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IMPACT OF DRUG EXPOSURE DEFINITIONS ON OBSERVED ASSOCIATIONS IN PHARMACOEPIDEMIOLOGY RESEARCH

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ABSTRACT

BACKGROUND

A variety of methods used to define exposure in pharmacoepidemiological studies. Although each method has known biases, the relative effect of these biases on an observed association has not been fully examined.

OBJECTIVE

To explore the influence of different exposure definitions on estimates, using the association between metformin and all-cause mortality as a proto-typical model.

METHODS

New users of oral anti-hyperglycemic drugs identified using administrative health databases from Alberta, Canada between 1998 and 2010. Drug exposure was described using definitions that are commonly used in observational studies. All analyses included the same covariates of age, gender, and a comorbidity score, and subjects not exposed to metformin served as the reference group. The measure of association assessed using a Cox Proportional Hazards model for cohort studies and conditional logistic regression for case-control studies.

RESULTS

We identified 64,293 new oral anti-hyperglycemic drugs users; mean age 68.9 years, 33,131 (52%) males, and 24,745 (39%) deaths during a mean follow-up of 6 years. In adjusted models, the association between

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metformin and mortality ranged from 0.23 (95% CI 0.22–0.25) to 0.96 (95% CI 0.93–0.99). Most metformin exposure definitions, however, provided estimates in the 0.6–0.8 reduction range, aligning with the results of previous observational studies.

CONCLUSIONS

The variety of exposure definitions tested in this analysis produced a wide range of associations between metformin and mortality risk. Therefore, pharmacoepidemiological studies should include sensitivity analyses using at least two exposure definitions with complementary risks of bias to improve the validity of study results.

Few head-to-head randomized trials comparing oral antihyperglycemic medications on hard clinical outcomes (e.g., mortality, cardiovascular outcomes) exist. As a result, a large amount of evidence comparing antihyperglycemic medications effectiveness in diabetes comes from observational studies. Accurate estimation of medication use is an essential component of any pharmacoepidemiological research as exposure misclassification will threaten study validity and lead to spurious associations.¹

Many observational studies, however, use crude definitions, such as the categorical “any versus no use” to classify exposure, which has potentially serious drawbacks.² This approach has led to numerous highly publicized observational studies of the effect of diabetes medications on health outcomes reporting exaggerated relationships^{3,4} that were later contradicted by randomized controlled trials.⁵ Although selection bias, unmeasured confounding, and many other factors contribute to the discrepancies, one critical element, which is often overlooked, is the method used to define exposure.^{4,6} Most agree that time-varying (TVA) or Nested Case Control (NCC) analyses are preferred to time-fixed analyses, but little guidance has been given on how best to implement these approaches. Therefore, the novelty of our research work is to demonstrate the difference in the estimates when comparing different exposure definition methods, and, although, some literature exists highlighting the bias certain measures may have on the estimates, no paper has looked at all major exposure definitions and have quantified the degree of bias that each method may introduce.

The association between metformin and all-cause mortality is a good proto-typical model to examine the influence of exposure definitions because of the

differences observed in pharmacoepidemiological studies and randomized controlled trials. Numerous observational studies in patients with diabetes have consistently shown metformin to be associated with ~30% reduction in all-cause or cardiovascular-specific mortality compared to other oral antihyperglycemic agents.^{7,8} Yet, only one small, sub-study within the UKPDS randomized controlled trial has suggested a similar benefit in obese patients with type 2 diabetes.⁹ Indeed, a recent meta-analysis of 13 RCTs found no benefit of metformin *per se* relative to other treatments.⁵

It is possible some, if not all, of the benefit, observed with metformin in observational studies may be related to analytic design and exposure definitions.^{1,6} Thus, using a large administrative health database, similar to databases used to evaluate outcomes associated with metformin therapy in previous studies, we explored the potential impact of exposure definition on estimates of the association between metformin and all-cause mortality risk. Although we are using diabetes medication as our prototypical example, our results would be expected to apply to almost all pharmacoepidemiological studies of drug safety and effectiveness.

METHODS

Between January 1, 1998 and December 31, 2010, all new users of oral antihyperglycemic medications aged 66 years and older identified using the administrative health databases from Alberta, Canada. We used a standard approach by defining new users as those with no prescription record for any antihyperglycemic medication or insulin for one year before their index date.^{8,10} Among the new users, we then classified patients as “exposed” or “not exposed” to metformin according to our exposure definitions as

stated below. Thus, the analysis consisted of patients who used metformin therapy and who may have only used other antihyperglycemic agents like sulfonylureas during the follow-up. The restriction to patients 66 years or older was required as in Alberta only patients 65 years of age and older are eligible for universal drug coverage, allowing for 1 year to establish our new user cohort. Socio-demographic information was extracted from the Alberta Registry database and mortality was ascertained from Vital Statistics Registry data.

Exposure Definitions

Based on a comprehensive search of the literature, we identified the most common exposure definitions, and their variants, used in pharmacoepidemiological research of antihyperglycemic medications (Table 1). Three general approaches to exposure definitions were identified: (1) time-fixed approaches, (2) time-varying approaches, and (3) nested case control approach.

Definitions using a time-fixed approach establish medication exposure at a single point based on a portion or all of the prescription records in the study observation period. This exposure definition does not change during the follow-up period. Examples of this approach include ‘any versus no’ prescription record (i.e., “ever” users as exposed, who filled at least one metformin prescription during the follow-up versus ‘never’ users as unexposed, who did not have any metformin prescription records throughout the follow-up)^{6,11–13}; and filling at least 2 prescriptions within a defined interval, such as the entire study period¹⁴ or within 180 days.^{15,16} For the latter definition, those who only filled a single metformin prescription would be considered as unexposed. These exposure definitions are entered into multivariable models as a dichotomous variable to describe exposure status. A variation of these definitions is to use either the interval between first and last prescription record or the cumulative days of supply information to define exposure as a continuous variable.^{6,17–19}

Definitions using TVA approach examine a patient’s prescription records at multiple points during the follow-up period to establish exposure status. The simplest method to define exposure using this approach is the legacy effect, where subjects are

considered “unexposed” until the first prescription record, then considered “exposed” until the end of the follow-up, regardless of subsequent prescription information.^{11,20,21} A variation of this definition is to discontinue follow-up (i.e., censor patients) if there is no evidence of ongoing medication use among exposed and unexposed patients.^{13,21,22}

Other TVA definitions divide the follow-up period into set intervals or “windows,” determine exposure within each window, and use this information as a time dependent variable in the analytical model.²³ Numerous examples of cohort studies using Cox Proportional Hazards models were identified in the literature, with the time windows ranging from 1 day to 1 year, or according to actual prescription records.^{21,24–27} To limit the total number of analyses completed, we elected to focus on the more commonly used windows of 30, 90, 180, 365 days or actual prescription records used in diabetes research to determine drug exposure. We also followed the most common procedure by defining time zero as the start of the first antihyperglycemic medication use,^{10,28,29} then splitting the follow-up time into consecutive windows. To establish exposure status within the window, we found several different methods, including a single prescription record within the window²⁷; any use within a window based on expected availability from the prescription date and days of supply information^{21,24,26}; and any use within a window based on expected availability from the prescription date, days of supply information, plus a “carry-over effect” of 10% to allow for poor adherence.²¹

Exposure definitions in NCC studies used either a prescription record or evidence of medication use (based on prescription date and days of supply information) within a set time-period (usually 30, 90, 180 or 365 days) prior to case event date.^{30–33} In addition, some NCC studies categorized exposure status as current (prescription date plus days of supply overlap the case event date), past (prescription date plus days of supply end before the case event date) or never (no prescription records prior to the case event date).^{34,35}

Analytic Design

In all of our models, we adjusted for age, sex, and a comorbidity score.³⁶ We used a variation of the Elixhauser comorbidity score as time-fixed variable

Table 1 Exposure Methods Reference Source

Reference		Chateerakij, 2016	Tseng CH, 2015	Lee et al, 2011	Mamtani, 2014	Margel, 2013	Bowker, 2010	Simpson, 2016	Abdelmoneim, 2016
Exposure Method									
Time-fixed analysis	'Ever' versus 'never' users	✓	✓						
	Filling at least 2 prescriptions			✓	✓				
	Cumulative exposure in years					✓			
Time-varying analysis	Legacy effect	✓							
	Discontinue the follow up if no evidence of ongoing exposure								
	Any prescription fill within a time window						✓		
	Any use within a time window based on days of supply							✓	✓
	Cary over effect of 10%								
Nested Case Control	Any prescription fill prior to the event date								
	Any use prior to the event date								
	Current use, Past use or Never								

in all models, which uses ICD-9/10 codes to identify a defined list of diseases and generate a single ordinal variable that is an independent predictor of mortality risk.^{21,26,30,37} All comorbidities identified based on hospital discharge records and emergency department visit records within one year prior to starting the first antihyperglycemic medication. We elected to use the Elixhauser comorbidity score as a time-fixed measure at baseline to ensure that all models accounted for comorbidities in a consistent fashion (i.e., to ensure that only the exposure definitions were changing between the numerous models to all comparisons across models on estimates obtained); however, in

pharmacoepidemiology research, this may not always be appropriate.

Our reference group for all models was subjects who did not meet the definition for metformin exposure under study. Depending on the study design and exposure definition, this unexposed group would be patients who did not receive any metformin prescriptions during the entire follow-up time, during an individual window, or during the follow-up time prior to the first metformin prescription record. In all the models, numerous variants of the exposure definitions (e.g., 2 prescriptions within 180 days, or within the follow-up period; different cut-points based on

Table 1 Exposure Methods Reference Source (*Continued*)

Reference Exposure Method		Eurich, 2013	Calip, 2015	Failie, 2014	MacDonald, 2010	Bensimon, 2014	Azoulay, 2016	Lipscombe, 2007	Shih, 2015
Time-fixed analysis	'Ever' versus 'never' users								
	Filling at least 2 prescriptions								
	Cumulative exposure in years								
Time-varying analysis	Legacy effect	✓	✓						
	Discontinue the follow up if no evidence of ongoing exposure	✓		✓					
	Any prescription fill within a time window								
	Any use within a time window based on days of supply	✓							
	Cary over effect of 10%	✓							
Nested Case Control	Any prescription fill prior to the event date				✓	✓			
	Any use prior to the event date						✓		
	Current use, Past use or Never							✓	✓

time, etc.) were explored to determine if these subtle changes in the definitions would substantially affect the estimate. All variants were consistent with the more standard definitions identified in the literature; therefore, these additional analyses are not presented but are available on request from the authors (DTE).

In the cohort studies, individuals followed from the index date (first antihyperglycemic medication prescription record) until death or censoring. Individuals censored at the earliest of the end of the study period (December 31, 2010), or departure from the provincial database. We used Cox Proportional hazard regression models for the cohort study designs

to calculate adjusted hazard ratios (aHR) and 95% confidence intervals (CI).

In the NCC studies, we followed conventional risk-set sampling methods by defining cases as patients with our event of interest (all-cause mortality) and selecting five controls from among those who have not experienced the event after the same duration of follow-up as the case. Adjusted odds ratios (aOR) and 95% CI were calculated using conditional logistic regression models.

We fully acknowledge that our models are prone to additional confounding factors. However, our goal is not to establish whether metformin is associated

with mortality but to explore the effects of different exposure definitions. As we are using the same source of information and the same set of variables for all analyses, we would expect that all models would have the same relative degree of confounding. The only change among models is the method used to define metformin exposure. Thus, any changes in estimates between models would be expected to be driven, in large part, by the underlying biases associated with the definition used to classify metformin exposure.

RESULTS AND DISCUSSION

Our cohort consisted of 64,293 new antihyperglycemic medication users. The average age in the cohort was 69 years, and 52% were male. Overall, 86% of the cohort (55,525 patients) filled at least one metformin prescription (Table 2). Compared to non-metformin users, metformin users tended to be slightly younger (69 vs. 71 years) and have a lower level of comorbidity (5 vs. 7). After an average follow-up of 6 (SD±4) years, 39% of patients died from any cause. Fewer metformin users died (19,636; 35.4%) relative to those not using metformin (5,109; 58.3%) at any point in the follow-up.

Time-Fixed Definitions

The various definitions using a time-fixed approach to establish exposure status produced consistent

estimates of metformin effect on all-cause mortality, relative to those not using metformin (Figure 1). When a single prescription record was used to define exposure, regardless of timing in the follow-up period, any metformin use was associated with a substantial reduction in the risk of death (aHR 0.64, 0.62-0.66). However, ignoring the interval between first antihyperglycemic drug use and first metformin prescription may introduce unintended immortal time bias and lead to an overestimation of the effect. Starting follow-up for the exposed group from first metformin prescription date, will aid in eliminating some survival bias and improve estimation of the effect.^{38,39}

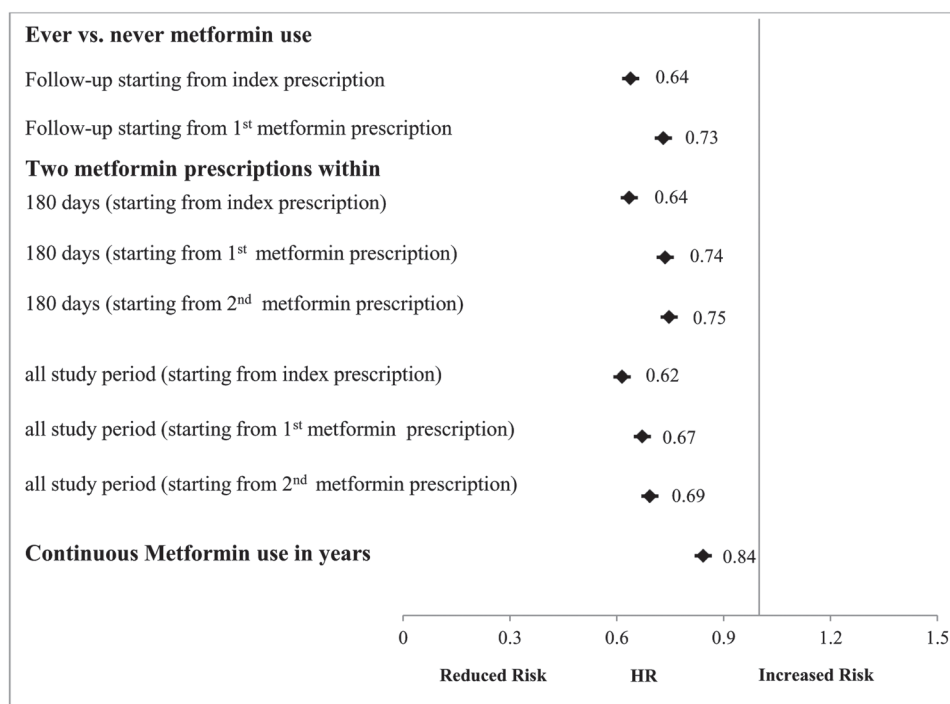
A major limitation of using a single prescription record to define exposure is that all exposed patients are considered similar, regardless of the number of prescription records or duration of use.² Using two or more prescription records to define exposure may mitigate this problem; however, patients with only one prescription record will be classified as non-exposed, when in fact they did have some exposure. Furthermore, this method is still dependent on when follow-up for the exposed group started and provides similar adjusted hazard ratios, regardless of the number of prescription records used to define exposure. For example, starting the follow-up at the first antihyperglycemic medication prescription produced an aHR 0.64 (95%

TABLE 2 Patient Characteristics Incident Oral Hypoglycemic Agents Users Cohort, Alberta, Canada, 1998-2010

	>1 Metformin Prescription (n=55,525)	No Metformin Prescriptions (n=8,768)	p-value [‡]
Age, mean (SD), yr	69 (±4)	71 (±6)	< 0.001
Men, (%)	28,547 (51.4%)	4,584 (52.3%)	< 0.131
Elixhauser Comorbidity Score, mean (SD)	5 (±7)	7 (±8)	< 0.001
Follow-up, mean (SD), yr	6 (±4)	5 (±4)	< 0.001
Death, no. (%)	19,636 (35.4%)	5,109 (58.3%)	< 0.001

SD = standard deviation, yr - year

[‡] p-value is for difference in characteristics between groups, when metformin users and non-users within a treatment cohort are compared by analysis of variance or by χ^2 test.

FIG. 1 Association of metformin on all-cause mortality using time-fixed exposure definitions.

CI 0.62-0.66) when a single metformin prescription record is used to define exposure, while the aHR was 0.64 (95% CI 0.59-0.68) when using two metformin prescription records within 180 days, and 0.62 (95% CI 0.60-0.63), when using two metformin prescription records within the entire study period.

Time-fixed analyses are particularly prone to exposure misclassification and to immortal time bias to varying degrees.³⁸ For example, an analysis that defines exposure based on 2 prescription records inherently assumes that the person had to be alive long enough to fill a second prescription, thus the period between the subject's cohort entry date and the 2nd prescription would be considered immortal time. The amount of immortal time bias depends on when follow-up is initiated (index antihyperglycemic drug prescription, and 1st or 2nd metformin prescription).⁴⁰ Therefore, the combination of using two prescription records within a defined period of time and starting follow-up on the date of the second prescription provides a further refinement to the exposure definition. However, selection bias can also be introduced when immortal time periods are differentially excluded in a

time-fixed analysis. This can occur when the start of the follow-up is defined as first metformin prescription fill for exposed group and first antihyperglycemic drug prescription record for comparator.⁴¹ Although editorials often criticize studies using time-fixed approaches with regards to immortal time bias,^{38,42} few studies have quantified the impact of immortal time on study estimates within the same data and population. Our analyses indicate that time-fixed exposure definitions, particularly when two prescriptions are required, can introduce substantial immortal time in the estimates.

Defining the exposure as a continuous variable (by calculating the interval between first and last prescriptions) produced a relatively large risk reduction estimate associated with metformin use: 0.84, 95%CI (0.83-0.85). In other words, each year of metformin use is associated with a 16% reduction in all-cause mortality risk compared to non-users. Authors have suggested this exposure definition may circumvent potential survival bias in observational studies and add consideration of a dose-response relationship, which would strengthen evidence for causality.^{18,43}

Furthermore, authors suggest it provides more precise exposure definition and a more robust variable for statistical analysis, unlike commonly used dichotomous ‘any versus no’ exposure definitions.^{2,44} Although this may be true, we believe the definition also inherently integrates some form of survival bias in the definition (i.e., by definition patients with the largest cumulative exposure also inherently had to live the longest; patients who die early cannot have a large cumulative exposure). Moreover, a continuous exposure definition does not account for gaps between refills, when the supply from one prescription record is finished well before a subsequent prescription record. For example, the interval between first and last prescription record may be several months or years, but if these are the only two prescription records there would be a substantial unaccounted gap in exposure. Thus, a time-fixed definition does not allow for variation in exposure during the follow-up period.

Overall, the estimates in the time-fixed approach were relatively consistent with previous observational studies, showing 30–45% lower risk, with the exception of the continuous variable analysis. Several solutions have been proposed to prevent immortal time bias, a well-known limitation of the time-fixed approach to defining exposure, including using TVA approaches and NCC analysis.^{19,41}

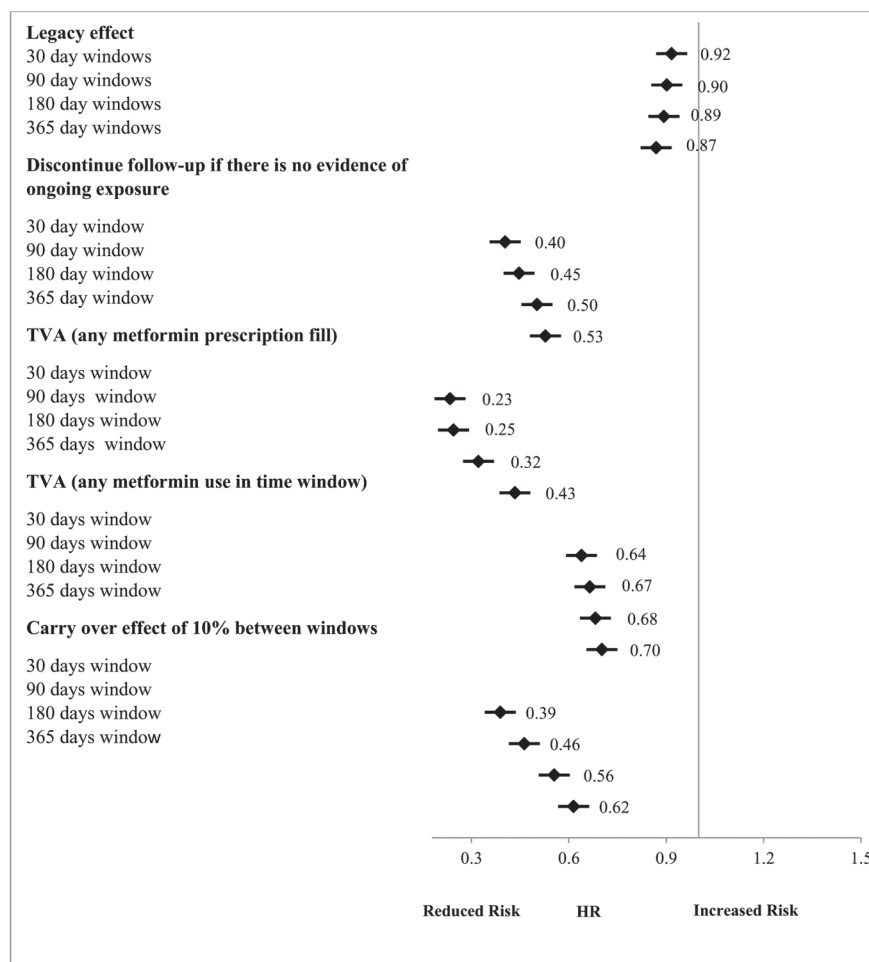
Time-varying Definitions

Further refinement of exposure using time-varying Cox analysis produced substantial variation in the estimates (Figure 2). The legacy effect analysis, whereby once a person is exposed they considered always exposed (i.e., intention to treat), shifted the estimates to 0.87–0.92. This method for defining exposure is similar to the time-fixed ‘ever versus never’ analysis because exposure starts with the first metformin prescription. However, there was a substantial difference between the observed associations (0.73 versus 0.87–0.92). One possible explanation for this difference is the treatment of time between index antihyperglycemic medication and first metformin prescription. In the time-fixed ‘ever versus never’ definition, this interval is ignored. The advantage of a legacy-based exposure definition is that all observation time can be used in the analysis and its similarity to the principles of intention to treat

analysis. The interval between the patient’s index antihyperglycemic medication date and first metformin prescription contributes to the “unexposed” group in a legacy effect analysis.³⁹ However, the major limitation of the legacy approach is the inability to account for future treatment discontinuation, where the patient is still erroneously characterized as exposed.¹

An approach to address potential misclassification when treatment is discontinued is to censor patients with no evidence of ongoing therapy, such as, stopping the follow-up in the exposed and unexposed groups after 1 window without medication use.^{13,22} This approach resulted in a substantial decrease in time at risk for cohort participants and low risk estimates ranging from 0.40 to 0.53. Censoring based on absence of a prescription record within a defined time-period is highly dependent on when the patient obtains a refill. If there is a delay because of poor adherence or intermittent medication use, the prescription record could appear after the end of the window used to identify discontinuation of therapy. This can be especially problematic if the windows are shorter than the usual refill interval, leading to erroneous censoring. Furthermore, treatment may have been discontinued because of advancing disease (for example, switching from metformin to insulin), thus censored patients may be at a different level of risk than those who continue to be followed in the cohort. As a result, this method for defining exposure could violate the Cox proportional hazards model key assumption of non-informative censoring and participants who drop out of the study do so for reasons unrelated to the study will not have similar survival probabilities to the participants who continued to be followed (i.e., bias due to competing risks).

In the TVA approach, notable differences were observed which were dependent on the method used to determine exposure within the window. For example, defining exposure based on any metformin prescription record within a window resulted in extremely low estimates with aHR ranging from 0.25 to 0.43. As discussed with the censoring approach above, this approach is highly dependent on the timing of a refill and can lead to misclassification, especially if the windows are shorter than the usual refill interval. Many provincial health jurisdictions in Canada allow

FIG. 2 association of metformin on all-cause mortality using time-varying exposure definitions.

a 100-day supply for each metformin refill. Thus, a time-varying exposure definition with short windows (e.g., 30 days) would create a majority of windows with no prescription fill *per se* and thus misclassify windows as unexposed. In contrast, long windows may introduce misclassification because only a single prescription record is required to define exposure within a window. For example, a patient may obtain only a single prescription for 100 days' supply of drug within a 365-day window; yet, they will be considered exposed for the entire 365-day window, introducing a significant amount of misclassification (265 days are truly unexposed). Therefore, time windows used in the study should more appropriately reflect the utilization of the drug in the real world in terms of prescription refill frequency and days of supply may

provide a better estimate of exposure over multiple windows in time-varying exposure definition.

Accounting for days of medication supply can improve exposure accuracy, since single prescription days of supply can cover several short windows. The estimates of any metformin use based on this exposure definition produced estimates ranging from 0.64 to 0.70. An advantage over previous definitions is the ability to describe periods in the follow-up where there are gaps in medication supply and account for intermittent drug use, which commonly seen in chronic diseases. One serious limitation in drug exposure definition, however, is the inability to account for poor adherence, which is quite common in chronic disease management.^{45,46} Poor adherence could extend the duration of exposure beyond the interval defined

by the days of supply information in the prescription data resulting in exposed periods, which may be inadvertently considered as unexposed. While on the other hand the interval determined as exposed based on prescription record can be actually unexposed one due to poor adherence (i.e., patient has drug but is not actively taking the drug due to poor adherence).

In order to account for poor adherence, an additional 10% 'carry over' of medication supply has been used in the literature (i.e., a 100-day supply is assumed to cover 110 days from the prescription date). This exposure definition produced lower risk estimates relative to the definition based on days of supply alone, with estimates ranging from 0.39 to 0.62. Although this definition would account for poor adherence, it creates a differential introduction of an additional 10% of time which the patients are considered exposed compared to the unexposed group. This differential introduction would favour the exposed group and lead to larger observed protective effects.

Overall, TVA approach provided consistent estimates of a 30–40% lower risk, when accounting for days of medication supply and follow-up time. These estimates did not materially change when different durations for the windows used within the same exposure definition. However, censoring patients in the absence of prescription records within a defined period yielded highly biased results and is not advocated, particularly given that the censoring may be the result of competing risks which is highly problematic within Cox models. The advantage of TVA approach is the ability to obtain precise risk estimates by accounting for intermittent drug use,¹⁹ and minimizing the influence of survival bias, immortal time bias, and confounding by duration.^{27,40}

Nested Case Control

Although NCC approach has rapidly been taken up in pharmacoepidemiology research, further considerations must be accounted for in this model. In the NCC study design we followed conventional risk-set sampling methods by identifying 24,743 cases as patients who had died and matching up to 5 controls from among those with the same duration of follow-up as each case patient, but who had not died (123,700). Analyses of any metformin prescription record prior to

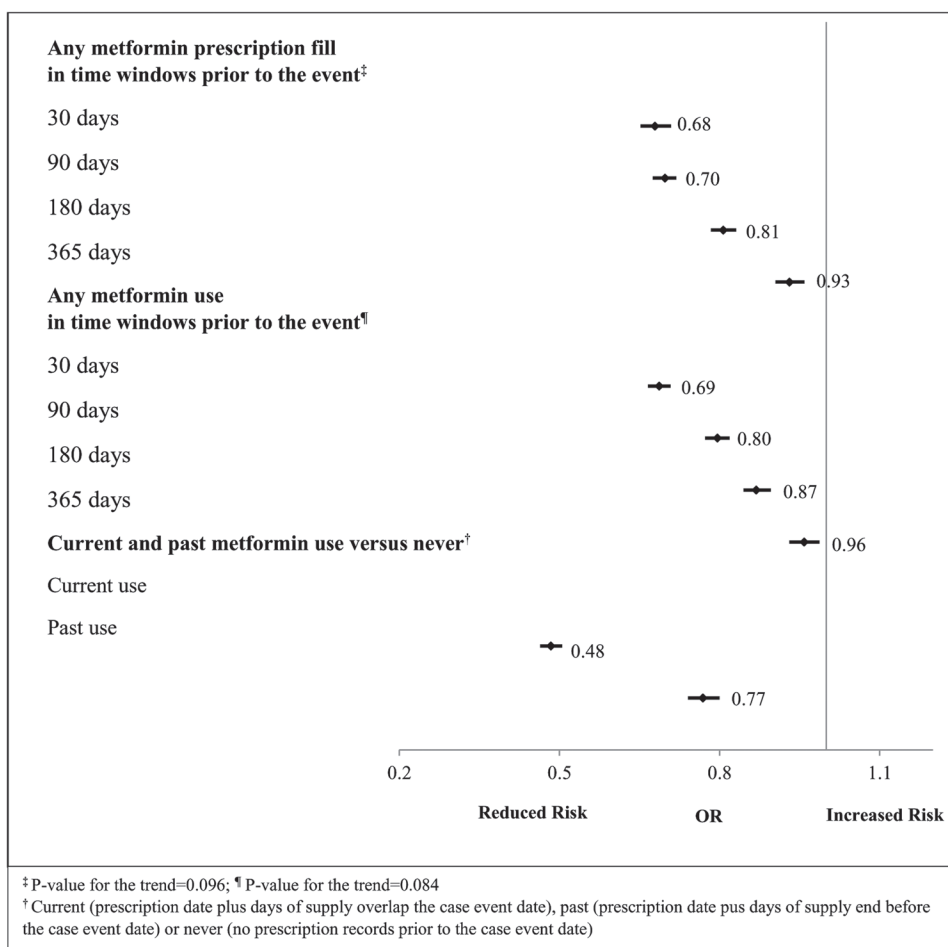
the event date resulted in adjusted odds ratios (aORs) ranging from 0.68 to 0.96 (Figure 3). Including days of supply information in the exposure definition may improve accuracy. However, similar issues as noted previously with TVA will also hold true in the NCC and resulted in aORs ranging from 0.71 to 0.87.

The NCC design provides an efficient and flexible analysis of the association between immediate exposure and outcomes; however, it does not account for long-term treatment effects, which may be important in patients who use a medication for many years in the management of a chronic disease. Indeed, the NCC only uses the window immediately before the event to determine exposure status. Moreover, the NCC does not easily account for changes in patient's characteristics over time, changes in pertinent risk factors, disease severity and all of the initial treatment period is excluded from the analysis. For example, for critically ill patients, metformin treatment is often switched to insulin and therefore prior to the event the patient may be misclassified as unexposed despite previous metformin use. Patients who discontinue medication use long before the outcome may have a different risk profile than patients who continue using the medication closer to the event, which may be highly correlated with the outcome of interest, introducing a potential selection bias in the estimates.

One refinement to the NCC design that has frequently been used is to categorize exposure into current, past, or never.^{34,35} This approach attempts to capture exposure which may have occurred immediately prior to the event. Using this approach, a substantially smaller benefit for current use 0.93, 95% CI (0.9-0.96), and no benefit for past use 1.00, 95%CI (0.96-1.04) compared to never users observed. This approach yielded results which were similar to two previous NCC analyses that showed 0.93, 95%CI (0.91-0.96) and 0.87, 95%CI (0.84-0.89) reductions for any prescription record or any medication use 365 days prior to the event, respectively.^{30,32}

Overall, NCC analyses provided a wide spread of estimates ranging from 0.68 to 0.96, which would produce a wide range of clinical interpretations. Our analyses indicate that the observed association between metformin and mortality risk could change materially not only between the different exposure approaches

FIG. 3 Association of metformin on all-cause mortality using nested case control exposure definitions.



used in NCC analyses, but also between windows within the same exposure definition. Although the NCC is often preferred due to its computational efficiency over cohort studies, in today's era of 'inexpensive' computing power this relative advantage declines and time-varying approaches may be better suited to capture the full exposure profile of drugs used in the management of chronic diseases.⁴⁷ Furthermore, TVA and NCC study designs are widely considered equivalent in the literature; however, in our prototypical model we obtained results, which were not as congruent as expected. Several factors may be driving these differences including the length of time window defined in the analysis, and changing patient's characteristics with diabetes progression, which are not fully accounted in NCC analysis.

Collectively, our results suggest that sensitivity analyses of the exposure definition should be performed in pharmacoepidemiological research to help identify potential biases introduced by the primary method used to define drug exposure. Clearly, time-fixed methods which introduce immortal time bias, as we have illustrated, should be avoided. However, the potential for bias in other approaches (e.g., TVA and NCC) may be less obvious. As a result, investigators should conduct sensitivity analyses using at least two substantially different exposure definitions in order to assess the comparability of study estimates and to provide more robust and potentially valid study results. For example, if a time-fixed approach is used for the primary analysis, investigators should consider a TVA or NCC as a sensitivity analysis. Similarly, in

TVA analyses investigators should consider a NCC approach (and vice versa if a NCC was used as the primary approach). Importantly, in both the TVA and NCC, investigators should fully evaluate the impact of varying window sizes as well as differences in exposures defined based on a prescription within a window or ‘drug availability’ within a window on the estimate.

Despite several strengths of our study, including the large population-based sample, the replication of numerous exposure definitions and advanced statistical techniques used in the literature, several limitations are inherent to our work. Firstly, and most importantly, we fully acknowledge that additional unmeasured confounding can be present in our study. Our intent was not to establish whether metformin is or is not associated with mortality, but to fully explore the impact of different exposure definitions used in pharmacoepidemiology. Indeed, as all models used the same data, adjusted for the same covariates, and had the same outcomes, the degree of unmeasured confounding expected to be similar in all the analyses. The differences in observed estimates are solely driven by exposure definitions and bias introduced by those definitions. Secondly, the administrative databases only indicate the drug was dispensed and do not indicate whether the drugs were taken as prescribed. Our assumption that metformin was used if there was a prescription record may lead to an overestimation with any exposure definition. This limitation is inherent to most observational studies using administrative drug data. Third, although in some instances the degree and deflection of bias is readily identifiable (e.g., immortal time bias in fixed-time analyses), in many cases, the substantial change in estimates is unknown.

CONCLUSION

In this prototypical model, the observed estimates ranged from 4–77% lower risk of all-cause mortality risk associated with metformin use. The differences in observed estimates were completely driven by the exposure definitions and no single method to define drug exposure is completely free of bias. Therefore, given the range of observed estimates, we recommend an implementation of sensitivity analyses of exposure definition in any pharmacoepidemiological study by

using at least two substantially different exposure definitions with complementary risk of bias to provide more robust and potentially valid study estimates.

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DISCLOSURE

The authors have no conflicts of interest in relation to the article.

AUTHORS CONTRIBUTION

ME was responsible for the study design, statistical analysis and interpretation of data, drafting the manuscript. DTE and SHS were responsible for the study design, interpretation of data and critical revision of manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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