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Incidence in pharmacoepidemiology: A conceptual framework for incidence of a single substance or group of substances with statins as an example

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Abstract

A framework for analysing incidence in pharmacoepidemiology and drug statistics is suggested using statins as an example. A new case of statin use (first-ever use or recurrence of treatment) can be defined as new on the group (NoG), new on substance whether new on the group or not (NoS), new on substance and new on the group (NoS_and_NoG), new on substance and not new on the group (NoS_not_NoG).

Method: Individual-level dispensations of statins 2006–2019 for 1 017 058 individuals with at least one dispensation 2019 in Sweden.

Results: With 12-month run-in, corresponding to at least 8 months without treatment, the incidence proportion of NoG was 13.39 new cases per 1000 inhabitants and 8.40 with 10-year run-in. Thus, 37% had first been treated with any statin between 12 months and 10 years before the index date.

For atorvastatin, NoS was 10.69, NoS_and_NoG 9.99, and NoS_not_NoG 0.70 per 1000 inhabitants. 0.70 per 1000 inhabitants or 6.6% of new cases of atorvastatin represented a change from another statin during the run-in.

Conclusion: It is essential to separate new cases that are new both on the substance and on the group from those that represent a change of therapy during the run-in.

KEYWORDS
incidence, misclassification, pharmacoepidemiology, run-in, statins

1 | INTRODUCTION

In pharmacoepidemiology, the concept of incidence—a new case of drug use—is important from several different perspectives. A new case of drug use defines the start of a specific period of drug exposure. It also represents a decision by the prescriber to either treat a patient for the first time with a specific substance or group of substances (the first-ever case of drug treatment with this substance of this patient) or to initiate a new period of drug treatment.

In pharmacoepidemiology, dispensations of drugs are commonly used as a proxy for actual drug use over the period covered by the amount dispensed. The first dispensation of a drug is probably more sensitive to changes

in prescribing habits than subsequent prescriptions or successive dispensations of the same prescription.

Repeated treatment episodes with the substance, or a group of substances, over time with periods without treatment in between have to be analysed when studying incidence in pharmacoepidemiology. For instance, a new case of drug treatment should be differentiated from continuing treatment. In addition, first-ever use has to be distinguished from a recurrent treatment episode.[1]

In epidemiology, measures of disease frequency such as incidence and prevalence are well defined,[2] based initially on a simple illness–death model (also known as the disability model).[3] Drug use is often intermittent for chronic diseases, either due to changes in the severity of the disease or non-compliance. Drugs are mainly used to treat a disease or as secondary prevention in order to prevent possible future complications of a disease. However, they are also used for primary prevention of future disease in otherwise healthy individuals with an increased risk of becoming ill. The original simple model of incidence based on infectious diseases with immunity thus needs to be extended to be applicable for drug treatment where we consider treatment status instead of disease status (see Figure 1).[1]

The definition of incidence is made more complicated because multiple drugs can be combined or used consecutively to treat a disease. It is essential to consider whether a new case of drug use representing a new case of treatment with the specific substance is preceded or not by other possible substitutes within or outside a specific pharmacological group defined, for instance, by the ATC system.[4]

A switch from one substance to another may have many different reasons. For the lipid-lowering groups of statins (HMG-CoA reductase inhibitors), the reasons might, for instance, be adverse drug reactions, an unsatisfactory lowering of blood lipid levels, or an increased risk for the patient of cardiovascular events. Other factors might be changes in the costs for the society or the patient, new generic competition, and changes in the pharmaceutical benefit scheme.

With a strict definition of different types of new cases of drug use and a well-defined methodology, it is possible to report incidence not only in studies of drug utilization but also as a standard measure in routine statistics of drug use. Incidence is already part of national standard annual drug utilization statistics from the National Board of Health and Welfare of Sweden,[5] albeit only for some groups of substances. A more stringent methodology and a standardized mode of reporting the different incidences are essential when incidence becomes more widely adopted as a standard measure in publicly available drug utilization statistics.

2 | AIM

This article aims to explore incidence as new cases of treatment with a specific drug or group of drugs and to

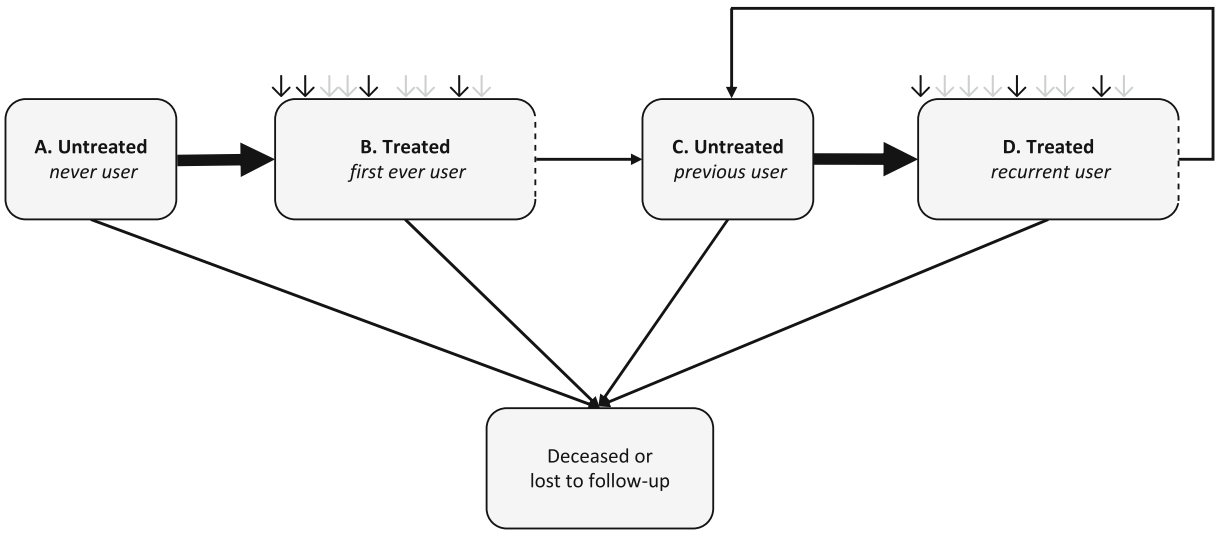

FIGURE 1 Model for repeat treatment in pharmacoepidemiology. Reprinted with permission from Hoffmann and Støvring.[1] In pharmacoepidemiology, transitions from A → B and C → D (bold arrows) define new cases together. A → B represents first-ever use, while C → D represents recurrence of drug treatment. Downward arrows represent dispensations (black = first dispensation of a prescription, grey = repeat dispensations of a previous prescription) in hypothetical first-ever and recurrent user episodes.

develop a corresponding methodology and terminology for consistent reporting in drug utilization studies and national drug statistics.

An additional aim is to illustrate this by analysing the initiation of treatment with statins in Sweden 2019.

3 | MATERIAL AND METHODS

The Swedish Prescribed Drug Registry data were extracted as patient-level data, fully anonymized and classified as statistics by the National Board of Health and Welfare.[6] Substances were classified according to the Anatomical Therapeutic Chemical (ATC) classification system in 2020.[4,7]

All first individual occurrences of the dispensation of C10AA HMG-CoA reductase inhibitors and fixed combinations of HMG-CoA reductase inhibitors in C10BA in Sweden for both sexes and all ages during 2019 were extracted, together with the ATC code and the number of days since the last dispensation of the same ATC code (total population = 10 230 185 with n of individuals with a dispensation of at least one statin = 1 017 058 corresponding to a 1-year prevalence of 9.9%). In addition, the number of days since the last dispensation of any other studied substances was obtained with information on ATC code, gender, age (5-year intervals up to ≥85) and Swedish citizen status on 1 January in 2009 and 2019. Stata[8] was used for all data analyses.

Simvastatin, pravastatin, atorvastatin and rosuvastatin in monotherapy constituted >99.9% of the 1-year prevalence for all statins in C10AA during 2010–2019 in Sweden. The available fixed-combination products C10BA02 simvastatin + ezetimibe and C10BA05 atorvastatin + ezetimibe represented 0.31% and 0.07% of the sale of respective statins in monotherapy (0.29% and 0.14% in 1-year prevalence).

The incidence proportion was calculated with the number of new cases (first-ever or recurrent treatment) defined by different run-in periods as the numerator and the population at the beginning of the year as the denominator. The positive predictive value was calculated as the ratio between the incidence proportions for different lengths of the run-in compared with a run-in of 10 years.[1] It can be interpreted as the fraction of the new cases given a specific run-in that represents first-ever use, that is, no dispensation 10 years before the index dispensation. Using a 10-year run-in as a reference represented a pragmatic approximation defining users as actual first-ever users of statins. The reason for this approach is the limitation of data available over time in many countries with national prescription databases covering individual-level patient data of dispensations.[1] Extending the run-in from 10 to 13 years (the longest possible for dispensations in 2019 in Sweden) had a minimal impact on the incidence proportion (see Section 4).

3.1 | Methodological considerations when defining a new case of drug use

Before we consider the main problem of patients being new to a specific substance or a group of substances, we briefly review the concepts of a run-in period and incidence rates *versus* incidence proportion, as these are fundamental for analysing treatment initiation.

3.1.1 | The effects of run-in on different misclassifications

There are several possible misclassifications when studying incidence. We have previously explored the concepts of a new case, first-ever use and recurrent treatment and different types of misclassifications of incidence associated with varying the length of the run-in period.[1]

A run-in period (sometimes also called a washout period) is commonly used to differentiate between a dispensation indicating a new case of drug use and one representing a continuation of treatment. A short run-in period will not differentiate well between first-ever use and recurrence of treatment. With a long run-in, a more significant fraction of new cases of drug use will represent first-ever use.[1]

The run-in consists of the total period without treatment and the assumed duration of the last dispensation. This pragmatic practice in register-based studies will not be influenced by previous hoarding, change in dosage or a decision to end the treatment early (either by the prescriber or the patient). When comparing the incidence of drug use between countries and clinical settings, the assumed duration without treatment, and not the actual run-in, must be considered since the average treatment duration of a dispensation varies between countries due to clinical practice and regulations. Suppose the average duration is 3–4 months as in Sweden due to the rules of the pharmaceutical benefit scheme. In that case, a 12-month run-in will usually represent a period between 8 and 12 months without treatment, while a 16-month run-in will represent at least a full year without treatment. If the average duration of a dispensation is 1 month, then the same run-in period of 12 months in most cases will correspond to 11–12 months without treatment.

3.1.2 | Incidence, incidence rate and proportion

The incidence, the number of new cases in a defined population, is often presented as a rate or a proportion. In incidence rate, the denominator is the aggregated study time contributed by each studied individual (actual person-time). The denominator in incidence proportion (also called the cumulative incidence) is the population at risk at the beginning of a time interval, for instance, a calendar year. For incidence proportions, individuals that emigrate or die during the studied interval will still contribute to the denominator for the entire interval. Thus, all other things being equal, the incidence proportion will be lower than the incidence rate in a population with high mortality, such as the elderly population at risk, if defined as the population at the beginning of a time interval.

With a high level of immigration, the incidence proportion, all other things being equal, will be higher than the incidence rate if immigrants are not censored. If censoring for immigration, each individual should be censored in the numerator and the denominator for the length of the run-in after the date of immigration since a prevalent user otherwise would be potentially misclassified as a new case of drug treatment.

The traditional definition of incidence rate and incidence proportion in epidemiology focuses on persons at risk as the denominator. In pharmacoepidemiology (whether or not a cohort in rate or a population in a proportion), that would represent only those not classified as prevalent users. However, in drug utilization studies reporting incidence proportion, the whole population is often the denominator (see also Section 5).

3.1.3 | Substance or condition

The reason for prescribing the substance might be considered when studying new cases of drug use if the information is available. However, this information is not registered in large claims or population databases in most instances.[9] Where reasons for prescribing are available, they are not always reliable due to external factors such as reimbursement rules or a heavy workload influencing reporting. Linking prescriptions to specific diagnoses for the same or earlier healthcare episodes is possible in limited situations but creates considerable methodological challenges.[10]

Each prescription might be made for several different reasons, which might change over time. A disease such as depression often fluctuates in severity over several years. A new prescription leading to a dispensation, that is, a case of recurrent treatment, can then represent either a repeat treatment for the same reason or treatment with the same substance or group of substances for other reasons.

3.1.4 | New on a drug or new on a group of drugs

New cases of drug use can relate to a single substance or a group of substances. However, the number of new cases of a group of substances does not equal the sum of the number of new users of each substance since a patient that starts treatment with one substance might have been treated with another substance belonging to the same group earlier.

When placing both individual substances and groups of these substances into a simple two-level model, four different situations can be described:

1. New on a group regardless of the substance—**NoG**
2. New on a specified substance, whether treated earlier with another substance in the group or not—**NoS**
3. New on a specified substance and new on the group—**NoS_and_NoG**
4. New on specified substance and not new on group—**NoS_not_NoG**

This classification can be exemplified as an analysis with two levels for a group with four different substances (see Table 1 and Figure 2). During the studied period of 2009–2019, with 10 years of run-in for dispensations during 2019, only four different statins were dispensed in Sweden (Table 2).

4 | RESULTS

Table 2 shows the incidence proportion with the total population as the denominator in 2019 and a different run-in for new on statins as a group (NoG); new on each statin whether treated earlier with another statin or not (NoS); new on each statin and new on statins (NoS_and_NoG); and new on each statin and not new on group (NoS_not_NoG).

For a run-in of 12 months, the incidence of new on statins (NoG) was 13.39 new cases per 1000 inhabitants, with a positive predictive value for first-ever use of 63%. New on a specified statin and new on statins (NoS_and_NoG) varied between 9.99 new cases per 1000 inhabitants for atorvastatin and 0.06 for pravastatin. New

TABLE 1 A theoretical example of incidence related to prior use or not of substitutes within the same group, exemplified by studying statins (C10AA HMG-CoA reductase inhibitors)

Theoretical example for a group of four substances		Example of statins/atorvastatin
New on group regardless of substance = sum of new on specified substance also new on group for all drugs in the group E or the sum (A ⋂ E + B ⋂ E + C ⋂ E + D ⋂ E)	NoG	A new case of statin treatment, regardless of which statin
New on a specified substance, whether treated earlier with another substance in the group or not A, B, C or D	NoS	A new case of atorvastatin treatment, whether treated before with another statin or not
New on specified substance AND new on group = new on substance and not earlier treated with another substance in the group A ⋂ E; B ⋂ E; C ⋂ E or D ⋂ E	NoS_and_NoG	A new case of atorvastatin treatment and at the same time representing a new case of statin treatment
New on specified substance AND NOT new on group = new on substance and treated earlier with another substance in the group (switch) A − A ⋂ E; B − B ⋂ E; C − C ⋂ E; or D − D ⋂ E	NoS_not_NoG	A new case of atorvastatin treatment and not a new case of statin treatment

Note: See also Figure 2 for visualization.

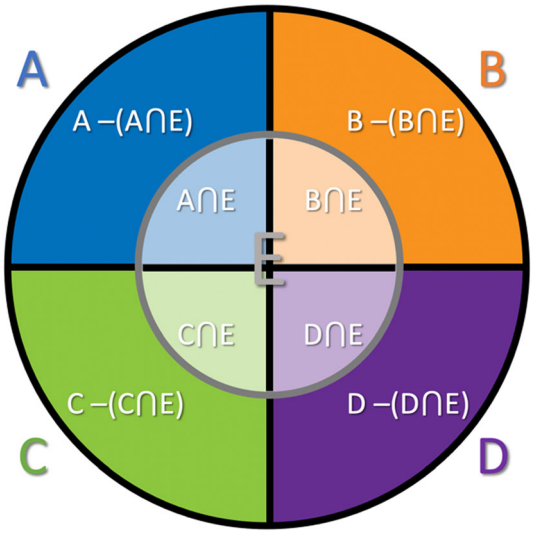

FIGURE 2 A theoretical example of incidence related to prior use or not of substitutes within the same group, exemplified with basic notation from set theory. NoG E = A ⋂ E + B ⋂ E + C ⋂ E + D ⋂ E—new on group regardless of substance. NoS A—new on the substance a. NoS B—new on the substance b. NoS C—new on the substance c. NoS D—new on the substance d. NoS_and_NoG A ⋂ E—new on the substance a AND new on group. NoS_and_NoG B ⋂ E—new on the substance b AND new on group, etc. NoS_not_NoG A − (A ⋂ E)—new on the substance a AND NOT new on group. NoS_not_NoG B − (B ⋂ E)—new on the substance b AND NOT new on group, etc.

on a specified statin, but not new on statins (NoS_not_NoG), varied between 0.70 for atorvastatin and 0.03 for pravastatin.

In addition, 1.27 per 1000 inhabitants started treatment with any statin but had been treated with another statin during the run-in (the difference between the sum of NoS_not_NoG for the individual substances and NoG). This corresponded to 9.5% of the individuals being new on statins (NoG).

Extending the run-in from 10 to 13 years (the longest possible run-in for dispensations in 2019 in Sweden) had a minimal impact on the incidence proportion. For new on statins as a group, the decrease was less than 1% (from 8.40 to 8.34 new cases per 1000 inhabitants) in 2019.

With increasing length of the run-in period, the incidences for new on statins (NoG) and new both on a specified statin and on statins (NoS_and_NoG) decreased as expected, while their respective positive predictive value compared with a run-in of 10 years increased. Concurrently, the incidence of new on a specified statin but not new on statins (NoS_not_NoG) increased since the observed time during which another statin might have been dispensed lengthened.

5 | DISCUSSION

The focus of this study is the distinction between new cases of drug use in analyses for groups of substances (NoG) and the individual substances of the group defined in three different ways (NoS, NoS_and_NoG, NoS_not_NoG).

The incidence and prevalence of statin use have been studied in different countries, periods and age groups.

TABLE 2 New cases for each statin and statins as a group with different run-in periods, both sexes of all ages, in 2019

Run-in (months)	Group or substance	NoG New on group		NoS New on substance—whether new on group or not		NoS_and_NoG New on substance—and new on group		NoS_not_NoG New on substance—and not new on group		Fraction not new on group/new on group
		New cases/1000 inh	PPV	New cases/1000 inh	PPV	New cases/1000 inh	PPV	New cases/1000 inh	PPV	
12	Any statin C10AA	**13.39**	63%							
	C10AA01 simvastatin			**2.24**	50%	**2.14**	48%	**0.10**	42%	
	C10AA03 pravastatin			**0.08**	62%	**0.06**	19%	**0.03**	88%	
	C10AA05 atorvastatin			**10.69**	80%	**9.99**	68%	**0.70**	83%	
	C10AA07 rosuvastatin			**1.65**	82%	**1.21**	44%	**0.44**	92%	
	Sum of incidence of 4 statins			**14.66**	n.a.	**13.39**	n.a.	**1.27**	n.a.	9.5%
16	Any statin C10AA	**12.00**	70%							
	C10AA01 simvastatin			**1.82**	62%	**1.72**	60%	**0.10**	47%	
	C10AA03 pravastatin			**0.07**	76%	**0.04**	28%	**0.03**	92%	
	C10AA05 atorvastatin			**9.99**	86%	**9.20**	74%	**0.79**	85%	
	C10AA07 rosuvastatin			**1.55**	88%	**1.03**	51%	**0.51**	93%	
	Sum of incidence of 4 statins			**13.43**	n.a.	**12.00**	n.a.	**1.44**	n.a.	12.0%
36	Any statin C10AA	**10.13**	83%							
	C10AA01 simvastatin			**1.40**	81%	**1.28**	81%	**0.12**	61%	
	C10AA03 pravastatin			**0.05**	94%	**0.02**	58%	**0.04**	97%	
	C10AA05 atorvastatin			**9.10**	94%	**8.07**	85%	**1.03**	90%	
	C10AA07 rosuvastatin			**1.44**	95%	**0.76**	70%	**0.68**	95%	
	Sum of incidence of 4 statins			**11.99**	n.a.	**10.13**	n.a.	**1.86**	n.a.	18.4%
60	Any statin C10AA	**9.36**	90%							
	C10AA01 simvastatin			**1.28**	89%	**1.15**	89%	**0.12**	72%	
	C10AA03 pravastatin			**0.05**	97%	**0.01**	77%	**0.04**	97%	
	C10AA05 atorvastatin			**8.79**	97%	**7.55**	90%	**1.24**	94%	
	C10AA07 rosuvastatin			**1.40**	97%	**0.65**	83%	**0.76**	97%	
				11.52	n.a.	**9.36**	n.a.	**2.15**	n.a.	23.0%

(Continues)

TABLE 2 (Continued)

Run-in (months)	Group or substance	NoG New on group		NoS New on substance—whether new on group or not		NoS_and_NoG New on substance—and new on group		NoS_not_NoG New on substance—and not new on group		Fraction not new on group/new on group
		New cases/1000 inh	PPV	New cases/1000 inh	PPV	New cases/1000 inh	PPV	New cases/1000 inh	PPV	
	Sum of incidence of 4 statins									
120	Any statin C10AA	**8.40**	100%							
	C10AA01 simvastatin			**1.13**	100%	**1.03**	100%	**0.10**	100%	
	C10AA03 pravastatin			**0.05**	100%	**0.01**	100%	**0.04**	100%	
	C10AA05 atorvastatin			**8.57**	100%	**6.82**	100%	**1.74**	100%	
	C10AA07 rosuvastatin			**1.36**	100%	**0.53**	100%	**0.83**	100%	
	Sum of incidence of 4 statins			**11.11**	n.a.	**8.40**	n.a.	**2.71**	n.a.	32.3%

Note: Positive predictive value (PPV) compared with suggested reference run-in of 10 years for different substances and statins as a group.

There is a significant variation in methodology between studies of statin incidence. Both incidence rates[11–13] and incidence proportions[14–18] are used when studying incidence. Individuals not at risk[15,16,18] or the total population regardless of treatment status[14,17] were used as denominators for incidence proportions in the different studies.

Studying only individuals at risk as a rate (per person-time) or a proportion (during a defined period) describes the introduction of the drug among those not treated and thus available to become treated. Relating the new cases to all individuals is more straightforward in a study based on population registers. The latter approach is often the preferred choice for the incidence proportion based on register data since there is often no need to adjust for the prevalence in a simple time-trend analysis.

When comparing incidence proportion based on the total population between early and later phases of the introduction of a drug or between high- and low-prevalence populations, it is advisable to assess the incidence in relation to the prevalence. With a commonly used group of substances such as statins, the difference in incidence between using persons at risk and the total population as the denominator will be significant if the prevalence is high. This is relevant for statins in Sweden, where the 1-year prevalence in the whole population is 9.9%. This article calculates the reported incidence proportions of statins with the total population as the denominator. Correcting for a 1-year prevalence of 9.9% would result in an approximately 11% higher incidence proportion for the non-prevalent population. This could be further studied for different subpopulations.

There is a wide variation in handling the length of the run-in in reports of incidence treatment with statins. For statins, a fixed run-in of 12 months is common,[11,14,17] but it can vary between 6 months and several years.[12] The run-in length should be defined based on the clinical question and whether the focus is on all new cases, only first-ever use, or recurrence of treatment.

In several studies, the length of the run-in is not fixed based on the index date. Instead, the first dispensation during a calendar year is considered a new case of statin prescription if the individual had no dispensation during the preceding calendar year. In these cases, the chosen run-in varies between 12 and 24 months depending on the date of the first dispensation.[13,15,16,18,19]

Well-defined incidence measures are needed not only for studies of drug utilization but also as a part of general drug statistics. Changes in incidence could be used as an indicator of possible future changes in prevalence but also for more sensitive studies of the effects of

TABLE 3 Suggestions for presentation and discussion of incidence presented in drug utilisation review and as drug utilization statistics

	Perspective	Comment
Type of incidence	New case	
	First-ever use	
	Recurrent treatment	
Level of incidence	New on group regardless of substance	NoG
	New on specified substance, whether treated earlier with another substance in the group or not	NoS
	New on specified substance and new on group	NoS_and_NoG
	New on specified substance and not new on group	NoS_not_NoG
Measure	Number of cases	
	Incidence rate	Actual person time
	Incidence proportion (cumulative incidence)	Defined period
Denominator	Only susceptible individuals	Individuals not on treatment/considered non-prevalent
	All individuals	
	For incidence proportion: beginning, mid-period or end of studied time period or another alternative	
Migration	Immigrants will present as a new case if not censored from the date of migration for the same period as the applied run-in If censored, immigrants ought not to be included neither in the nominator nor in the denominator for the corresponding period	Handled in incidence rate through person-time Analysis of possible misclassification in incidence proportion due to migration
Run-in[a]	The rationale for the chosen run-in	See the type of incidence
Misclassification	Sensitivity analysis of run-in for the type of incidence and different levels of incidence studied	Suggested predictive probability or relative misclassification[1]

[a]Or estimated run-in in used methodology for waiting-time distribution.[1]

interventions through, for instance, interrupted time-series analyses of incidence instead of the number of dispensations or defined daily doses. For statins, an increased incidence has been reported related in time to the results of the 4S trial[20] in 1994[14] and to both 4S and the West of Scotland Coronary Prevention Study (WOSCOPS).[21] Kildemoes et al studied the relationship between the incidence of statins according to indication in Denmark in the period of 1996–2009 and several external factors such as evolving clinical evidence, international guidelines on CVD prevention, national CVD guidelines and healthcare policies and statin costs.[13]

There is a need for further development of methodology and terminology for incidence rates or proportions when presented in studies of drug utilization or introduced as a measure in regular aggregated statistics of drug use.[5] In addition, the estimated misclassification depending on the length of run-in and which types of new cases are studied (all new cases, first-ever use or recurrent treatment) should be presented. Table 3 summarizes suggestions for presenting incidence for a drug utilization review.

6 | CONCLUSIONS

When studying new cases of drug treatment, it is essential to differentiate between those new to both the substance and possible substitutes (NoS_and_NoG) and those new to the substance but who have been treated earlier with substitutes during the chosen run-in (NoS_not_NoG).

In order to allow for consistent comparisons over time and between populations, new incidence measures with validated methodology and descriptions of the degree of misclassification are needed both for scientific studies of drug utilization and when introducing incidence as a measure in aggregated drug statistics.

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CONFLICT OF INTEREST

The authors report no conflicts of interest according to the ICMJE Disclosure Form.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available from the corresponding author, MH, upon reasonable request.

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