# Misclassification in assessment of diabetogenic risk using electronic health records[†]

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## Abstract

**Purpose**—Suspected diabetogenic effects or drug indication may increase testing for diabetes mellitus (DM), resulting in measurement bias when evaluating diabetogenic drug effects. We sought to evaluate the validity of electronic health record data in determining DM risk.

**Methods**—We used time-dependent Cox proportional hazard models within a retrospective cohort design to assess associations between use of antihypertensives, statins, atypical antipsychotics, and antidepressants, and two endpoints: (i) DM onset defined as fasting blood glucose (BG) 126 mg/dl, random BG 200 mg/dl, HbA1c 7.0%, or antidiabetic drug initiation; and (ii) first negative DM test. We used Poisson regression to assess the influence of these drugs on DM testing rates. Patients aged 35–64 years enrolled in Kaiser Permanente Northwest between

1997 and 2010 entered the cohort at the first negative BG test after 6 months without manifest DM.

**Results**—All drug classes showed significant associations not only with DM onset but also with first negative BG test and with DM testing rates. Antipsychotics had the greatest diabetogenic risk (adjusted hazard ratio [HR] = 1.73 [1.44–2.08]), the greatest propensity for a first negative test (adjusted HR = 1.87 [1.74–2.01]), and the highest testing rate (adjusted rate ratio = 1.76 [1.72–1.81]. Although renin–angiotensin system blockers and calcium channel blockers have shown no diabetogenic risk in clinical trials, both were associated with DM (HR = 1.19 [1.12–1.26] and 1.27 [1.17–1.38]), a negative glucose test (1.38 [1.35–1.41] and 1.24 [1.20–1.28]), and increased testing rates (rate ratio = 1.26 [1.24–1.27] and 1.27 [1.25–1.28]).

**Conclusion**—Caution should be used when diabetogenic risk is evaluated using data that rely on DM testing in general practice.

### Keywords

measurement bias; diabetogenic risk; drug safety; electronic health records; antihypertensives; antipsychotics; statins; pharmacoepidemiology

## INTRODUCTION

Increasing availability of rich, population-based, clinical or administrative data sets as well as long-term clinical trial data allow detailed examination of drug side effects such as diabetes mellitus (DM). For example, thiazide diuretics (TD) and beta blockers (BB) appear to increase risk for DM, and calcium channel blockers (CCB) are thought to be neutral, while renin–angiotensin system blockers (RASB), including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, have been shown to reduce DM risk.[1–4] While clinical trial data are expected to deliver the strongest evidence, safety concerns may be evaluated as secondary outcomes that are not necessarily ascertained with the same prospective protocols as the primary efficacy endpoint. If ascertainment of DM onset relies on patient self-report or other uncontrolled methods, and if treatment assignments and the potential for diabetogenic side effects are known to provider and patients, DM testing may become associated with current treatment, and thus, the detection of DM may be biased.

An extension of the same concern is found in observational studies that rely on clinical practice or billing data as have been employed for the majority of analyses involving diabetogenic risk of antihypertensives, atypical antipsychotics (AAP), and statins (ST).[5–14] Here, increased DM testing associated with more frequent provider encounters, because of chronic medication use, or patient or provider concern regarding diabetogenic side effects would result in earlier detection of DM, which presents in its early manifestation with limited clinical symptoms. Furthermore, the drug indication itself might increase DM testing such as concerns regarding presence of metabolic syndrome in patients treated with antihypertensives or ST. While research on the effect of missingness in epidemiologic studies are abundant, to our knowledge, no study has evaluated the presence of misclassification bias concerning DM onset in clinical or billing data used to evaluate diabetogenic side effects.

We sought to evaluate the validity of electronic health record (EHR) data from the Kaiser Permanente Northwest (KPNW) health-care system in determining DM onset. We selected this data set from an integrated health-care delivery system, because it allows access to laboratory data and because KPNW encourages and monitors lipid screening, which is often accompanied by DM screening, among its members.

## METHODS

### Data source

Kaiser Permanente Northwest is a group–model health maintenance organization serving approximately 475,000 enrollees in both Oregon and Washington. The organization provides online medical guidelines to assist clinicians in patient management. One such guideline recommends annual lipid screening for men aged 35 years and older, and women aged 45 years and older. Fasting blood glucose (FBG) tests are routinely ordered with these lipid panels.

The KPNW maintains an EHR that captures all patient encounters and laboratory tests. To complete each patient visit, the clinician is required to enter between 1 and 20 diagnoses in the EHR, which are coded in International Classification of Disease—9th Revision— Clinical Modification (ICD-9-CM) format. Height, weight, and blood pressure (BP) are also continuously collected in the EHR during routine physician care. KPNW captures pharmacy-dispensing data in the same EHR database including national drug code, dispensing date, dispensed quantities, and dispensed days' supply.

### Study participants

Study eligible subjects included all patients between ages 35 and 64 years who were enrolled between January 1997 and December 2010, and had comprehensive drug and medical service coverage. Patients entered the study cohort at the first negative FBG test less than 126 mg/dl, following a 6-month look-back period without evidence for manifest DM based on absence of pharmacy dispensings for antihyperglycemic medications, glucose, or glycosylated hemoglobin tests (HbA1c) above diagnostic thresholds, and inpatient or outpatient visits with a DM diagnosis [ICD-9-CM 250. x]. Patients were required to have at least 1 year of plan eligibility after cohort entry. Patients contributed time to the analysis between cohort index date and onset of the respective study endpoint, their 65th birthday, the end of enrollment, or the end of the study period, whichever came first.

### Study endpoints

For the purposes of this analysis, incident DM was defined as a new FBG    126 mg/dl, random blood glucose    200 mg/dl, an HbA1c    7.0%, or a new DM prescription, whichever occurred first. We did not use DM diagnosis codes because of validity concerns and because they would unlikely be made without glucose testing, which was available to us. Because guidelines for use of HbA1c    6.5% as a DM diagnostic criterion were not in place in the USA until early in 2010,[15] we used a cutoff of 7% in our study to better reflect diagnostic practice during the study period.

Two additional endpoints were used to explore measurement bias, including the onset of the first negative DM test defined as a FBG <126 mg/dl, random blood glucose <200 mg/dl, or HBA1c <7.0% after the start of follow-up, and the overall DM (BG or HbA1c) testing rate during follow-up.

### Drug exposure

Pharmacy dispensing date and dispensed days' supply were used to ascertain exposure information to drug classes of interest, including BB, ST, TD, antidepressants (AD) (selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors/tricyclics), AAP, RASB, and CCB. A patient was considered exposed from the date the prescription was dispensed until 30 days after the end of the days' supply. Exposure to study drugs was assessed by week for the duration of the study period and required at least one active day of supply during a given week.

### Covariates

Covariates recorded at cohort index date included age, gender, calendar year, and FBG level at index date. Lipid values (high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides [TRI]), BP (systolic, diastolic), and body mass index (BMI) were extracted from the 6 months prior to the cohort index date. If more than one laboratory test was available, the mean value of all tests was used.

We used fully conditional specification multiple imputation methods[16] to impute missing values for all covariates. Age, calendar year, and use of non-topical corticosteroids were included as time-varying covariates that were assessed in weekly segments. Analogous to our assessment of study drug exposures, corticosteroid exposure required at least 1 day of supply in a given week. Finally, we defined presence of cardiovascular disease as diagnosis in the inpatient or outpatient setting of coronary artery disease (ICD-9-CM 414), congestive heart failure (428), myocardial infarction (410, 412), peripheral vascular disease (441, 443.9, 785.4, V43.4), or cerebrovascular disease (430–438, inpatient diagnoses only) during the 6-month look-back period.

### Statistical analysis

We used time-dependent Cox proportional hazards regression[17] to estimate the relative effect of drug exposure versus non-exposure on DM onset and onset of first negative DM test. Proportionality of hazards was assessed graphically using Schoenfeld residual plots.[17] We used Poisson regression[18] to assess the relative effects of the drug classes on DM testing rates during follow-up. In all of our statistical models, we used restricted cubic splines[19] to characterize the nonlinear association between time-dependent age and our outcomes. The Akaike information criterion[20] was used to determine the optimal number of restricted cubic spline knots for modeling age in each of our final outcomes models. All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC, USA).

### Sensitivity analysis

For cases that were defined on the basis of the presence of one random or fasting BG value above threshold, we added a sensitivity analysis that required a second subsequent BG value

above threshold, a subsequent HbA1c 7.0%, or initiation of an antidiabetic medication within up to 1 year after the first positive BG test. Cases that were initially defined on the basis of drug initiation or HbA1c were not confirmed because of expected high specificity.

## RESULTS

Our study cohort included 126,376 patients, and a total of 8183 patients developed DM during the follow-up period. Diagnosis of diabetes was based on a laboratory test in 7583 (92.7%) cases, while the remaining 600 (7.3%) cases were first diagnosed on the basis of antidiabetic drug initiation. Characteristics of the population at baseline according to drug class exposure are summarized in Table 1. The incidence rate (IR) for development of new DM in our study population was 12.7 cases/1000 patients per year. The percent missingness for study covariates was as follows: HDL 11.2%, LDL 14.6%, TRI 9.1%, BP 5.4%, and BMI 12.0%.

Unadjusted and adjusted hazard ratios for developing DM are shown in Table 2A. All drug classes were found to have a significantly increased risk for manifestation of diabetes compared with no exposure to the respective drug class. Importantly, hazard ratios quantifying the diabetogenic risk of each drug class coarsely tracked the hazard ratios for a first negative glucose test (Table 2B) and the rate ratios for DM testing during follow-up (Table 2C). AAP use periods had the highest DM testing rate (1.28 tests/year, 95% CI: 1.24–1.31) and periods of use of any drug class had more frequent DM tests than non-use periods (Table 1).

Further evaluation of our cases found that 5092 (62.2%) could be confirmed using the criteria employed in the sensitivity analysis. An analysis restricted to confirmed cases found a similar increased risk of DM in all drug classes (within 3%–18%, data not shown).

## DISCUSSION

In concordance with clinical trial data, our study found a significant association between diabetes onset and BB,[1,3,4,21] ST,[22] and TD.[4,21,23] Likewise, randomized mechanistic short-term studies in healthy volunteers demonstrating a risk for hyperglycemia associated with AAP were mirrored by our study findings.[24] Long-term clinical trial data addressing the diabetogenic risk of AAP or AD as a class are scarce and results inconsistent,[25] but within-class comparisons suggest an increased risk of olanzapine when compared with other antipsychotics.[26,27] Interestingly, our study also found a significant increase in diabetogenic risk during exposure to RASB and CCBs, while randomized clinical trial data have usually found protective effects of RASB and neutral effects of CCBs.

Our findings may be explained in part by misclassification bias of our ascertainment of diabetes manifestation. All drug classes were associated with an increased probability for both DM onset and a negative DM test, and overall testing rates were elevated for all drug classes. Interestingly, RASB, which have solid clinical trial evidence negating any diabetogenic risk, showed weaker associations for DM onset than for a negative test, while this relationship was reversed for TD. Thus, relative comparisons across drug classes were not completely distorted.

Differential misclassification of diabetes onset related to DM testing rates would occur if increased testing in exposure groups would result in earlier detection of diabetes. Estimates of the National Health and Nutrition Examination Survey 2003–2007, which includes HbA1c screening, suggest that 21.5% of all diabetes cases are undiagnosed, likely because early stages of diabetes present with limited or no symptoms.[28] Furthermore, on the basis of extrapolations of the linear relationship between onset of diabetic retinopathy and duration of diabetes, an earlier study estimated that type 2 diabetes manifests between 4 and 7 years before diagnosis.[29] Thus, it is conceivable that increased DM screening can result in an increased detection of DM, resulting in increased incidence rates.

Several explanations for increased diabetes testing are plausible. First, screening for metabolic side effects in patients who receive AAP is recommended by clinical guidelines, and while still not comprehensively implemented, glucose testing is more frequent than in non-users of this drug class.[30,31] Likewise, potential diabetogenic effects of certain antihypertensive drug classes, specifically BBs and TDs, may have been known to providers, resulting in increased vigilance. RASBs and CCBs, on the other hand, may have been channeled toward patients with increased risk for diabetes, who may be more closely monitored for diabetes manifestation. A simpler explanation may be the fact that hypertension is oftentimes associated with other metabolic complications or cardiovascular disease, resulting in increased vigilance, or simply, that chronic medication use is typically associated with more frequent physician encounters, which in turn may result in increased routine testing.

An alternative explanation of the observed associations between drug exposure and DM onset and DM testing is confounding. Specifically, rather than drug exposure itself, a set of confounders such as age and hypertension may exert an effect on both DM testing and onset of diabetes. In fact, adjustment did reduce all presented risk ratios, suggesting presence of confounding in both DM onset and DM testing models. Confounding by indication is a particular concern for RASBs because of their protective effect against diabetes, resulting in channeling toward those patients with prediabetes. However, several observations speak against residual confounding as sole explanation for our results.

First, access to EHRs and in particular laboratory data allowed for adjustment of key markers of metabolic risk, which are not available in billing data, but some DM risk factors such as smoking, family history, and exercise were not fully available. Second, adjustments for DM risk factors resulted in sizeable reductions of risk ratios quantifying diabetogenic risk (7%–26% decrease), while adjustments for the risk of a first negative DM test or for DM testing rates had much less impact (1%–12% change). Third, because of their indications, antipsychotics and AD would be expected to have fewer or different confounding mechanisms than antihypertensives and ST, yet they show similarly elevated DM testing rates. Of note, adjustments for DM risk factors increased the antipsychotics risk ratio for a first negative test and the rate ratio for DM testing rather than decreasing these measures, suggesting that confounders in the DM pathway had no effect. Thus, it appears that in our study population, adjustment for traditional DM risk factors in the evaluation of diabetogenic risk will not fully balance for increased DM testing rates in the exposure

groups, regardless of the underlying mechanism (exposure versus confounder as determinant of DM testing rates).

Importantly, the majority of observational studies on diabetogenic risk have relied on billing (diagnosis) data alone or included laboratory test data but did not balance for the propensity of testing.[5–14] Likewise, secondary analyses of clinical trial data where diabetes onset was not ascertained according to an explicit testing protocol, as well as findings of clinical trial or prospective cohort data that were enhanced with EHR or claims records, would be expected to show a similar DM testing pattern associated with drug exposure.

Of note, our study cannot, and is not meant to, provide a solution to observed inconsistencies in study results on diabetogenic risk (see, for example, meta-analyses describing large heterogeneity).[32] While measurement bias might explain some of these inconsistencies, it might be of different magnitude across settings (depending on diabetes screening practices or protocols) or study designs (e.g., with or without blinding). For example, while most observational studies based on administrative claims data agree on the diabetogenic risk of AAP, a study in long-term care residents in Quebec, a setting where regular diabetes screening might be more standardized, found no diabetogenic risk of atypical antispychotics when compared with benzodiazepine users.[33] Likewise, using administrative claims data, one study describes an increased risk for new onset diabetes in younger (OR = 8.9 for 0–24 years) but not older users of AAP (OR = 0.93 for those 65 years and older).[34] This effect modification could be in part a reflection of generally increased DM screening practices in older age groups that might surpass increased vigilance in antipsychotic users, but other pharmacologic explanations might exist. On the other hand, while our evidently biased results suggest a diabetogenic risk of all antihypertensives, a study using claims data of the Taiwanese National Insurance System replicated clinical trial findings by solely relying on diabetes diagnosis codes; the study found slightly elevated rates of new onset diabetes in BB and TD users but no such effects for users of other antihypertensive classes suggesting no measurement bias.[35] Finally, post hoc analyses of the Heart Outcomes Prevention Evaluation (HOPE)[36] study reported a 34% reduction in self-reported diabetes risk among ramipril-allocated subjects compared with placebo, but protective effects of ramipril were not borne out in the Diabetes Reduction Assessment with Ramipril and Rosiglitazone (DREAM)[37] trial, which used a diabetes testing protocol.

The KPNW is known for its implementation of evidence-based practice with generally increased probability for diabetes testing as a by-product of guideline-recommended lipid screening, suggesting that drug-dependent differences in DM testing might be even more pronounced in other settings. The availability of laboratory tests provided a unique advantage for the assessment of measurement bias relative to use of billing data. Because BG testing is oftentimes not separately charged by providers and thus not reliably ascertainable in billing data, sole reliance on billing data (or EHR diagnoses) for the assessment of diabetogenic risk would have precluded us from detecting the potential for measurement bias.

If detailed information on diabetes testing is available, several methods to derive unbiased estimates of diabetogenic risk can be considered. We chose to match cases with new diabetes

onset to controls with negative BG tests to balance for the propensity of testing and were able to replicate clinical trial findings of antihypertensives that used standardized glucose testing protocols.[38] If information on DM testing is unavailable, caution should be exercised in employing these data for the assessment of diabetogenic risk.

In summary, we present evidence that testing for diabetes in patients in the KPNW setting who were receiving any of the study drug classes was not random. Possible explanations are residual confounding and/or measurement bias. Studies that rely on DM testing in general practice and have not examined the potential for measurement bias should be interpreted with caution.

## Acknowledgments

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## KEY POINTS

- Assessment of diabetogenic effects of antihypertensives, statins, and atypical antipsychotics using data from general practice showed substantial misclassification.

- While misclassification is a well-recognized problem in pharmacoepidemiology, it has not been demonstrated in the assessment of diabetogenic risk.

- Existing evidence should be enhanced in light of these findings, especially in therapeutic areas with missing or limited evidence from clinical trials, that used standardized diabetes screening protocols.

**Table 1**

Population characteristics

| | Beta blockers | Statins | Thiazide diuretics | Antidepressants | Atypical antipsychotics | Renin–angiotensin system blockers | Calcium channel blockers | Unexposed to any study drug class |
|---|---|---|---|---|---|---|---|---|
| Patients, # (%) | 29,895 (23.7) | 24,234 (19.1) | 25,848 (20.5) | 40,232 (31.8) | 2364 (1.9) | 24,460 (19.4) | 9250 (7.3) | 50,393 (39.9) |
| **Diabetes cases** | | | | | | | | |
| While exposed, # (%) | 2394 (8.0) | 1615 (6.7) | 1935 (7.5) | 1737 (4.3) | 119 (5.0) | 1923 (7.9) | 678 (7.3) | — |
| At any time, # (%) | 3177 (10.6) | 2181 (9.0) | 2834 (11.0) | 2902 (7.2) | 200 (8.5) | 2497 (10.2) | 1009 (10.9) | 1951 (3.9) |
| **Follow-up (weeks)** | | | | | | | | |
| Exposed, median (IQR) | 101 (34–216) | 103 (41–206) | 88 (32–188) | 73 (23–178) | 47 (16–129) | 102 (41–205) | 72 (22–165) | — |
| Total, median (IQR) | 268 (157–428) | 290 (171–456) | 275 (163–435) | 267 (161–422) | 260 (156–404) | 279 (167–437) | 272 (156–434) | 198 (116–313) |
| **Age (years)** | | | | | | | | |
| Median (IQR) | 52 (47–57) | 53 (48–57) | 52 (46–57) | 49 (43–54) | 48 (42–53) | 52 (467–57) | 53 (47–58) | 48 (42–55) |
| 35–45, # (%) | 5994 (20.1) | 3886 (16.0) | 5369 (20.8) | 13,610 (33.8) | 905 (38.3) | 4729 (19.3) | 1705 (18.4) | 19,021 (37.8) |
| 45–55, # (%) | 13,040 (43.6) | 11,283 (46.6) | 11,638 (45.0) | 17,639 (43.8) | 1057 (44.7) | 11,153 (45.6) | 3913 (42.3) | 19,389 (38.5) |
| 55–65, # (%) | 10,861 (36.3) | 9065 (37.4) | 8841 (34.2) | 8983 (22.3) | 402 (17.0) | 8578 (35.1) | 3632 (39.3) | 11,983 (23.8) |
| Male, # (%) | 14,116 (47.2) | 14,199 (58.6) | 10,100 (39.1) | 12,158 (30.2) | 874 (37.0) | 12,993 (53.1) | 4366 (47.2) | 23,603 (46.8) |
| FBG* (mg/dl), median (IQR) | 95 (88–102) | 95 (89–102) | 95 (88–102) | 92 (86–99) | 92 (86–100) | 95 (89–102) | 95 (88–102) | 92 (86–98) |
| **Blood pressure (mmHg)** | | | | | | | | |
| Systolic, median (IQR) | 135 (123–147) | 130 (120–141) | 138 (128–150) | 124 (115–136) | 123 (114–133) | 138 (128–150) | 138 (126–150) | 120 (112–130) |
| Diastolic, median (IQR) | 84 (78–90) | 81 (75–88) | 86 (80–92) | 80 (72–85) | 79 (72–84) | 86 (80–92) | 84 (78–91) | 77 (70–82) |
| BMI (kg/m²), median (IQR) | 30 (26–35) | 29 (26–33) | 31 (27–36) | 29 (25–34) | 29 (25–34) | 31 (27–35) | 30 (27–35) | 27 (24–31) |
| Corticosteroid use, # (%) | 5962 (19.9) | 4585 (18.9) | 5130 (19.9) | 8713 (21.7) | 391 (16.5) | 5180 (21.2) | 2169 (23.5) | 8286 (16.4) |
| Cardiovascular disease, # (%) | 2315 (7.7) | 2253 (9.3) | 667 (2.6) | 942 (2.3) | 49 (2.1) | 1628 (6.7) | 749 (8.1) | 156 (0.3) |
| **Lipid panel (mg/dl)** | | | | | | | | |
| HDL, median (IQR) | 47 (39–58) | 46 (39–55) | 49 (40–59) | 51 (42–62) | 49 (40–61) | 47 (39–57) | 48 (39–59) | 51 (42–62) |
| LDL, median (IQR) | 126 (103–150) | 150 (124–174) | 126 (104–149) | 124 (102–148) | 124 (102–149) | 127 (105–150) | 125 (103–149) | 120 (100–142) |
| TRI, median (IQR) | 143 (95–214) | 157 (109–228) | 141 (94–209) | 123 (80–190) | 131 (82–208) | 143 (96–213) | 143 (94–213) | 103 (69–156) |
| **DM testing rate†** | | | | | | | | |
| # tests/year, mean (CI) | 0.96 (0.95–0.96) | 0.98 (0.97–0.99) | 0.88 (0.87–0.88) | 0.79 (0.78–0.79) | 1.28 (1.24–1.31) | 0.98 (0.98–0.99) | 1.12 (1.11–1.14) | 0.37 (0.37–0.37) |

IQR, interquartile range; CI, 95% confidence interval; FBG, fasting blood glucose; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TRI, triglycerides; DM, diabetes mellitus.

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*Fasting blood glucose measured on cohort entry date.

†Fasting blood glucose, random blood glucose, and HbA1c tests were included in estimates of DM testing rates.

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**Table 2**

Risk of Diabetes Manifestation and First Negative Diabetes Test by Drug Class

| Drug exposure | Unadjusted | Adjusted |
|---|---|---|
| A: Hazard ratios (95% confidence intervals) for diabetes manifestation [*] (first positive glucose test or initiation of antidiabetic drugs) | | |
| Beta blockers | 1.90 (1.81–2.00) | 1.41 (1.34–1.49) |
| Statins | 1.32 (1.25–1.40) | 1.15 (1.08–1.22) |
| Thiazide diuretics | 1.80 (1.71–1.91) | 1.49 (1.41–1.58) |
| Antidepressants | 1.35 (1.28–1.43) | 1.26 (1.19–1.33) |
| Atypical antipsychotics | 1.99 (1.66–2.39) | 1.73 (1.44–2.08) |
| Renin–angiotensin system blockers | 1.61 (1.52–1.70) | 1.19 (1.12–1.26) |
| Calcium channel blockers | 1.63 (1.50–1.76) | 1.27 (1.17–1.38) |
| B: Hazard ratios (95% CIs) for first negative glucose test [*] | | |
| Beta blockers | 1.47 (1.44–1.50) | 1.38 (1.35–1.40) |
| Statins | 1.61 (1.57–1.65) | 1.42 (1.38–1.46) |
| Thiazide diuretics | 1.43 (1.40–1.46) | 1.36 (1.33–1.39) |
| Antidepressants | 1.40 (1.38–1.43) | 1.36 (1.34–1.38) |
| Atypical antipsychotics | 1.82 (1.69–1.96) | 1.87 (1.74–2.01) |
| Renin–angiotensin system blockers | 1.42 (1.39–1.45) | 1.38 (1.35–1.41) |
| Calcium channel blockers | 1.35 (1.30–1.40) | 1.24 (1.20–1.28) |
| **C**: Rate ratios (95% CIs) for glucose testing [*] (all glucose tests during follow-up) | | |
| Beta blockers | 1.32 (1.31–1.33) | 1.27 (1.26–1.28) |
| Statins | 1.21 (1.20–1.22) | 1.16 (1.15–1.17) |
| Thiazide diuretics | 1.13 (1.12–1.14) | 1.13 (1.12–1.14) |
| Antidepressants | 1.22 (1.21–1.23) | 1.21 (1.20–1.22) |
| Atypical antipsychotics | 1.71 (1.67–1.76) | 1.76 (1.72–1.81) |
| Renin–angiotensin system blockers | 1.27 (1.26–1.28) | 1.26 (1.24–1.27) |
| Calcium channel blockers | 1.38 (1.36–1.40) | 1.27 (1.25–1.28) |

[*] Reference is no exposure to the respective drug class; "unadjusted" hazard and rate ratios are adjusted only for concomitant use of other drug classes; "adjusted" hazard and rate ratios are additionally adjusted for time-varying covariates (age, calendar year, non-topical corticosteroid use), baseline covariates (gender, FBG level at index date), and covariates derived from laboratory tests and inpatient or outpatient visits during the 6-month look-back period (LDL, HDL, TRI, BP, BMI, and cardiovascular disease, consisting of coronary artery disease, congestive heart failure, myocardial infarction, peripheral vascular disease, or cerebrovascular disease).