51 (2.41) | 6.33 (2.62) | 3.25 (2.01) | 3.44 (2.04) | 2.82 (1.88) | <0.001 | 1.63 |
| **Duration of schizophrenia at the index date, mean (SD)** | 6.19 (3.92) | 6.39 (3.91) | 5.80 (3.93) | 7.12 (3.73) | 7.53 (3.64) | 6.19 (3.78) | <0.001 | 0.45 |

*Note.* CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease

**eTable 8.** Incidence rates and IRRs of all-cause and cause-specific mortality stratified by clozapine prescription of samples recruited between 2005 and 2014

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cause of death** | **Clozapine users**N=3,107 | **Non-clozapine antipsychotic users**N=6,214 | **IRR (95% CI)** | **P value** |
| **Events, n** | **Incidence per 100 person-years (95% CI)** | **Events, n** | **Incidence per 100 person-years (95% CI)** |
|  All-cause | 361 | 1.09 (0.98–1.21) | 726 | 1.11 (1.03–1.19) | 0.98 (0.87–1.12) | 0.80 |
|  Suicide | 50 | 0.15 (0.11–0.20) | 137 | 0.21 (0.18–0.25) | 0.72 (0.52–1.00) | 0.048 |
|  CVD | 26 | 0.08 (0.05–0.11) | 81 | 0.12 (0.10–0.15) | 0.63 (0.41–0.99) | 0.042 |
|  Infection | 97 | 0.29 (0.24–0.36) | 135 | 0.21 (0.17–0.24) | 1.42 (1.09–1.84) | 0.0080 |
|  Cancer | 45 | 0.14 (0.10–0.18) | 86 | 0.13 (0.11–0.16) | 1.03 (0.72–1.48) | 0.85 |

*Note.* CVD, cardiovascular disease; IRR, incidence rate ratio

**eTable 9.** Risk of mortality associated with continuous and discontinuous use of clozapine compared to continuous use of other antipsychotics within samples recruited between 2005 and 2014

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All-cause** | **Suicide** | **CVD** |  | **Infection** |  | **Cancer** |  |
| **Factors**  | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** |
| **Antipsychotic use (Ref. Continuous other antipsychotics)** |  |  |  |  |  |  |  |  |  |  |
|  Discontinuous other antipsychotics | 0.97 (0.78–1.20) | 1.00 | 1.07 (0.57–2.02) | 1.00 | 1.47 (0.74–2.94) | 0.76 | 0.98 (0.68–1.42) | 1.00 | 1.02 (0.61–1.70) | 1.00 |
|  Discontinuous clozapine | 1.20 (0.91–1.59) | 0.48 | 2.02 (0.81–5.09) | 0.24 | 1.82 (0.70–4.71) | 0.53 | 0.83 (0.54–1.28) | 1.00 | 1.03 (0.54–1.97) | 1.00 |
|  Continuous clozapine | 1.17 (0.91–1.49) | 0.52 | **3.64 (1.49–8.90)** | **<0.001** | 1.58 (0.72–3.49) | 0.68 | 0.75 (0.52–1.10) | 0.26 | 0.90 (0.52–1.58) | 1.00 |

*Note.* Accelerated failure time (AFT) models are controlled for 12 imbalanced covariates out of 33 covariates (standardized mean difference (SMD)>0.1; i.e., age, educational level, anxiety disorder, and alcohol use disorder before or at the first antipsychotic date, diabetes, cancer, anxiety disorder, alcohol use disorder, substance use disorder and suicidal attempt between the first antipsychotic date and the index date, schizophrenia duration, and count of previous antipsychotics)

**eTable 10.** Risk of mortality associated with clozapine monotherapy and polypharmacy compared to continuous use of other antipsychotics within samples recruited between 2005 and 2014

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All-cause** | **Suicide** | **CVD** |  | **Infection** |  | **Cancer** |  |
| **Factors**  | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** |
| **Antipsychotic use (Ref. Continuous other antipsychotics)** |  |  |  |  |  |  |  |  |  |  |
|  Discontinuous other antipsychotics  | 0.95 (0.77–1.17) | 1.00 | 1.08 (0.57–2.03) | 1.00 | 1.52 (0.76–3.05) | 0.60 | 0.93 (0.64–1.34) | 1.00 | 1.01 (0.61–1.68) | 1.00 |
|  Discontinuous clozapine monotherapy | 1.18 (0.86–1.63) | 0.84 | 1.64 (0.60–4.50) | 1.00 | 2.25 (0.73–6.98) | 0.33 | 0.76 (0.48–1.21) | 0.65 | 1.14 (0.53–2.44) | 1.00 |
|  Continuous clozapine monotherapy | 1.08 (0.81–1.45) | 1.00 | **3.45 (1.13–10.40)** | **0.021** | 1.66 (0.63–4.40) | 0.89 | 0.78 (0.50–1.22) | 0.75 | 0.75 (0.40–1.39) | 1.00 |
|  Discontinuous clozapine polypharmacy | 1.32 (0.87–1.99) | 0.43 | 3.26 (0.71–14.90) | 0.23 | 1.49 (0.40–5.59) | 1.00 | 1.00 (0.51–1.96) | 1.00 | 0.91 (0.38–2.19) | 1.00 |
|  Continuous clozapine polypharmacy | 1.31 (0.97–1.78) | 0.095 | **4.03 (1.33–12.20)** | **0.0059** | 1.52 (0.57–4.08) | 1.00 | 0.73 (0.47–1.15) | 0.38 | 1.21 (0.56–2.60) | 1.00 |

*Note.* Accelerated failure time (AFT) models are controlled for 21 imbalanced covariates out of 33 covariates (standardized mean difference (SMD)>0.1; i.e., age, sex, educational level, cardiovascular disease (CVD), hypertension, chronic obstructive pulmonary disease (COPD), anxiety disorder, and alcohol use before or at the first antipsychotic date, CVD, hypertension, diabetes, cancer, dyslipidemia, depression, anxiety disorder, personality disorder, alcohol use disorder, substance use disorder and suicidal attempt between the first antipsychotic date and the index date, schizophrenia duration, and count of previous antipsychotics)



**eFigure 2.** Distribution of the percentage of clozapine use

**eTable 11.** Risk of mortality associated with the percentage of clozapine use during the entire observation period within samples recruited between 2003 and 2012

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All-cause** | **Suicide** | **CVD** |  | **Infection** |  | **Cancer** |  |
| **Factors**  | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** | **AF (99% CI)** | **Adjusted *p* value** |
| **Percentage of clozapine use during the entire observation period** | 1.09 (0.89–1.34) | 1.00 | **2.99 (1.46–6.08)** | **<0.001** | 1.28 (0.69–2.38) | 1.00 | 0.76 (0.57–1.01) | 0.059 | 0.89 (0.56–1.43) | 1.00 |

*Note.* Accelerated failure time (AFT) models are controlled for covariates (i.e., age, sex, educational level, cardiovascular disease (CVD), hypertension, atrial fibrillation, diabetes, cancer, dyslipidemia, chronic obstructive pulmonary disease (COPD), depression, anxiety disorder, bipolar disorder, personality disorder, alcohol use disorder, substance use disorder and suicidal attempt before or at the first antipsychotic date, CVD, hypertension, atrial fibrillation, diabetes, cancer, dyslipidemia, COPD, depression, anxiety disorder, bipolar disorder, personality disorder, alcohol use disorder, substance use disorder and suicidal attempt between the first antipsychotic date and the index date, schizophrenia duration, and count of previous antipsychotics)

**eTable 12.** Results of Gray’s test for cause-specific mortality comparing continuous vs. discontinuous use of clozapine and other antipsychotics

|  |  |  |
| --- | --- | --- |
|  | **Gray’s test statistic** | ***p* value** |
| **Suicide death** | 8.88 | 0.031 |
| **CVD death** | 13.55 | 0.0036 |
| **Infection death** | 10.17 | 0.017 |
| **Cancer death** | 1.75 | 0.63 |

**eTable 13.** Results of Gray’s test for cause-specific mortality comparing continuous vs. discontinuous clozapine monotherapy, polypharmacy, and other antipsychotics

|  |  |  |
| --- | --- | --- |
|  | **Gray’s test statistic** | ***p* value** |
| **Suicide death** | 11.01 | 0.051 |
| **CVD death** | 13.73 | 0.017 |
| **Infection death** | 22.91 | <0.001 |
| **Cancer death** | 5.52 | 0.36 |

**eTable 14.** Risk of mortality associated with continuous and discontinuous use of clozapine compared to continuous use of other antipsychotics: Fine-Gray model estimates

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Suicide** | **CVD** |  | **Infection** |  | **Cancer** |  |
| **Factors**  | **HR (99% CI)** | **Adjusted *p* value** | **HR (99% CI)** | **Adjusted *p* value** | **HR (99% CI)** | **Adjusted *p* value** | **HR (99% CI)** | **Adjusted *p* value** |
| **Antipsychotic use (Ref. Continuous other antipsychotics)** |  |  |  |  |  |  |  |  |
|  Discontinuous other antipsychotics | 1.17 (0.76–1.79) | 1.00 | 0.58 (0.29–1.17) | 0.23 | 1.06 (0.65–1.71) | 1.00 | 1.09 (0.61–1.94) | 1.00 |
|  Discontinuous clozapine | 0.58 (0.30–1.12) | 0.16 | 0.67 (0.29–1.59) | 1.00 | 1.27 (0.71–2.29) | 1.00 | 1.02 (0.53–1.98) | 1.00 |
|  Continuous clozapine | **0.42 (0.23–0.78)** | **0.0015** | 0.63 (0.28–1.42) | 0.70 | **1.68 (1.05–2.69)** | **0.024** | 0.93 (0.49–1.79) | 1.00 |

*Note.* Fine-Gray models are controlled for 13 imbalanced covariates out of 33 covariates (standardized mean difference (SMD)>0.1; i.e., age, educational level, anxiety disorder, bipolar affective disorder and alcohol use disorder before or at the first antipsychotic date, diabetes, cancer, anxiety disorder,  alcohol use disorder, substance use disorder and suicidal attempt between the first antipsychotic date and the index date, schizophrenia duration, and count of previous antipsychotics)

**eTable 15.** Risk of mortality associated with clozapine monotherapy and polypharmacy compared to continuous use of other antipsychotics: Fine-Gray model estimates

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Suicide** | **CVD** |  | **Infection** |  | **Cancer** |  |
| **Factors**  | **HR (99% CI)** | **Adjusted *p* value** | **HR (99% CI)** | **Adjusted *p* value** | **HR (99% CI)** | **Adjusted *p* value** | **HR (99% CI)** | **Adjusted *p* value** |
| **Antipsychotic use (Ref. Continuous other antipsychotics)** |  |  |  |  |  |  |  |  |
|  Discontinuous other antipsychotics  | 1.18 (0.77–1.81) | 1.00 | 0.60 (0.30–1.21) | 0.31 | 1.19 (0.73–1.94) | 1.00 | 1.05 (0.59–1.88) | 1.00 |
|  Discontinuous clozapine monotherapy | 0.71 (0.34–1.47) | 1.00 | 0.64 (0.24–1.72) | 1.00 | 1.58 (0.86–2.90) | 0.27 | 0.74 (0.32–1.68) | 1.00 |
|  Continuous clozapine monotherapy | 0.49 (0.24–1.02) | 0.061 | 0.54 (0.19–1.56) | 0.66 | 1.64 (0.95–2.86) | 0.10 | 1.14 (0.52–2.49) | 1.00 |
|  Discontinuous clozapine polypharmacy | 0.38 (0.14–1.07) | 0.079 | 0.70 (0.19–2.52) | 1.00 | 0.78 (0.28–2.24) | 1.00 | 1.43 (0.57–3.59) | 1.00 |
|  Continuous clozapine polypharmacy | **0.36 (0.17–0.79)** | **0.0043** | 0.71 (0.26–1.92) | 1.00 | 1.60 (0.87–2.93) | 0.23 | 0.70 (0.29–1.69) | 1.00 |

*Note.* Fine-Gray models are controlled for 22 imbalanced covariates out of 33 covariates (standardized mean difference (SMD)>0.1; i.e., age, sex, educational level, hypertension, cancer, anxiety disorder, bipolar affective disorder, alcohol use disorder and substance use disorder before or at the first antipsychotic date, cardiovascular disease (CVD), hypertension, diabetes, cancer, dyslipidemia, depression, anxiety disorder, personality disorder, alcohol use disorder, substance use disorder and suicidal attempt between the first antipsychotic date and the index date, schizophrenia duration, and count of previous antipsychotics)