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**e-Figure 1.** Study flow diagram

Taiwan population, from January 1, 2000, to December 31, 2019

(N ≈ 23 000 000)

Patients receiving diagnosis of schizophrenia (*ICD-9-CM* code 295.xx; *ICD-10* codes F20.x, F25.x) between January 1, 2001, and December 31, 2019

(N = 212 601)

Exclusion of patients with at least one diagnosis of bipolar disorder (*ICD-9-CM* codes 296.0-296.16, 296.4-296.81, 296.89, 296.9; *ICD-10* codes: F30.x, F31.x) between January 1, 2001, and December 31, 2019

(N = 99 011)

Patients with diagnosis of schizophrenia between January 1, 2001, and December 31, 2019

(N = 113 590)

Exclusion of patients without sex or birth date data

(n = 3290)

Patients with diagnosis of schizophrenia

(N = 110 300)

Linking with national mortality database for single-cause mortality between January 1, 2001, and December 31, 2019

All-cause (n = 22 528), natural (n = 19 754), suicide mortality (n = 1606), and other unnatural death (n = 1168)

Abbreviations: *ICD-9-CM* = *International Classification of Diseases, Ninth Edition, Clinical Modification*; *ICD-10* = *International Classification of Diseases, Tenth Edition*

**e-Figure 2.** Survival curves for all-cause, natural, and suicide mortality during the 5-year follow-up period in the schizophrenia cohort, stratified by sex







**e-Table 1.** ATC codes for lipid-modifying agents and concomitant medications

|  |  |
| --- | --- |
| **Medications** | ATC codes |
| Cardiovascular drugs |  |
| Agents acting on renin-angiotensin system | C09 |
| Beta blockers | C07 |
| Calcium channel blockers | C08 |
| Diuretic agents | C03 |
| Antihypertensives | C02 |
| Lipid-modifying agents | C10 |
| Statin | C10AA |
| Atorvastatin | C10AA05 |
| Rosuvastatin | C10AA07 |
| Simvastatin | C10AA01 |
| Pitavastatin | C10AA08 |
| Fluvastatin | C10AA04 |
| Pravastatin | C10AA03 |
| Lovastatin | C10AA02 |
| Fibrate | C10AB |
| Fenofibrate | C10AB05 |
| Gemfibrozil | C10AB04 |
| Bezafibrate | C10AB02 |
| Bile acid sequestrant | C10AC |
| Nicotinic acid and derivatives | C10AD |
| Drugs used for diabetes | A10 |
| Antithrombotic agents | B01 |
| Respiratory drugs |  |
| Nasal preparations | R01 |
| Cough and cold preparation | R05 |
| Drugs for obstructive airway diseases | R03 |
| Antihistamines | R06 |
| Corticosteroids for systemic use | H02 |
| Anti-Parkinson drugs | N04 |
| First generation antipsychotics | N05AA01、N05AD01、N05AF01、N05AH01、N05AA02、N05AB02、N05AB03、N05AB06、N05AC02、N05AC04、N05AD04、N05AF02、N05AF03、N05AF04、N05AF05、N05AG02、N05AG03、N05AH06、N05AL01、N05AL07、N05AX09 |
| Second generation antipsychotics | N05AH02、N05AH03、N05AH04、N05AX11、N05AX08、N05AL05、N05AX12、N05AE04、N05AE05、N05AH05、N05AX13 |
| Antidepressants | N06A |
| Mood stabilizers | N05AN01、N03AF、N03AG、N03AX |
| Benzodiazepines | N05CD09、N05BE01、N05CD08、N05CD05、N05CF03、N05CF02、N05CF01、N05BA12、N05BA08、N05CD04、N05CD03、N05BA06、N05CD06、N05BA04、N05CD07、N05BA02、N05BA09、N03AE01、N05BA22、N05BA01、N05BA06、N05CD01、N05BA03、N05CD02、N05BA16、N05BA05、A12BA |

**e-Table 2.** ICD-9-CM codes for physical illnesses and psychiatric comorbidities

|  |  |
| --- | --- |
| **Physical comorbidities** | *ICD-9-CM* codes |
| Cardiovascular disease |  |
| Hypertension | 401–405 |
| Ischemic heart disease | 410–414 |
| Congestive heart failure | 428, 429.3, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 |
| Other forms of heart disease | 420–429 |
| Diseases of arteries, arterioles, and capillaries | 440–449 |
| Diseases of veins and lymphatics | 451–459 |
| Cerebrovascular diseases | 430–438 |
| Respiratory diseases |  |
| URI | 460 |
| Pneumonia | 480–486, 507 |
| Asthma | 493 |
| Chronic bronchitis | 491 |
| COPD | 490, 491, 492, 496, A323, A325 |
| Tuberculosis | 010–018 |
| Gastrointestinal diseases |  |
| Chronic hepatic disease | 571 |
| Ulcer | 531–534 |
| Irritable bowel syndrome | 564.1 |
| Renal diseases |  |
| Chronic kidney disease and renal failure | 585, 586, V56, V420, V451, 39.27, 39.42, 39.93, 39.94, 39.95, 54.98 |
| Endocrine/metabolic diseases |  |
| Diabetes mellitus | 250 |
| Hyperlipidemia | 272 |
| Musculoskeletal/integument diseases |  |
| Connective tissue disease | 710, 714 |
| Atopic dermatitis | 691 |
| HIV infection | 042, 043, 044 |
| Cancer | 140–209 |
| **Psychiatric comorbidities** | *ICD-9-CM* codes |
| Neurocognitive disorder | 294、290 |
| Alcohol-use-related disorder | 291、303、305.0 |
| Substance-use-related disorder | 292、304、305 (exclude 305.0) |
| Depressive disorder | 296.2、296.3、300.4、311 |
| Anxiety disorder | 300.0、300.9 |
| Intellectual disability | 317、318、319 |

Abbreviations: COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; *ICD-9-CM* = *International Classification of Diseases, Ninth Edition, Clinical Modification*; URI = upper respiratory tract infection

**e-Table 3.** ICD-10-CM codes for physical illnesses and psychiatric comorbidities

|  |  |
| --- | --- |
| **Physical comorbidities** | *ICD-10-CM* codes |
| Cardiovascular Disease |  |
| Hypertension | I10、I110、I119、I129、I120、I1310、I130、I1311、I132 |
| Ischemic heart disease | I2109、R0989、I220、I2101、I2102、I2119、I221、I2111、I2129、I228、I214、I222、I2121、I213、I229、I241、I200、I240、I248、I249、I252、I208、I201、I209、I2582、I2583、I2510、I25110、I25111、I25118、I25119、I25700、I25701、I25708、I25709、I25710、I25711、I25718、I25719、I25720、I25721、I25728、I25729、I25730、I25731、I25738、I25739、I25750、I25751、I25758、I25759、I25760、I25761、I25768、I25769、I25790、I25791、I25798、I25799、I25810、I25811、I25812、I253、I2541、I2542、I255、I256、I2589、I259 |
| Congestive heart failure | I110、I130、I132、I420、I421、I422、I423、I424、I425、I426、I427、I428、I429、I501、I509、I517' I5020、I5021、I5022、I5023、I5030、I5031、I5032、I5033、I5040、I5041、I5042、I5043、I43 |
| Other forms of heart disease | I301、I309、I300、I308、I330、 I339、 I409、I400、I401、I408、I312、I310、I311、 I318、I313、I314、I319、I340、I341、I342、I348、I349、I350、I351、I352、I358、I359、I360、I361、I362、I368、I369、I370、I371、I372、I378、I379、 I423、I421、I428、I424、I420、I422、I425、I429、I426、I427、I442、I443、I440、I441、I444、I445、I446、I447、I450、I451、I454、I452、I453、I455、I456、I458、I459、I471、I492、I470、I472、I493、I479、I480、I482、I489、I481、I483、I484、I490、I462、I468、I469、I494、I491、I495、R001、I498、I499、I502、I503、I504、I509、I501、I514、I32、I41、I38、I43、I39 |
| Diseases of arteries, arterioles, and capillaries | I700、I701、I758、I702、I709、I750、I703、I706、I707、I704、I705、I708、I710、I711、I712、I713、I714、I718、I715、I716、I719、I778、I790、I721、I722、I777、I723、I724、I720、I728、I729、I730、I731、I791、I798、I738、I739、I740、I741、I742、I743、I744、I745、I748、I749、M300、M302、M308、M317、M303、M310、M312、M301、M313、M315、M316、M311、M314、I770、I771、I772、I773、I774、I775、M318、M319、I776、I779、I780、I781、I788、I789 |
| Diseases of veins and lymphatics | I800、I801、I802、I803、I808、I809、I81、I820、I821、I822、I823、I824、I825、I826、I827、I828、I829、I82A、I82B、I82C、I830、I831、I832、I838、I839、K640、K641、K642、K643、K648、K644、K645、K649、I850、I851、I860、I861、I862、I863、I864、I868、I972、I890、I891、I898、I899、I951、I950、I958、I952、I953、I959、R58 |
| Cerebrovascular disease | I60、I61、I62、I65、I63、I66、G45、G46、I67 |
| Respiratory diseases |  |
| URI | J00 |
| Pneumonia | J14、J17、J13、J120、J121、J122、J123、J128、J128、J129、J181、J150、J151、J154、J154、J153、J154、J152、J152、J152、J158、J155、J156、A481、J158、J159、J157、J160、J168、B250、A379、A221、B440、J180、J188、J189、J690、J691、J698 |
| Asthma | J452、J453、J454、J455、J459、J449、J440、J441 |
| Chronic bronchitis | J42、J410、J411、J418、J449、J441、J440 |
| COPD | J410、J411、J449、J440、J441、J418、J439、J430、J431、J432、J438、J439、J449 |
| Gastrointestinal diseases |  |
| Chronic hepatic disease | K70、K73、K75、K74、K76、R16 |
| Ulcer disease | K25、K31、K56、K26、K27、K28 |
| Irritable bowel syndrome | K580、K589 |
| Renal diseases |  |
| Chronic kidney disease and renal failure | N184、N185、N186、N189 Procedures code (0313、0314、0315、0316、0317、0318、0319、031A、031B、031C、0312、03WY、03PY、5A1D、3E1M) |
| Endocrine/metabolic diseases |  |
| Hyperlipidemia | E780、E781、E782、E783、E784、E785、E786、E881、E752、E753、E770、E771、E778、E779、E713、E755、E787、E788、E882、E888、E756、E789 |
| Diabetes mellitus | E119、E139、E109、E116、E106、E101、E080、E090、E110、E130、E086、E096、E131、E136、E112、E132、E102、E083、E093、E113、E133、E103、E084、E094、E114、E134、E104、E085、E095、E115、E135、E105、E088、E098、E118、E138、E108 |
| Musculoskeletal/integument diseases |  |
| Connective tissue disease | M32、M34、M35、M33、M36、M05、M06、M08、M12 |
| Atopic dermatitis | L22、L200、L208、L209 |
| HIV infection | B20 |
| Cancer | C01、C07、C12、C19、C20、C23、C33、C37、C55、C58、C52、C61、C73、D45、C000、Z511、C001、C003、C004、C005、C006、C008、C002、C009、C020、C021、C022、C023、C028、C024、C029、C080、C081、C089、C030、C031、C039、C040、C041、C048、C049、C060、C061、C050、C051、C052、C058、C059、C062、C068、C069、C098、C099、C090、C091、C100、C101、C108、C102、C103、C104、C109、C110、C111、C112、C113、C118、C119、C130、C131、C132、C138、C139、C140、C142、C148、C153、C154、C155、C158、C159、C160、C7A0、C164、C163、C161、C162、C165、C166、C168、C169、C170、C171、C172、C173、C178、C179、C183、C184、C186、C187、C180、C181、C182、C185、C188、C189、C211、C210、C212、C218、C220、C222、C223、C224、C227、C228、C221、C229、C240、C241、C248、C249、C250、C251、C252、C253、C254、C257、C258、C259、C480、C451、C481、C488、C482、C260、C261、C269、C300、C301、C310、C311、C312、C313、C318、C319、C320、C321、C322、C323、C328、C329、C340、C341、C342、C343、C348、C349、C384、C450、C380、C452、C381、C382、C388、C383、C390、C399、C410、C411、C412、C413、C400、C401、C414、C402、C403、C408、C409、C419、C470、C490、C471、C491、C472、C492、C473、C493、C474、C494、C475、C495、C476、C496、C478、C498、C479、C499、C430、D030、C431、D031、C432、D032、C433、D033、C434、D034、C435、D035、C436、D036、C437、D037、C438、D038、C439、D039、C440、C4A0、C441、C4A1、C442、C4A2、C443、C4A3、C444、C4A4、C445、C4A5、C446、C4A6、C447、C4A7、C448、C4A8、C449、C4A9、C500、C501、C502、C503、C504、C505、C506、C508、C509、C460、C461、C462、C464、C465、C463、C467、C469、C530、C531、C538、C539、C58、C541、C542、C543、C549、C540、C548、C561、C562、C569、C570、C571、C573、C572、C574、C510、C511、C512、C519、C518、C577、C578、C579、C620、C621、C629、C600、C601、C602、C609、C630、C631、C632、C608、C637、C638、C639、C670、C671、C672、C673、C674、C675、C676、C677、C678、C679、C641、C642、C649、C651、C652、C659、C661、C662、C669、C680、C681、C688、C689、C694、C696、C695、C690、C691、C692、C693、C698、C699、C710、C711、C712、C713、C714、C715、C716、C717、C719、C722、C723、C724、C725、C700、C709、C720、C721、C701、C729、E312、C740、C741、C749、C750、C751、C752、C753、C754、C755、C758、C759、C760、C761、C762、C763、C764、C765、C457、C768、C770、C7B0、C771、C772、C773、C774、C775、C778、C779、C780、C781、C782、J910、C783、C784、C785、C786、R180、C787、C788、C790、C791、C792、C793、C794、C795、C796、C797、C798、C799、C7A1、C7A8、C7B1、C7B8、C800、D3A8、C459、C801、C833、C846、C847、C852、C964、C965、C835、C837、C830、C838、C839、C865、C866、C817、C819、C810、C814、C811、C812、C813、C820、C821、C822、C823、C824、C825、C826、C828、C829、C840、C844、C849、C84A、C84Z、C860、C862、C863、C861、C841、C96A、C914、C960、C962、C831、C851、C858、C859、C864、C884、C969、C96Z、C900、C901、C882、C883、C888、C889、C902、C903、C910、C911、C91Z、C913、C915、C916、C91A、C919、C920、C924、C925、C926、C92A、C921、C922、C923、C92Z、C929、C933、C930、C931、C939、C93Z、C940、C942、C943、C948、C950 |
| **Psychiatric comorbidities** | *ICD-10-CM* codes |
| Neurocognitive disorder | F04、F09、F05、F015、F0390 |
| Alcohol-use-related disorder | F1012、F1022、F1023、F1092、F1026、F1096、F1097、F1027、F1015、F1025、F1095、F1014、F1018、F1024、F1028、F1098、F1019、F1029、F1094、F1099、F101、F102 |
| Substance-use-related disorder | F1123、F1193、F1323、F1393、F1423、F1523、F1593、F1720、F1721、F1722、F1729、F1923、F1993、F1115、F1125、F1195、F1215、F1225、F1295、F1315、F1325、F1395、F1415、F1425、F1495、F1515、F1525、F1595、F1120、F1121、F1320、F1321、F1420、F1421、F1220、F1221、F1520、F1521、F1620、F1621、F1820、F1920、F1821、F1921、F172、F121、F129、F161、F169、F131、F139、F111、F119、F141、F149、F151、F159、F191、F199、F181、F189、F550、F551、F552、F553、F554、F558 |
| Depressive disorder | F329~F325、F334、F339、F330、F331、F332、F333、F341 |
| Anxiety disorder | F411、F419、F413、F418、F410、F419、F489、R452、R455、R456、F99 |
| Intellectual disability | F70、F71、F72、F73、F78、F79 |

Abbreviations: COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; *ICD-10-CM* = *International Classification of Diseases, Tenth Edition, Clinical Modification*; URI = upper respiratory tract infection

**e-Table 4.** Standardized mortality ratios of each causes of death among a nationwide cohort of patients with schizophrenia, 2001-2019 (N = 110 300), stratified by sex

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Men (n = 59 894) | | | Women (n = 50 406) | | | Total (n = 110 300) | | |
| Observed | Expected | SMR (95% CI) | Observed | Expected | SMR (95% CI) | Observed | Expected | SMR (95% CI) |
| Causes of death |  |  |  |  |  |  |  |  |  |
| Total | 13326 | 2244.19 | 5.94 (5.84-6.04) | 9202 | 1607.34 | 5.72 (5.61-5.84) | 22528 | 3851.53 | 5.85 (5.77-5.93) |
| Natural causes | 11401 | 1903.36 | 5.99 (5.88-6.10) | 8353 | 1489.50 | 5.61 (5.49-5.73) | 19754 | 3392.86 | 5.82 (5.74-5.90) |
| Endocrine diseases | 761 | 113.15 | 6.73 (6.26-7.22) | 833 | 142.04 | 5.86 (5.47-6.28) | 1594 | 255.19 | 6.25 (5.94-6.56) |
| Cardiovascular disease | 1865 | 282.83 | 6.59 (6.30-6.90) | 1576 | 229.90 | 6.86 (6.52-7.20) | 3441 | 512.74 | 6.71 (6.49-6.94) |
| Cerebrovascular disease | 814 | 134.97 | 6.03 (5.62-6.46) | 535 | 115.36 | 4.64 (4.25-5.05) | 1349 | 250.33 | 5.39 (5.11-5.68) |
| Neurological disease | 365 | 31.32 | 11.65 (10.49-12.91) | 247 | 23.76 | 10.40 (9.14-11.78) | 612 | 55.08 | 11.11 (10.25-12.03) |
| Respiratory diseases | 2056 | 185.07 | 11.11 (10.63-11.60) | 1190 | 128.94 | 9.23 (8.71-9.77) | 3246 | 314.01 | 10.34 (9.98-10.70) |
| Gastrointestinal diseases | 1108 | 189.13 | 5.86 (5.52-6.21) | 462 | 88.04 | 5.25 (4.78-5.75) | 1570 | 277.17 | 5.66 (5.39-5.95) |
| Genitourinary diseases | 520 | 63.93 | 8.13 (7.45-8.86) | 618 | 90.63 | 6.82 (6.29-7.38) | 1138 | 154.56 | 7.36 (6.94-7.80) |
| Dermatological diseases | 83 | 6.87 | 12.09 (9.63-14.98) | 58 | 8.95 | 6.48 (4.92-8.38) | 141 | 15.82 | 8.91 (7.50-10.51) |
| Bone diseases | 88 | 12.04 | 7.31 (5.86-9.00) | 70 | 14.90 | 4.70 (3.66-5.94) | 158 | 26.94 | 5.87 (4.99-6.85) |
| Cancer | 1799 | 668.48 | 2.69 (2.57-2.82) | 1459 | 502.30 | 2.90 (2.76-3.06) | 3258 | 1170.78 | 2.78 (2.69-2.88) |
| Others | 1942 | 215.57 | 9.01 (8.61-9.42) | 1305 | 147.20 | 8.87 (8.39-9.36) | 3247 | 362.76 | 8.95 (8.65-9.26) |
| Unnatural causes | 1925 | 340.83 | 5.65 (5.40-5.91) | 849 | 117.84 | 7.20 (6.73-7.71) | 2774 | 458.67 | 6.05 (5.82-6.28) |
| Suicide | 1087 | 113.62 | 9.57 (9.01-10.15) | 519 | 48.80 | 10.64 (9.74-11.59) | 1606 | 162.42 | 9.89 (9.41-10.38) |
| Homicide | 35 | 6.96 | 5.03 (3.50-7.00) | 8 | 2.20 | 3.64 (1.57-7.18) | 43 | 9.15 | 4.70 (3.40-6.33) |
| Accidental death | 729 | 213.65 | 3.41 (3.17-3.67) | 274 | 64.62 | 4.24 (3.75-4.77) | 1003 | 278.27 | 3.60 (3.38-3.83) |
| Others | 74 | 6.60 | 11.21 (8.80-14.07) | 48 | 2.22 | 21.57 (15.91-28.60) | 122 | 8.83 | 13.82 (11.48-16.50) |

Abbreviations: SMR = standardized mortality ratio

**e-Table 5.** Distributions of medication use during 5-year follow-up period in schizophrenia cohort and among patients who died from any cause (N = 110 300)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cohort**  **(N = 110** **300)** |  | **All-Cause Mortality**  **(n =12** **817)** |  |
|  | n | % | n | % |
| Cardiovascular drugs |  |  |  |  |
| Agents acting on renin-angiotensin system | 16634 | 15.1 | 4012 | 31.3 |
| Beta blockers | 42223 | 38.3 | 4925 | 38.4 |
| Calcium channel blockers | 22547 | 20.4 | 5761 | 44.9 |
| Diuretic agents | 20697 | 18.8 | 7286 | 56.8 |
| Antihypertensives | 6363 | 5.8 | 1641 | 12.8 |
| Lipid-modifying agents | 11583 | 10.5 | 1345 | 10.5 |
| Drugs used for diabetes | 13484 | 12.2 | 4310 | 33.6 |
| Antithrombotic agents | 18346 | 16.6 | 5114 | 39.9 |
| Respiratory drugs |  |  |  |  |
| Nasal preparations | 54291 | 49.2 | 3230 | 25.2 |
| Cough and cold preparations | 86761 | 78.7 | 9750 | 76.1 |
| Drugs for obstructive airway diseases | 59792 | 54.2 | 8019 | 62.6 |
| Antihistamines | 85149 | 77.2 | 8584 | 67.0 |
| Corticosteroids for systemic use | 48269 | 43.8 | 7119 | 55.5 |
| Anti-Parkinson drugs | 56547 | 51.3 | 5075 | 39.6 |
| First generation antipsychotics | 56953 | 51.6 | 6236 | 48.7 |
| Second generation antipsychotics | 73223 | 66.4 | 7598 | 59.3 |
| Antidepressants | 41952 | 38.0 | 4299 | 33.5 |
| Mood stabilizers | 20122 | 18.2 | 2635 | 20.6 |
| Benzodiazepines | 89575 | 81.2 | 10462 | 81.6 |

**e-Table 6.** Distributions of medication use during 5-year follow-up period in schizophrenia cohort and among patients who died from natural cause (N =110 300)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cohort**  **(N = 110** **300)** |  | **Natural Mortality**  **(n = 11** **049)** |  |
|  | n | % | n | % |
| Cardiovascular drugs |  |  |  |  |
| Agents acting on renin-angiotensin system | 16634 | 15.1 | 3863 | 35.0 |
| Beta blockers | 42223 | 38.3 | 4309 | 39.0 |
| Calcium channel blockers | 22547 | 20.4 | 5509 | 49.9 |
| Diuretic agents | 20697 | 18.8 | 7000 | 63.4 |
| Antihypertensives | 6363 | 5.8 | 1570 | 14.2 |
| Lipid-modifying agents | 11583 | 10.5 | 1247 | 11.3 |
| Drugs used for diabetes | 13484 | 12.2 | 4103 | 37.1 |
| Antithrombotic agents | 18346 | 16.6 | 4882 | 44.2 |
| Respiratory drugs |  |  |  |  |
| Nasal preparations | 54291 | 49.2 | 2709 | 24.5 |
| Cough and cold preparations | 86761 | 78.7 | 8758 | 79.3 |
| Drugs for obstructive airway diseases | 59792 | 54.2 | 7465 | 67.6 |
| Antihistamines | 85149 | 77.2 | 7629 | 69.0 |
| Corticosteroids for systemic use | 48269 | 43.8 | 6578 | 59.5 |
| Anti-Parkinson drugs | 56547 | 51.3 | 4115 | 37.2 |
| First generation antipsychotics | 56953 | 51.6 | 5239 | 47.4 |
| Second generation antipsychotics | 73223 | 66.4 | 6511 | 58.9 |
| Antidepressants | 41952 | 38.0 | 3591 | 32.5 |
| Mood stabilizers | 20122 | 18.2 | 2300 | 20.8 |
| Benzodiazepines | 89575 | 81.2 | 8979 | 81.3 |

**e-Table 7.** Distributions of medication use during 5-year follow-up period in schizophrenia cohort and among patients who died from suicide (N = 110 300)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cohort**  **(N = 110** **300)** |  | **Suicide Mortality**  **(n = 1090)** |  |
|  | n | % | n | % |
| Cardiovascular drugs |  |  |  |  |
| Agents acting on renin-angiotensin system | 16634 | 15.1 | 54 | 5.0 |
| Beta blockers | 42223 | 38.3 | 383 | 35.1 |
| Calcium channel blockers | 22547 | 20.4 | 100 | 9.2 |
| Diuretic agents | 20697 | 18.8 | 115 | 10.6 |
| Antihypertensives | 6363 | 5.8 | 31 | 2.8 |
| Lipid-modifying agents | 11583 | 10.5 | 46 | 4.2 |
| Drugs used for diabetes | 13484 | 12.2 | 75 | 6.9 |
| Antithrombotic agents | 18346 | 16.6 | 101 | 9.3 |
| Respiratory drugs |  |  |  |  |
| Nasal preparations | 54291 | 49.2 | 307 | 28.2 |
| Cough and cold preparations | 86761 | 78.7 | 563 | 51.7 |
| Drugs for obstructive airway diseases | 59792 | 54.2 | 290 | 26.6 |
| Antihistamines | 85149 | 77.2 | 561 | 51.5 |
| Corticosteroids for systemic use | 48269 | 43.8 | 289 | 26.5 |
| Anti-Parkinson drugs | 56547 | 51.3 | 614 | 56.3 |
| First generation antipsychotics | 56953 | 51.6 | 622 | 57.1 |
| Second generation antipsychotics | 73223 | 66.4 | 699 | 64.1 |
| Antidepressants | 41952 | 38.0 | 448 | 41.1 |
| Mood stabilizers | 20122 | 18.2 | 174 | 16.0 |
| Benzodiazepines | 89575 | 81.2 | 917 | 84.1 |

**e-Table 8.** Associations of unadjusted risk of all-cause, natural, and suicide mortality with use of lipid-modifying agents during the 5-year follow-up period in schizophrenia cohort (N = 110 300)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristics | **All-Cause Mortality**  **(n = 12** **817)** | | | **Natural Mortality**  **(n = 11** **049)** | | | **Suicide Mortality**  **(n = 1090)** | | |
|  | Crude HRa | 95% CI | *P* value | Crude HRa | 95% CI | *P* value | Crude HRa | 95% CI | *P* value |
| Lipid**-**modifying agent | 0.75 | 0.64-0.87 | <.001 | 0.36 | 0.17-0.76 | 0.008 | 0.80 | 0.68-0.94 | 0.005 |
| Statin | 0.77 | 0.65-0.92 | 0.004 | 0.82 | 0.68-0.99 | 0.034 | 0.44 | 0.20-0.97 | 0.042 |
| Atorvastatin | 0.84 | 0.64-1.09 | 0.181 | 0.83 | 0.63-1.10 | 0.200 | 0.70 | 0.26-1.88 | 0.483 |
| Rosuvastatin | 0.81 | 0.57-1.14 | 0.225 | 0.94 | 0.66-1.33 | 0.713 | – | – | – |
| Simvastatin | 0.58 | 0.29-1.16 | 0.126 | 0.59 | 0.28-1.24 | 0.163 | – | – | – |
| Pitavastatin | 0.89 | 0.48-1.66 | 0.723 | 1.03 | 0.56-1.92 | 0.923 | – | – | – |
| Fluvastatin | 0.38 | 0.14-1.00 | 0.050 | 0.44 | 0.16-1.16 | 0.096 | – | – | – |
| Pravastatin | 1.42 | 0.86-2.36 | 0.174 | 1.54 | 0.91-2.60 | 0.105 | 1.13 | 0.16-7.98 | 0.902 |
| Lovastatin | 0.19 | 0.05-0.77 | 0.019 | 0.11 | 0.02-0.79 | 0.028 | 1.15 | 0.16-8.13 | 0.886 |
| Fibrate | 0.52 | 0.36-0.75 | <.001 | 0.56 | 0.38-0.82 | 0.003 | 0.22 | 0.03-1.59 | 0.135 |
| Fenofibrate | 0.59 | 0.37-0.94 | 0.027 | 0.65 | 0.40-1.04 | 0.071 | – | – | – |
| Gemfibrozil | 0.48 | 0.25-0.92 | 0.027 | 0.49 | 0.25-0.99 | 0.045 | 0.64 | 0.09-4.53 | 0.655 |
| Bezafibrate | 0.28 | 0.04-1.94 | 0.196 | 0.32 | 0.05-2.25 | 0.251 | – | – | – |
| Bile acid sequestrant | 6.82 | 3.06-15.18 | <.001 | 8.01 | 3.61-17.77 | <.001 | – | – | – |
| Nicotinic acid and derivatives | 1.87 | 0.27-13.00 | 0.526 | 2.12 | 0.30-15.04 | 0.451 | – | – | – |

a Estimated using univariable Cox proportional hazards regression with a time-dependent model

Abbreviations: HR = hazard ratio

**e-Table 9.** Associations of duration of use and defined daily dose of lipid-modifying agents with risks of all-cause, natural, and suicide mortality during 5-year follow-up period in schizophrenia cohort (N = 110 300)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristics | **All-Cause Mortality**  **(n = 12** **817)** | | | **Natural Mortality**  **(n = 11** **049)** | | | **Suicide Mortality**  **(n = 1090)** | | |
|  | aHRa,b | 95% CI | *P* value | aHRa,c | 95% CI | *P* value | aHRa,d | 95% CI | *P* value |
| **Cumulative duration (per 10 days)** |  |  |  |  |  |  |  |  |  |
| Statins | 0.71 | 0.67-0.75 | <.001 | 0.70 | 0.66-0.75 | <.001 | 0.80 | 0.59-1.09 | 0.155 |
| Fibrates | 0.76 | 0.68-0.86 | <.001 | 0.77 | 0.68-0.87 | <.001 | 0.69 | 0.38-1.24 | 0.212 |
| Bile acid sequestrant | 1.37 | 1.12-1.68 | 0.002 | 1.35 | 1.10-1.66 | 0.005 | – | –. | – |
| Nicotinic acid and derivatives | 0.40 | 0.10-1.69 | 0.213 | 0.40 | 0.10-1.68 | 0.213 | – | –. | – |
| **Cumulative dose (per 10 DDDs)** |  |  |  |  |  |  |  |  |  |
| Statins | 0.67 | 0.62-0.73 | <.001 | 0.66 | 0.61-0.72 | <.001 | 0.83 | 0.60-1.13 | 0.237 |
| Fibrates | 0.70 | 0.60-0.82 | <.001 | 0.71 | 0.61-0.84 | <.001 | 0.59 | 0.26-1.35 | 0.209 |
| Bile acid sequestrant | 0.04 | 0-9.44 | 0.247 | 0.02 | 0-5.85 | 0.183 | – | –. | – |
| Nicotinic acid and derivatives | 0.53 | 0.17-1.66 | 0.276 | 0.53 | 0.17-1.64 | 0.272 | – | –. | – |

a Estimated using multivariable Cox proportional hazards regression with time-dependent model

b All-cause mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

c Natural mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

d Suicide mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

Abbreviation: aHR = adjusted hazard ratio; DDD = defined daily dose

**e-Table 10.** The first sensitivity analysis: Part 1. associations of adjusted risks of all-cause, natural, and suicide mortality with use of lipid-modifying agents during 10-year follow-up period in schizophrenia cohort (N = 110 300)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristics | **All-Cause Mortality**  **(n = 18 399)** | | | **Natural Mortality**  **(n = 16 025)** | | | **Suicide Mortality**  **(n = 1418)** | | |
|  | aHRa,b | 95% CI | *P* value | aHRa,c | 95% CI | *P* value | aHRa,d | 95% CI | *P* value |
| Lipid**-**modifying agent | 0.33 | 0.29-0.38 | <.001 | 0.34 | 0.29-0.39 | <.001 | 0.38 | 0.20-0.72 | 0.003 |
| Statin | 0.35 | 0.30-0.40 | <.001 | 0.35 | 0.30-0.41 | <.001 | 0.49 | 0.24-1.00 | 0.051 |
| Atorvastatin | 0.39 | 0.31-0.49 | <.001 | 0.38 | 0.30-0.48 | <.001 | 0.65 | 0.24-1.75 | 0.389 |
| Rosuvastatin | 0.42 | 0.32-0.55 | <.001 | 0.44 | 0.33-0.58 | <.001 | 0.25 | 0.03-1.77 | 0.164 |
| Simvastatin | 0.28 | 0.16-0.51 | <.001 | 0.28 | 0.15-0.52 | <.001 | – | – | – |
| Pitavastatin | 0.44 | 0.26-0.73 | 0.001 | 0.48 | 0.29-0.79 | 0.004 | – | – | – |
| Fluvastatin | 0.21 | 0.11-0.40 | <.001 | 0.22 | 0.11-0.42 | <.001 | – | – | – |
| Pravastatin | 0.58 | 0.36-0.93 | 0.023 | 0.60 | 0.36-0.97 | 0.039 | 0.95 | 0.13-6.77 | 0.957 |
| Lovastatin | 0.15 | 0.06-0.40 | <.001 | 0.08 | 0.02-0.32 | <.001 | 2.20 | 0.55-8.90 | 0.268 |
| Fibrate | 0.34 | 0.25-0.47 | <.001 | 0.35 | 0.26-0.49 | <.001 | 0.27 | 0.07-1.08 | 0.064 |
| Fenofibrate | 0.31 | 0.21-0.47 | <.001 | 0.30 | 0.20-0.47 | <.001 | 0.23 | 0.03-1.66 | 0.146 |
| Gemfibrozil | 0.44 | 0.27-0.72 | 0.001 | 0.47 | 0.28-0.78 | 0.004 | 0.41 | 0.06-2.94 | 0.376 |
| Bezafibrate | 0.29 | 0.07-1.17 | 0.083 | 0.36 | 0.09-1.42 | 0.143 | – | – | – |
| Bile acid sequestrant | 0.68 | 0.30-1.52 | 0.346 | 0.71 | 0.32-1.59 | 0.402 | – | – | – |
| Nicotinic acid and derivatives | 0.26 | 0.04-1.84 | 0.177 | 0.27 | 0.04-1.88 | 0.184 | – | – | – |

a Estimated using multivariable Cox proportional hazards regression with time-dependent model

b All-cause mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

c Natural mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

d Suicide mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

Abbreviation: aHR = adjusted hazard ratio

**e-Table 11.** The first sensitivity analysis: Part 2. associations of duration of use and defined daily dose of lipid-modifying agents with risks of all-cause, natural, and suicide mortality during 10-year follow-up period in schizophrenia cohort (N = 110 300)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristics | **All-Cause Mortality**  **(n = 18 399)** | | | **Natural Mortality**  **(n = 16 025)** | | | **Suicide Mortality**  **(n = 1418)** | | |
|  | aHRa,b | 95% CI | *P* value | aHRa,c | 95% CI | *P* value | aHRa,d | 95% CI | *P* value |
| **Cumulative duration (per 10 days)** |  |  |  |  |  |  |  |  |  |
| Statins | 0.72 | 0.68-0.75 | <.001 | 0.71 | 0.68-0.75 | <.001 | 0.86 | 0.68-1.08 | 0.200 |
| Fibrates | 0.80 | 0.73-0.87 | <.001 | 0.81 | 0.74-0.88 | <.001 | 0.75 | 0.50-1.12 | 0.161 |
| Bile acid sequestrant | 1.42 | 1.17-1.71 | <.001 | 1.43 | 1.18-1.72 | <.001 | – | –. | – |
| Nicotinic acid and derivatives | 0.36 | 0.08-1.57 | 0.174 | 0.37 | 0.09-1.57 | 0.176 | – | –. | – |
| **Cumulative dose (per 10 DDDs)** |  |  |  |  |  |  |  |  |  |
| Statins | 0.68 | 0.64-0.72 | <.001 | 0.67 | 0.63-0.71 | <.001 | 0.85 | 0.66-1.08 | 0.178 |
| Fibrates | 0.71 | 0.63-0.80 | <.001 | 0.72 | 0.64-0.81 | <.001 | 0.66 | 0.38-1.13 | 0.128 |
| Bile acid sequestrant | 0.13 | 0.00-25.61 | 0.444 | 0.11 | 0.00-22.94 | 0.421 | – | –. | – |
| Nicotinic acid and derivatives | 0.47 | 0.14-1.56 | 0.215 | 0.47 | 0.14-1.56 | 0.219 | – | –. | – |

a Estimated using multivariable Cox proportional hazards regression with time-dependent model

b All-cause mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

c Natural mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

d Suicide mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

Abbreviation: aHR = adjusted hazard ratio

**e-Table 12.** The second sensitivity analysis: Part 1. associations of adjusted risks of all-cause, natural, and suicide mortality with use of lipid-modifying agents during 5-year follow-up period in subcohort with comorbid cardiovascular disease (N = 15 307)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristics | **All-Cause Mortality**  **(n = 3753)** | | | **Natural Mortality**  **(n = 3538)** | | | **Suicide Mortality**  **(n = 99)** | | |
|  | aHRa,b | 95% CI | *P* value | aHRa,c | 95% CI | *P* value | aHRa,d | 95% CI | *P* value |
| Lipid**-**modifying agent | 0.33 | 0.26-0.42 | <.001 | 0.31 | 0.24-0.40 | <.001 | 1.10 | 0.37-3.27 | 0.858 |
| Statin | 0.34 | 0.26-0.45 | <.001 | 0.31 | 0.23-0.42 | <.001 | 1.73 | 0.58-5.13 | 0.325 |
| Atorvastatin | 0.31 | 0.20-0.48 | <.001 | 0.26 | 0.16-0.42 | <.001 | 2.14 | 0.50-9.17 | 0.306 |
| Rosuvastatin | 0.40 | 0.24-0.68 | <.001 | 0.43 | 0.25-0.72 | 0.002 | – | – | – |
| Simvastatin | 0.40 | 0.15-1.08 | 0.070 | 0.43 | 0.16-1.15 | 0.092 | – | – | – |
| Pitavastatin | 0.48 | 0.18-1.29 | 0.148 | 0.52 | 0.19-1.38 | 0.189 | – | – | – |
| Fluvastatin | 0.26 | 0.08-0.80 | 0.019 | 0.27 | 0.09-0.84 | 0.024 | – | – | – |
| Pravastatin | 0.86 | 0.41-1.82 | 0.698 | 0.79 | 0.35-1.76 | 0.559 | 6.07 | 0.81-45.56 | 0.080 |
| Lovastatin | 0.15 | 0.02-1.07 | 0.059 | – | – | – | 6.39 | 0.86-47.64 | 0.071 |
| Fibrate | 0.24 | 0.12-0.51 | <.001 | 0.23 | 0.10-0.51 | <.001 | – | – | – |
| Fenofibrate | 0.24 | 0.09-0.63 | 0.004 | 0.19 | 0.06-0.60 | 0.005 | – | – | – |
| Gemfibrozil | 0.32 | 0.10-1.00 | 0.050 | 0.35 | 0.11-1.09 | 0.070 | – | – | – |
| Bezafibrate | – | – | – | – | – | – | – | – | – |
| Bile acid sequestrant | 3.60 | 1.16-11.20 | 0.027 | 3.83 | 1.23-11.94 | 0.021 | – | – | – |
| Nicotinic acid and derivatives | – | – | – | – | – | – | – | – | – |

a Estimated using multivariable Cox proportional hazards regression with time-dependent model

b All-cause mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

c Natural mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

d Suicide mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

Abbreviation: aHR = adjusted hazard ratio

**e-Table 13.** The second sensitivity analysis: Part 2. associations of adjusted risks of all-cause, natural, and suicide mortality with use of lipid-modifying agents during 5-year follow-up period in subcohort with comorbid cerebrovascular disease (N = 6080)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristics | **All-Cause Mortality**  **(n = 2513)** | | | **Natural Mortality**  **(n = 2435)** | | | **Suicide Mortality**  **(n = 31)** | | |
|  | aHRa,b | 95% CI | *P* value | aHRa,c | 95% CI | *P* value | aHRa,d | 95% CI | *P* value |
| Lipid**-**modifying agent | 0.45 | 0.34-0.61 | <.001 | 0.46 | 0.34-0.62 | <.001 | 0.60 | 0.08-4.83 | 0.635 |
| Statin | 0.51 | 0.37-0.70 | <.001 | 0.52 | 0.37-0.72 | <.001 | 0.81 | 0.10-6.52 | 0.844 |
| Atorvastatin | 0.50 | 0.31-0.80 | 0.004 | 0.48 | 0.29-0.80 | 0.004 | 1.91 | 0.24-15.14 | 0.540 |
| Rosuvastatin | 0.72 | 0.39-1.30 | 0.274 | 0.76 | 0.42-1.38 | 0.359 | – | – | – |
| Simvastatin | 0.21 | 0.03-1.49 | 0.118 | 0.22 | 0.03-1.54 | 0.127 | – | – | – |
| Pitavastatin | 1.08 | 0.45-2.61 | 0.863 | 1.13 | 0.47-2.73 | 0.786 | – | – | – |
| Fluvastatin | 0.18 | 0.03-1.30 | 0.089 | 0.19 | 0.03-1.34 | 0.096 | – | – | – |
| Pravastatin | 0.83 | 0.31-2.23 | 0.717 | 0.87 | 0.32-2.31 | 0.773 | – | – | – |
| Lovastatin | – | – | – | – | – | – | – | – | – |
| Fibrate | 0.25 | 0.09-0.66 | 0.005 | 0.25 | 0.10-0.68 | 0.006 | – | – | – |
| Fenofibrate | 0.23 | 0.06-0.90 | 0.035 | 0.23 | 0.06-0.92 | 0.038 | – | – | – |
| Gemfibrozil | 0.16 | 0.02-1.14 | 0.067 | 0.17 | 0.02-1.18 | 0.072 | – | – | – |
| Bezafibrate | 1.19 | 0.17-8.50 | 0.860 | 1.23 | 0.17-8.79 | 0.834 | – | – | – |
| Bile acid sequestrant | – | – | – | – | – | – | – | – | – |
| Nicotinic acid and derivatives | 1.01 | 0.14-7.34 | 0.989 | 0.98 | 0.14-7.07 | 0.981 | – | – | – |

a Estimated using multivariable Cox proportional hazards regression with time-dependent model

b All-cause mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

c Natural mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

d Suicide mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

Abbreviation: aHR = adjusted hazard ratio

**e-Table 14.** The second sensitivity analysis: Part 3. associations of adjusted risks of all-cause, natural, and suicide mortality with use of lipid-modifying agents during 5-year follow-up period in subcohort with comorbid depressive disorder (N = 10 414)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristics | **All-Cause Mortality**  **(n = 1147)** | | | **Natural Mortality**  **(n = 902)** | | | **Suicide Mortality**  **(n = 160)** | | |
|  | aHRa,b | 95% CI | *P* value | aHRa,c | 95% CI | *P* value | aHRa,d | 95% CI | *P* value |
| Lipid**-**modifying agent | 0.40 | 0.24-0.66 | <.001 | 0.38 | 0.22-0.66 | <.001 | – | – | – |
| Statin | 0.42 | 0.24-0.74 | 0.003 | 0.41 | 0.22-0.76 | 0.004 | – | – | – |
| Atorvastatin | 0.33 | 0.12-0.88 | 0.026 | 0.27 | 0.09-0.84 | 0.024 | – | – | – |
| Rosuvastatin | 0.46 | 0.17-1.24 | 0.124 | 0.53 | 0.20-1.44 | 0.215 | – | – | – |
| Simvastatin | 1.18 | 0.29-4.76 | 0.813 | 0.76 | 0.11-5.40 | 0.782 | – | – | – |
| Pitavastatin | 0.63 | 0.16-2.56 | 0.519 | 0.74 | 0.18-3.03 | 0.680 | – | – | – |
| Fluvastatin | – | – | – | – | – | – | – | – | – |
| Pravastatin | 1.55 | 0.38-6.24 | 0.539 | 1.83 | 0.45-7.40 | 0.395 | – | – | – |
| Lovastatin | – | – | – | – | – | – | – | – | – |
| Fibrate | 0.33 | 0.08-1.31 | 0.114 | 0.20 | 0.03-1.45 | 0.112 | – | – | – |
| Fenofibrate | 0.25 | 0.04-1.78 | 0.165 | – | – | – | – | – | – |
| Gemfibrozil | 0.56 | 0.08-3.95 | 0.556 | 0.69 | 0.10-4.91 | 0.710 | – | – | – |
| Bezafibrate | – | – | – | – | – | – | – | – | – |
| Bile acid sequestrant | – | – | – | – | – | – | – | – | – |
| Nicotinic acid and derivatives | 12.95 | 1.78-94.43 | 0.012 | 13.67 | 1.86-100.30 | 0.010 | – | – | – |

a Estimated using multivariable Cox proportional hazards regression with time-dependent model

b All-cause mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

c Natural mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

d Suicide mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

Abbreviation: aHR = adjusted hazard ratio

**e-Table 15.** The second sensitivity analysis: Part 4. associations of adjusted risks of all-cause, natural, and suicide mortality with use of lipid-modifying agents during 5-year follow-up period in subcohort without any cardiovascular or cerebrovascular comorbidity (N = 88 913)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristics | **All-Cause Mortality**  **(n = 6551)** | | | **Natural Mortality**  **(n = 5076)** | | | **Suicide Mortality**  **(n = 960)** | | |
|  | aHRa,b | 95% CI | *P* value | aHRa,c | 95% CI | *P* value | aHRa,d | 95% CI | *P* value |
| Lipid**-**modifying agent | 0.38 | 0.29-0.50 | <.001 | 0.41 | 0.31-0.55 | <.001 | 0.22 | 0.05-0.87 | 0.031 |
| Statin | 0.33 | 0.24-0.46 | <.001 | 0.34 | 0.24-0.48 | <.001 | 0.17 | 0.02-1.22 | 0.079 |
| Atorvastatin | 0.48 | 0.30-0.75 | 0.001 | 0.46 | 0.28-0.76 | 0.002 | 0.43 | 0.06-3.04 | 0.395 |
| Rosuvastatin | 0.30 | 0.14-0.62 | 0.001 | 0.35 | 0.17-0.74 | 0.006 | – | –. | – |
| Simvastatin | 0.40 | 0.13-1.23 | 0.109 | 0.32 | 0.08-1.26 | 0.103 | – | –. | – |
| Pitavastatin | 0.08 | 0.01-0.56 | 0.011 | 0.08 | 0.01-0.57 | 0.012 | – | –. | – |
| Fluvastatin | – | –. | – | – | –. | – | – | –. | – |
| Pravastatin | 0.73 | 0.28-1.96 | 0.536 | 0.87 | 0.33-2.32 | 0.775 | – | –. | – |
| Lovastatin | 0.17 | 0.02-1.17 | 0.071 | 0.20 | 0.03-1.39 | 0.104 | – | –. | – |
| Fibrate | 0.61 | 0.38-0.99 | 0.043 | 0.75 | 0.46-1.23 | 0.260 | 0.34 | 0.05-2.45 | 0.286 |
| Fenofibrate | 0.73 | 0.41-1.29 | 0.278 | 0.94 | 0.53-1.66 | 0.822 | – | –. | – |
| Gemfibrozil | 0.56 | 0.23-1.34 | 0.194 | 0.61 | 0.23-1.62 | 0.320 | 0.87 | 0.12-6.21 | 0.892 |
| Bezafibrate | – | –. | – | – | –. | – | – | –. | – |
| Bile acid sequestrant | 1.13 | 0.36-3.51 | 0.835 | 1.37 | 0.44-4.26 | 0.590 | – | –. | – |
| Nicotinic acid and derivatives | – | –. | – | – | –. | – | – | –. | – |

a Estimated using multivariable Cox proportional hazards regression with time-dependent model

b All-cause mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

c Natural mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

d Suicide mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

Abbreviation: aHR = adjusted hazard ratio

**e-Table 16.** The third sensitivity analysis: associations of adjusted risks of mortality from cardiovascular disease, cerebrovascular disease, and myocardial infarction with use of lipid-modifying agents during 5-year follow-up period in schizophrenia cohort (N = 110 300)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristics | **Cardiovascular Disease**  **(n =1723)** | | | **Cerebrovascular Disease**  **(n = 812)** | | | **Myocardial infarction**  **(n = 332)** | | |
|  | aHRa,b | 95% CI | *P* value | aHRa,c | 95% CI | *P* value | aHRa,d | 95% CI | *P* value |
| Lipid**-**modifying agent | 0.59 | 0.43-0.80 | <.001 | 0.20 | 0.09-0.42 | <.001 | 0.95 | 0.55-1.64 | 0.856 |
| Statin | 0.63 | 0.45-0.89 | 0.009 | 0.23 | 0.10-0.52 | <.001 | 1.27 | 0.74-2.20 | 0.385 |
| Atorvastatin | 0.60 | 0.36-1.01 | 0.053 | 0.39 | 0.14-1.04 | 0.059 | 1.26 | 0.58-2.74 | 0.555 |
| Rosuvastatin | 0.98 | 0.56-1.71 | 0.941 | – | – | – | 2.33 | 1.06-5.09 | 0.035 |
| Simvastatin | 0.27 | 0.04-1.92 | 0.191 | – | – | – | – | – | – |
| Pitavastatin | 0.76 | 0.25-2.38 | 0.643 | – | – | – | 1.04 | 0.14-7.51 | 0.969 |
| Fluvastatin | 0.52 | 0.13-2.06 | 0.349 | 0.58 | 0.08-4.11 | 0.582 | – | – | – |
| Pravastatin | 0.93 | 0.30-2.89 | 0.899 | 0.67 | 0.09-4.78 | 0.690 | 1.36 | 0.19-9.76 | 0.761 |
| Lovastatin | – | – | – | – | – | – | – | – | – |
| Fibrate | 0.64 | 0.30-1.35 | 0.237 | – | – | – | – | – | – |
| Fenofibrate | 0.78 | 0.32-1.89 | 0.584 | – | – | – | – | – | – |
| Gemfibrozil | 0.26 | 0.04-1.87 | 0.182 | – | – | – | – | – | – |
| Bezafibrate | 1.54 | 0.22-10.99 | 0.666 | – | – | – | – | – | – |
| Bile acid sequestrant | – | – | – | – | – | – | – | – | – |
| Nicotinic acid and derivatives | 2.31 | 0.32-16.57 | 0.407 | – | – | – | – | – | – |

a Estimated using multivariable Cox proportional hazards regression with time-dependent model

b All-cause mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

c Natural mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

d Suicide mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1 and all time-varying variables in Table 2

Abbreviation: aHR = adjusted hazard ratio

**e-Table 17.** The fourth sensitivity analysis: associations of risks of all-cause, natural, and suicide mortality with use of lipid-modifying agents during 5-year follow-up period in schizophrenia cohort, adjusted for adherence to antipsychotics (N = 110 300)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristics | **All-Cause Mortality**  **(n = 12** **817)** | | | **Natural Mortality**  **(n = 11** **049)** | | | **Suicide Mortality**  **(n = 1090)** | | |
|  | aHRa,b | 95% CI | *P* value | aHRa,c | 95% CI | *P* value | aHRa,d | 95% CI | *P* value |
| Lipid**-**modifying agent | 0.37 | 0.32-0.44 | <.001 | 0.38 | 0.32-0.44 | <.001 | 0.42 | 0.20-0.92 | 0.029 |
| Statin | 0.37 | 0.31-0.45 | <.001 | 0.37 | 0.31-0.45 | <.001 | 0.57 | 0.25-1.30 | 0.182 |
| Atorvastatin | 0.42 | 0.32-0.54 | <.001 | 0.38 | 0.29-0.51 | <.001 | 0.98 | 0.36-2.68 | 0.971 |
| Rosuvastatin | 0.42 | 0.29-0.59 | <.001 | 0.45 | 0.32-0.64 | <.001 | – | – | – |
| Simvastatin | 0.35 | 0.18-0.71 | 0.003 | 0.34 | 0.16-0.71 | 0.004 | – | – | – |
| Pitavastatin | 0.46 | 0.25-0.85 | 0.013 | 0.50 | 0.27-0.93 | 0.028 | – | – | – |
| Fluvastatin | 0.17 | 0.06-0.45 | <.001 | 0.18 | 0.07-0.48 | <.001 | – | – | – |
| Pravastatin | 0.80 | 0.48-1.32 | 0.381 | 0.82 | 0.48-1.39 | 0.456 | 1.42 | 0.20-10.19 | 0.727 |
| Lovastatin | 0.11 | 0.03-0.43 | 0.002 | 0.06 | 0.01-0.41 | 0.004 | 1.48 | 0.21-10.60 | 0.697 |
| Fibrate | 0.39 | 0.27-0.57 | <.001 | 0.42 | 0.28-0.61 | <.001 | 0.22 | 0.03-1.60 | 0.136 |
| Fenofibrate | 0.43 | 0.27-0.69 | <.001 | 0.46 | 0.29-0.75 | 0.002 | – | – | – |
| Gemfibrozil | 0.37 | 0.20-0.72 | 0.003 | 0.38 | 0.19-0.77 | 0.007 | 0.63 | 0.09-4.51 | 0.647 |
| Bezafibrate | 0.21 | 0.03-1.49 | 0.118 | 0.25 | 0.04-1.80 | 0.169 | – | – | – |
| Bile acid sequestrant | 0.87 | 0.39-1.94 | 0.726 | 0.88 | 0.39-1.97 | 0.752 | – | – | – |
| Nicotinic acid and derivatives | 0.32 | 0.05-2.27 | 0.254 | 0.32 | 0.05-2.26 | 0.252 | – | – | – |

a Estimated using multivariable Cox proportional hazards regression with time-dependent model

b All-cause mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1, all time-varying variables in Table 2 and medication possession ratio to antipsychotics (≥ 80%: good adherence; < 80%: poor adherence)

c Natural mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1, all time-varying variables in Table 2 and medication possession ratio to antipsychotics (≥ 80%: good adherence; < 80%: poor adherence)

d Suicide mortality: adjusted for selected significant variables in multivariable regression (*P* < .01) in Table 1, all time-varying variables in Table 2 and medication possession ratio to antipsychotics (≥ 80%: good adherence; < 80%: poor adherence)

Abbreviation: aHR = adjusted hazard ratio