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ORIGINAL ARTICLE

Identifying diabetogenic drugs using real world health care databases: A Danish and Australian symmetry analysis

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Abstract

Aims: Drug-induced diabetes is underreported in conventional drug safety monitoring and may contribute to the increasing incidence of type 2 diabetes. Therefore, we used routinely collected prescription data to screen all commonly used drugs for diabetogenic effects.

Methods: Leveraging the Danish nationwide health registries, we used a case-only symmetry analysis design to evaluate all possible associations between drug initiation and subsequent diabetes. The study was conducted among individuals aged ≥40 years with a first-ever prescription for any antidiabetic drug 1996-2018 (n = 348 996). Sequence ratios (SRs) and 95% confidence intervals (CIs) were obtained for all possible drug class-diabetes combinations. A lower bound of the 95% CI >1.00 was considered a signal. Signals generated in Denmark were replicated using the Services Australia, Pharmaceutical Benefits Scheme 10% data extract.

Results: Overall, 386 drug classes were investigated, of which 70 generated a signal. In total, 43 were classified as previously known based on the SIDER database or a literature review, for example, glucocorticoids (SR 1.67, 95% CI 1.62-1.72) and β-blockers (SR 1.20, 95% CI 1.16-1.23). Of 27 new signals, three drug classes yielded a signal in both the Danish and Australian data source: digitalis glycosides (SR 2.15, 95% CI 2.04-2.27, and SR 1.76, 95% CI 1.50-2.08), macrolides (SR 1.20, 95% CI 1.16-1.24, and SR 1.11, 95% CI 1.06-1.16) and inhaled β2-agonists combined with glucocorticoids (SR 1.35, 95% CI 1.28-1.42, and SR 1.14, 95% CI 1.06-1.22).

Conclusion: We identified 70 drug-diabetes associations, of which 27 were classified as hitherto unknown. Further studies evaluating the hypotheses generated by this work are needed, particularly for the signal for digitalis glycosides.

KEYWORDS
adverse drug reactions, diabetes mellitus, pharmacoepidemiology

1 | INTRODUCTION

The incidence of drug-induced diabetes is unknown, but the condition is assumed to be underreported in clinical studies and pharmacovigilance schemes.[1] The drug class most well-known for a diabetogenic effect is glucocorticoids.[2] Other drugs for which diabetogenic effects have been reported are selected statins, β-blockers, thiazides, androgen deprivation therapy, highly active antiretroviral therapy and second-generation antipsychotics.[3]

Classical pharmacovigilance is dependent upon the reporting of single cases of suspected adverse drug reactions. Common conditions, such as diabetes, or conditions with an insidious onset will not necessarily be suspected as outcomes of using an often-prescribed drug, and may be overlooked in reporting-based schemes.[4] As an alternative, drug-induced diabetes can be identified in administrative databases by use of epidemiological methods. In these data sources, the outcome of diabetes is not dependent on vigilant clinicians' reporting but is captured as it occurs in the population at risk. If drug use and diagnoses are systematically registered and available, a large-scale epidemiological screening approach can be used to identify such associations.[5,6]

To our knowledge, no epidemiological hypothesis-generating study for drug-induced diabetes has been conducted. We therefore aimed to screen all commonly used drugs for an increased risk of developing diabetes after initiation of the drug.

2 | METHODS

Utilizing the Danish nation-wide registries, we used a symmetry analysis design[7] to estimate the relative risk of being prescribed antidiabetic (glucose-lowering) medication after the initiation of any given drug. New, potential safety signals were attempted replicated using the Services Australia, Pharmaceutical Benefits Scheme 10% data extract. This study is reported according to the 'Reporting of studies conducted using observational routinely collected health data statement' statement.[8] The source code used to conduct the main analyses can be found at https://gitlab.sdu.dk/lclund/diabetes-screening/.

2.1 | Study population

All Danish residents who received a new prescription for an antidiabetic drug [Anatomical therapeutic chemical classification (ATC): A10], defined as not previously having redeemed a prescription during the available lookback (minimum 1 year), during the period 1996 to 2018 and who were ≥40 years at the time of prescription were eligible for inclusion in the study. Information on prescription drug use, hospital diagnoses, age, sex and vital status was obtained for the study population from the Danish health registries[9-11] (Table S1).

2.2 | Study design

The symmetry analysis design[7] can be used to evaluate the prescription sequence of an exposure and outcome drug. If there is no causal relationship between the use of the exposure and outcome drug, it is as probable, all other things being equal, that the exposure drug is prescribed before the outcome drug as the opposite sequence. However, if there is a causal association, it will be more probable that the exposure drug is initiated before the outcome drug than vice versa. The sequence ratio (SR) is calculated as the number of people initiating the exposure drug before the outcome drug, divided by the number of people initiating the outcome drug before the exposure drug. Consider the prescription sequence of amlodipine, a drug commonly used to treat hypertension, and metformin. Among individuals who initiate both drugs within a given timeframe, we expect a similar number of people initiating amlodipine before metformin compared with after. However, if amlodipine had an unknown diabetogenic potential, there would be more individuals initiating amlodipine before metformin than vice versa.

The symmetry analysis is a case-only design and thus robust towards confounders that are stable over time.[12] Bias introduced by temporal trends in use of the outcome drug can be adjusted for using the null-effect SR.[13]

2.3 | Exposure

Using the Danish National Prescription Registry,[9] we identified drugs based on the ATC classification.[14] Drugs were analysed in chemically similar groups, corresponding to the fourth level of the ATC classification. Exposure drugs were defined by an individual's first prescription of a given drug class, excluding antidiabetics. To ensure that exposure drug usage was incident, only prescriptions redeemed at least 2 years after the beginning of data collection (1 January 1995) were considered.

2.4 | Outcome

The main outcome was initiation of any antidiabetic drug. We looked for such outcomes within 365 days before or after the initiation of a given exposure drug. To ensure that a given prescription represents a new diagnosis of diabetes, only prescriptions redeemed at least 1 year from the beginning of data collection (1 January 1995) were considered. Initiation of antidiabetic medication was used as a proxy for a diagnosis of diabetes, as diabetes usually is diagnosed by general practitioners and diagnoses from general practice are not available in the Danish Patient Registry. For a graphical representation of the timeline and study design see Figure 1.

2.5 | Statistical analyses

We calculated crude SRs as the number of individuals initiating the exposure drug before an antidiabetic drug divided by the number of

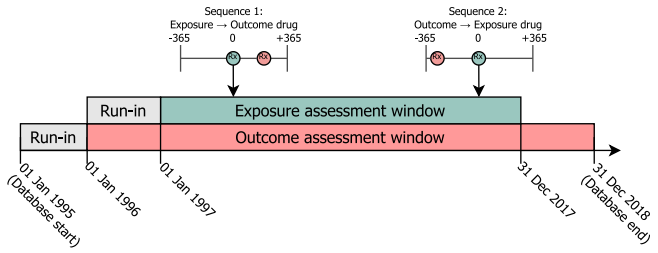


FIGURE 1 Graphical representation of the study design. Intervals for sequences 1 and 2 are in days, that is, 365 days before and after initiation of the exposure drug. Green circles represent redeeming a new prescription of the exposure drug, while red circles represent redeeming a new prescription of an outcome drug

individuals initiating the exposure drug after an antidiabetic drug and obtained 95% confidence intervals (CIs) based on exact confidence limits for binomial distributions.[15] To adjust for the increasing incidence of diabetes,[16] null-effect SRs[13] were calculated for all drugs and trend-adjusted SRs were obtained by dividing crude SRs with null-effect SRs. As the aim of the study was to identify unsuspected diabetogenic effects, we only report associations whose lower confidence limit of the trend-adjusted SR was >1. As this was considered a purely hypothesis-generating study, we made no adjustment for multiple comparisons.[17]

Adjustment for multiple comparisons reduces the type I error rate, that is, reduces the possibility of falsely dismissing the null hypothesis, but will also result in an increased rate of type II errors and the dismissal of signals with lower statistical precision. A previous symmetry analysis screening for adverse drug reactions showed that a major source of type I error is bias,[5] not chance. Biased estimates will often be statistically precise and therefore unaffected by adjustment for multiple comparisons.

All signals were ranked according to their putative public health impact obtained by calculating the number of attributable cases in the population as the numerical difference between individuals initiating the exposure drug before the outcome drug and individuals initiating the two drugs in the reverse order. Signals were then sorted in descending order based on the number of attributable cases.

Statistical analyses and data management were conducted using Stata MP version 15.1.[18] Figures were generated using R version 4.2.2,[19] ggplot2[20] and forestplot libraries.[21]

2.6 | Classification of signals

Detected drug-outcome associations were classified as known or new according to the 'Side Effect Resource' database version 4.1 (Table S2).[22] Drugs listed with a Medical Dictionary for Regulatory Activities[23] lower level or parent term indicating diabetes were considered known to be diabetogenic (Table S3). ATC codes were truncated to the fourth level for classification. An a priori literature search was conducted to identify known diabetogenic drugs for which diabetes is not listed as an adverse drug reaction in the SIDER database (Table S4).

2.7 | Sensitivity analyses

To explore the robustness of the signals, we performed multiple sensitivity analyses: (a) we re-estimated SRs with outcome assessment windows of 182 and (b) 547 days before and after initiation of the exposure drug; (c) to investigate whether some associations were caused by the index drug being prescribed in close temporal proximity of systemic corticosteroids, thus constituting time-dependent confounding, we repeated the entire analysis after excluding all individuals who were prescribed systemic corticosteroids before or within the observation period; (d) to investigate whether detected signals were drug-specific or represented a class effect, SRs were obtained for all single drug substances, that is, exposure classified according to the fifth level of the ATC classification; and (e) we repeated the main analysis using a composite outcome of a new prescription of any antidiabetic drug or a first diagnosis of diabetes during the period 1996-2018, whichever came first.

2.8 | Replication of signals

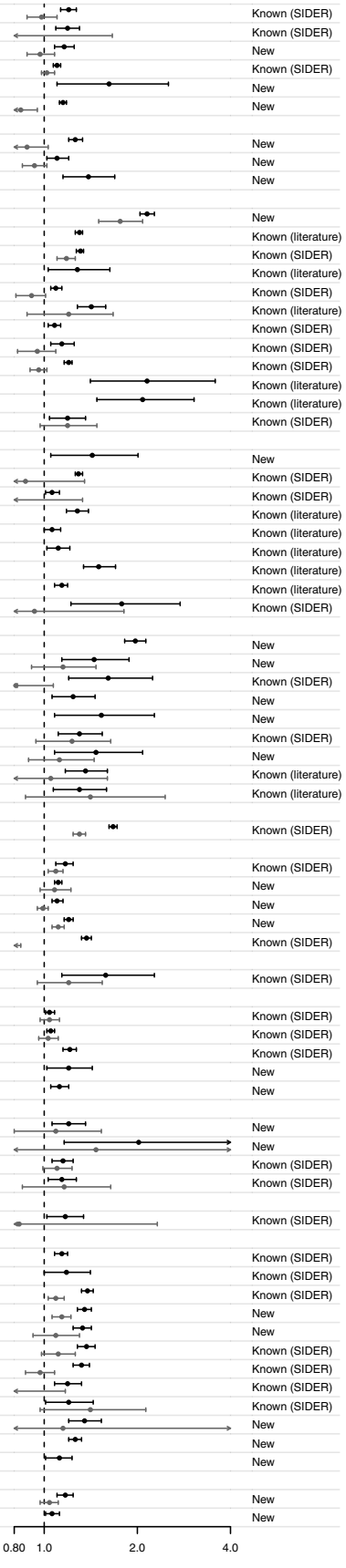
We sought to replicate all signals identified in the Danish data source using the Services Australia, Pharmaceutical Benefits Scheme 10% extract.[24] The main analysis was carried out according to the same specifications as the Danish analysis during the timeframe 2012-2019, excluding drugs marketed and/or used in Denmark, which are unavailable in Australia.

3 | RESULTS

In the Danish data source, we included 348 996 individuals initiating antidiabetic medication of whom 43% were female. The median age at the initiation of an antidiabetic drug was 63 years.

We evaluated 386 drug classes and detected 70 drug-diabetes associations that may represent safety signals (Figure 2, Table S5). Of these, 31 signals of 214 drugs (15%) listed as potentially diabetogenic according to the SIDER database were classified as known associations and an additional 12 signals were classified as known according to the a priori literature review. Multiple drug classes known to be diabetogenic were reproduced in this analysis, for example: systemic glucocorticoids (drug of interest initiated before antidiabetic medication/after antidiabetic medication 10521/6169 sequences, SR 1.67, 95% CI 1.62-1.72); loop diuretics (11 374/8522, SR 1.31, 95% CI 1.27-1.34); thiazides combined with potassium (10 035/7515, SR 1.30, 95% CI 1.26-1.33); and β-blockers (8962/7328, SR 1.20, 95% CI 1.16-1.23). Of the 27 associations classified as unknown, the highest ranked signals were identified for digitalis glycosides (4403/2001, SR 2.15, 95% CI 2.04-2.27); macrolide antibiotics (8559/6947, SR 1.20, 95% CI 1.16-1.24); and potassium supplement (10 484/8996, SR 1.15, 95% CI 1.12-1.18). On visual inspection, multiple signals exhibited a clear temporal asymmetry, not unlike the true signal for glucocorticoids (Figure 3).

Drug	ATC	Seq (DK)	SR (DK)	Seq (AUS)	SR (AUS)	Class.
Digestive system						
Antiinfectives and antiseptics for local oral treatment	A01AB	2425 / 1984	1.20 (1.13 – 1.27)	619 / 601	0.98 (0.88 – 1.10)	Known (SIDER)
Other agents for local oral treatment	A01AD	1090 / 894	1.19 (1.09 – 1.30)	8 / 12	0.62 (0.28 – 1.66)	Known (SIDER)
H2–receptor antagonists	A02BA	1586 / 1321	1.16 (1.08 – 1.25)	704 / 740	0.97 (0.88 – 1.08)	New
Proton pump inhibitors	A02BC	12487 / 11121	1.10 (1.07 – 1.13)	3464 / 3278	1.02 (0.98 – 1.08)	Known (SIDER)
Imidazole derivatives	A07AC	60 / 36	1.62 (1.10 – 2.52)	–	–	New
Potassium	A12BA	10484 / 8996	1.15 (1.12 – 1.18)	490 / 582	0.84 (0.75 – 0.95)	New
Blood and blood forming organs						
Vitamin K antagonists	B01AA	3688 / 2862	1.26 (1.20 – 1.33)	319 / 321	0.88 (0.75 – 1.03)	New
Direct factor Xa inhibitors	B01AF	1222 / 1113	1.10 (1.02 – 1.20)	914 / 1065	0.93 (0.85 – 1.02)	New
Vitamin K	B02BA	258 / 181	1.39 (1.15 – 1.69)	–	–	New
Cardiovascular system						
Digitalis glycosides	C01AA	4403 / 2001	2.15 (2.04 – 2.27)	402 / 225	1.76 (1.50 – 2.08)	New
Thiazides and potassium	C03AB	10035 / 7515	1.30 (1.26 – 1.33)	–	–	Known (literature)
Loop diuretics	C03CA	11374 / 8522	1.31 (1.27 – 1.34)	1713 / 1449	1.18 (1.10 – 1.26)	Known (SIDER)
Sulfonamides and potassium in combination	C03CB	168 / 125	1.28 (1.03 – 1.63)	–	–	Known (literature)
Aldosterone antagonists	C03DA	4679 / 4205	1.09 (1.05 – 1.14)	610 / 691	0.91 (0.81 – 1.01)	Known (SIDER)
Low–ceiling diuretics and potassium–sparing agents	C03EA	845 / 575	1.42 (1.28 – 1.58)	86 / 67	1.20 (0.88 – 1.67)	Known (literature)
Corticosteroids	C05AA	4214 / 3818	1.08 (1.03 – 1.13)	–	–	Known (SIDER)
Beta blocking agents, non–selective	C07AA	1144 / 973	1.14 (1.05 – 1.25)	381 / 413	0.95 (0.82 – 1.09)	Known (SIDER)
Beta–blocking agents	C07AB	8962 / 7328	1.20 (1.16 – 1.23)	1716 / 1803	0.96 (0.90 – 1.02)	Known (SIDER)
Beta blocking agents, selective, and thiazides	C07BB	58 / 26	2.15 (1.41 – 3.57)	–	–	Known (literature)
Beta blocking agents, selective, and other diuretics	C07CB	93 / 43	2.08 (1.48 – 3.05)	–	–	Known (literature)
Benzothiazepine derivatives	C08DB	486 / 395	1.19 (1.04 – 1.36)	190 / 159	1.19 (0.97 – 1.48)	Known (SIDER)
Dermatologicals						
Antibiotics	D01AA	91 / 61	1.43 (1.05 – 2.01)	NR	NR	New
Imidazole and triazole derivatives	D01AC	10626 / 8045	1.29 (1.26 – 1.33)	39 / 47	0.87 (0.58 – 1.35)	Known (SIDER)
Corticosteroids, very potent (group IV)	D07AD	3123 / 2896	1.06 (1.01 – 1.12)	15 / 25	0.67 (0.37 – 1.33)	Known (SIDER)
Corticosteroids, moderately potent, combinations with antiseptics	D07BB	1346 / 1007	1.28 (1.18 – 1.39)	–	–	Known (literature)
Corticosteroids, potent, combinations with antiseptics	D07BC	2021 / 1869	1.06 (1.00 – 1.13)	–	–	Known (literature)
Corticosteroids, weak, combinations with antibiotics	D07CA	1138 / 1006	1.11 (1.02 – 1.21)	–	–	Known (literature)
Corticosteroids, moderately potent, combinations with antibiotics	D07CB	693 / 439	1.50 (1.34 – 1.70)	–	–	Known (literature)
Corticosteroids, potent, combinations with antibiotics	D07CC	3597 / 3111	1.14 (1.08 – 1.19)	–	–	Known (literature)
Retinoids for treatment of acne	D10BA	65 / 36	1.78 (1.22 – 2.75)	19 / 21	0.93 (0.52 – 1.81)	Known (SIDER)
Genito urinary system and sex hormones						
Imidazole derivatives	G01AF	1960 / 970	1.97 (1.82 – 2.13)	–	–	New
Progestogens and estrogens, fixed combinations	G03AA	153 / 102	1.45 (1.14 – 1.88)	147 / 123	1.15 (0.91 – 1.47)	New
Progestogens	G03AC	104 / 64	1.61 (1.20 – 2.24)	95 / 115	0.81 (0.62 – 1.07)	Known (SIDER)
Synthetic estrogens, plain	G03CB	344 / 268	1.24 (1.06 – 1.46)	–	–	New
Other estrogens	G03CX	73 / 46	1.53 (1.08 – 2.27)	–	–	New
Pregnen (4) derivatives	G03DA	335 / 251	1.30 (1.11 – 1.54)	112 / 93	1.23 (0.94 – 1.64)	Known (SIDER)
Estren derivatives	G03DC	90 / 59	1.47 (1.08 – 2.08)	135 / 122	1.12 (0.89 – 1.45)	New
Progestogens and estrogens, fixed combinations	G03FA	371 / 264	1.36 (1.17 – 1.60)	49 / 48	1.05 (0.72 – 1.60)	Known (literature)
Progestogens and estrogens, sequential preparations	G03FB	222 / 166	1.30 (1.07 – 1.59)	34 / 25	1.41 (0.87 – 2.46)	Known (literature)
Systemic hormones						
Glucocorticoids	H02AB	10521 / 6169	1.67 (1.62 – 1.72)	3850 / 2953	1.30 (1.24 – 1.36)	Known (SIDER)
Antiinfectives for systemic use						
Tetracyclines	J01AA	2022 / 1699	1.17 (1.09 – 1.24)	2489 / 2318	1.09 (1.03 – 1.15)	Known (SIDER)
Beta–lactamase sensitive penicillins	J01CE	9519 / 8302	1.11 (1.08 – 1.14)	600 / 553	1.08 (0.97 – 1.22)	New
Combinations of penicillins, incl. beta–lactamase inhibitors	J01CR	4806 / 4418	1.10 (1.06 – 1.15)	4646 / 4546	0.99 (0.95 – 1.03)	New
Macrolides	J01FA	8559 / 6947	1.20 (1.16 – 1.24)	3507 / 3008	1.11 (1.06 – 1.16)	New
Triazole derivatives	J02AC	6850 / 4912	1.37 (1.32 – 1.42)	182 / 266	0.70 (0.58 – 0.84)	Known (SIDER)
Antineoplastic and immunomodulating agents						
Nitrogen mustard analogues	L01AA	87 / 53	1.58 (1.14 – 2.27)	144 / 121	1.20 (0.95 – 1.54)	Known (SIDER)
Musculo–skeletal system						
Acetic acid derivatives and related substances	M01AB	6585 / 6076	1.04 (1.01 – 1.08)	1580 / 1466	1.04 (0.97 – 1.12)	Known (SIDER)
Propionic acid derivatives	M01AE	9007 / 8392	1.05 (1.02 – 1.08)	1556 / 1473	1.03 (0.96 – 1.11)	Known (SIDER)
Other antiinflammatory and antirheumatic agents, non–steroids	M01AX	3231 / 2564	1.21 (1.15 – 1.27)	–	–	Known (SIDER)
Carbamic acid esters	M03BA	296 / 235	1.20 (1.02 – 1.43)	–	–	New
Oxazol, thiazine, and triazine derivatives	M03BB	1855 / 1635	1.12 (1.05 – 1.20)	–	–	New
Nervous system						
Other antimigraine preparations	N02CX	539 / 441	1.20 (1.06 – 1.36)	77 / 70	1.09 (0.80 – 1.53)	New
Anticholinesterases	N07AA	31 / 15	2.02 (1.16 – 4.03)	10 / 7	1.47 (0.64 – 4.57)	New
Drugs used in nicotine dependence	N07BA	1474 / 1241	1.15 (1.06 – 1.24)	734 / 622	1.10 (0.99 – 1.23)	Known (SIDER)
Drugs used in alcohol dependence	N07BB	773 / 661	1.14 (1.03 – 1.27)	75 / 66	1.16 (0.85 – 1.64)	Known (SIDER)
Antiparasitic products						
Benzimidazole derivatives	P02CA	455 / 386	1.17 (1.02 – 1.34)	8 / 10	0.83 (0.36 – 2.32)	Known (SIDER)
Respiratory system						
Corticosteroids	R01AD	3607 / 3114	1.14 (1.08 – 1.19)	–	–	Known (SIDER)
Other throat preparations	R02AX	285 / 247	1.18 (1.00 – 1.41)	–	–	Known (SIDER)
Selective beta–2–adrenoreceptor agonists	R03AC	5084 / 3622	1.38 (1.32 – 1.44)	2135 / 1915	1.09 (1.03 – 1.16)	Known (SIDER)
Inhaled beta–adrenergics & corticosteroids	R03AK	3581 / 2591	1.35 (1.28 – 1.42)	1629 / 1374	1.14 (1.06 – 1.22)	New
Adrenergics in combination with anticholinergics	R03AL	1989 / 1449	1.33 (1.24 – 1.42)	256 / 270	1.09 (0.92 – 1.30)	New
Glucocorticoids	R03BA	2215 / 1584	1.37 (1.28 – 1.46)	499 / 458	1.11 (0.98 – 1.26)	Known (SIDER)
Anticholinergics	R03BB	2604 / 1937	1.32 (1.24 – 1.40)	685 / 706	0.97 (0.87 – 1.08)	Known (SIDER)
Selective beta–2–adrenoreceptor agonists	R03CC	874 / 707	1.19 (1.08 – 1.32)	32 / 43	0.72 (0.47 – 1.17)	Known (SIDER)
Xanthines	R03DA	284 / 229	1.20 (1.01 – 1.44)	62 / 43	1.41 (0.97 – 2.13)	Known (SIDER)
Leukotriene receptor antagonists	R03DC	627 / 453	1.35 (1.20 – 1.53)	7 / 6	1.15 (0.46 – 4.15)	New
Opium derivatives and expectorants	R05FA	4374 / 3400	1.26 (1.20 – 1.32)	–	–	New
Phenothiazine derivatives	R06AD	871 / 773	1.12 (1.01 – 1.23)	NR	NR	New
Sensory organs						
Corticosteroids and antiinfectives in combination	S02CA	2394 / 2004	1.17 (1.10 – 1.24)	1842 / 1729	1.04 (0.97 – 1.11)	New
Corticosteroids and antiinfectives in combination	S03CA	2947 / 2720	1.06 (1.01 – 1.12)	–	–	New



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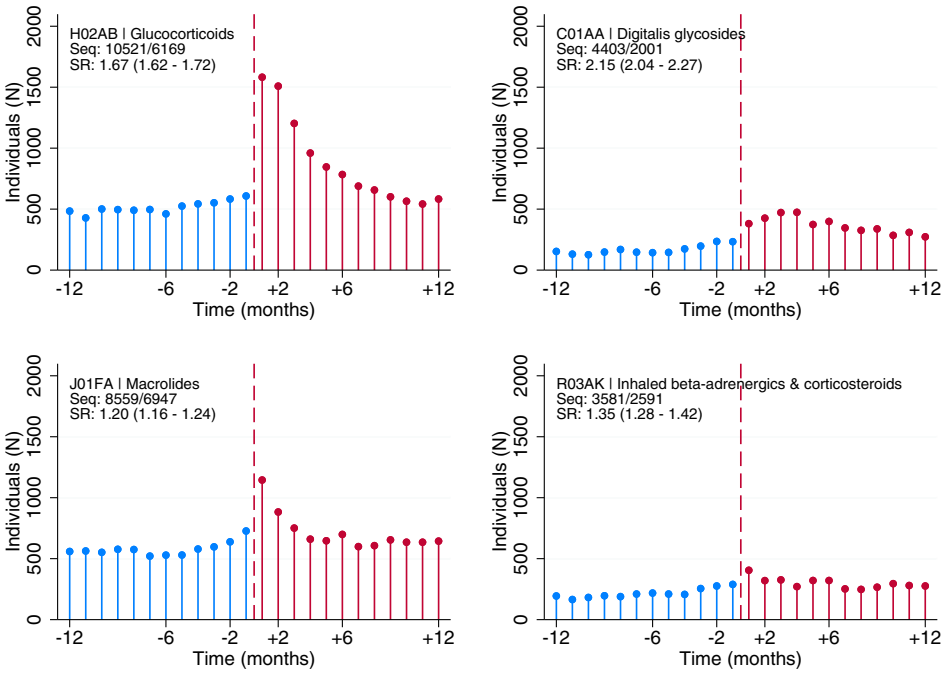


FIGURE 3 Temporal distribution of initiation of glucose-lowering drugs relative to initiation of the exposure drug. The dashed line represents the date of initiation of the exposure drug. Red segments represent the number of the sequence exposure drug first, glucose-lowering drugs last, while blue segments represent the sequence glucose-lowering drugs first, exposure drug last. *x*-axis: months before and after prescription date; *y*-axis, diabetes cases (N)

Several drugs used in the treatment of diseases of the digestive system, cardiovascular system, musculoskeletal system, respiratory system and systemic hormone therapy were found associated with the initiation of antidiabetic medication (Figure 4).

The identified signals were generally found to be robust in sensitivity analyses (Figure 5): Changing the window size for the symmetry analysis yielded slightly modified SRs, and for 49 of 70 signals both the shorter and longer observation windows yielded a lower bound of the 95% CI >1.0 (Table S6). After the exclusion of individuals who redeemed a prescription for systemic glucocorticoids before or during the observation period, 23 signals were eliminated, most notably the signal for very potent topical corticosteroids disappeared (SR 0.99, 95% CI 0.92-1.05) (Table S7). For drug classes associated with the initiation of antidiabetic medication, the most frequently used single drugs of a given class also produced a signal, for example: systemic corticosteroids and prednisolone (9744/5326, SR 1.80, 95% CI 1.74-1.86); digitalis glycosides and digoxin (4403/2001, SR 2.15, 95% CI 2.04-2.27); and macrolides and roxithromycin (6526/5138, SR 1.24, 95% CI 1.20-1.29) (Table S8). Similar results were obtained, when using a composite outcome of diabetes (Table S9).

In the Australian data source, we analysed prescription data from 160 124 individuals who were prescribed an antidiabetic drug with a median age of 63 of whom 46% were female. Of the 70 signals identified in Denmark, seven yielded an SR with a lower bound of the 95% CI >1.0 (Figure 2, Table S10) in the Australian data source. Among these were the known signals for systemic glucocorticoids (3850/2953, SR 1.30, 95% CI 1.24-1.36) and loop diuretics (1713/1449, SR 1.18, 95% CI 1.10-1.26). Of the 27 unknown signals, the signals for digitalis glycosides (402/225, SR 1.76, 95% CI 1.50-2.08), macrolides (3507/3008, SR 1.11, 95% CI 1.06-1.16) and inhaled β2-agonists combined with other drugs (1629/1374, SR 1.14, 95% CI 1.06-1.22) were replicated.

4 | DISCUSSION

Using a symmetry analysis design, we replicated 43 drugs known to be diabetogenic, validating the method, and found 27 new associations that may represent drugs with the potential to induce diabetes of which three were identified in both the Danish and Australian data source.

Our study has several strengths. The main strengths are the use of the highly valid Danish population-based registries[9] and its hypothesis-free approach, enabling us to detect rare and/or potentially unsuspected diabetogenic effects. Furthermore, we sought to validate study results in a different, geographically antipodal population using a 10% sample of all publicly funded medicines dispensed in Australia. Another strength is the elimination of time invariant confounding, because of the use of the symmetry analysis design[7] and bias because of temporal trends in drug usage, by adjusting estimates for the null-effect SR.[13] Finally, compared with established pharmacovigilance practice, our method is independent of health care personnel

FIGURE 2 All signals identified in the Danish data source and results of the replication in the Australian data source. Black points and whiskers represent sequence ratios obtained in Denmark, grey points and whiskers represent sequence ratios obtained using the Australian data source. ATC, Anatomical therapeutical classification; AUS, Australia; DK, Denmark; Seq, prescription sequence (drug of interest initiated before antidiabetic medication/drug of interest initiated after antidiabetic medication); SR, null-effect adjusted sequence ratio.

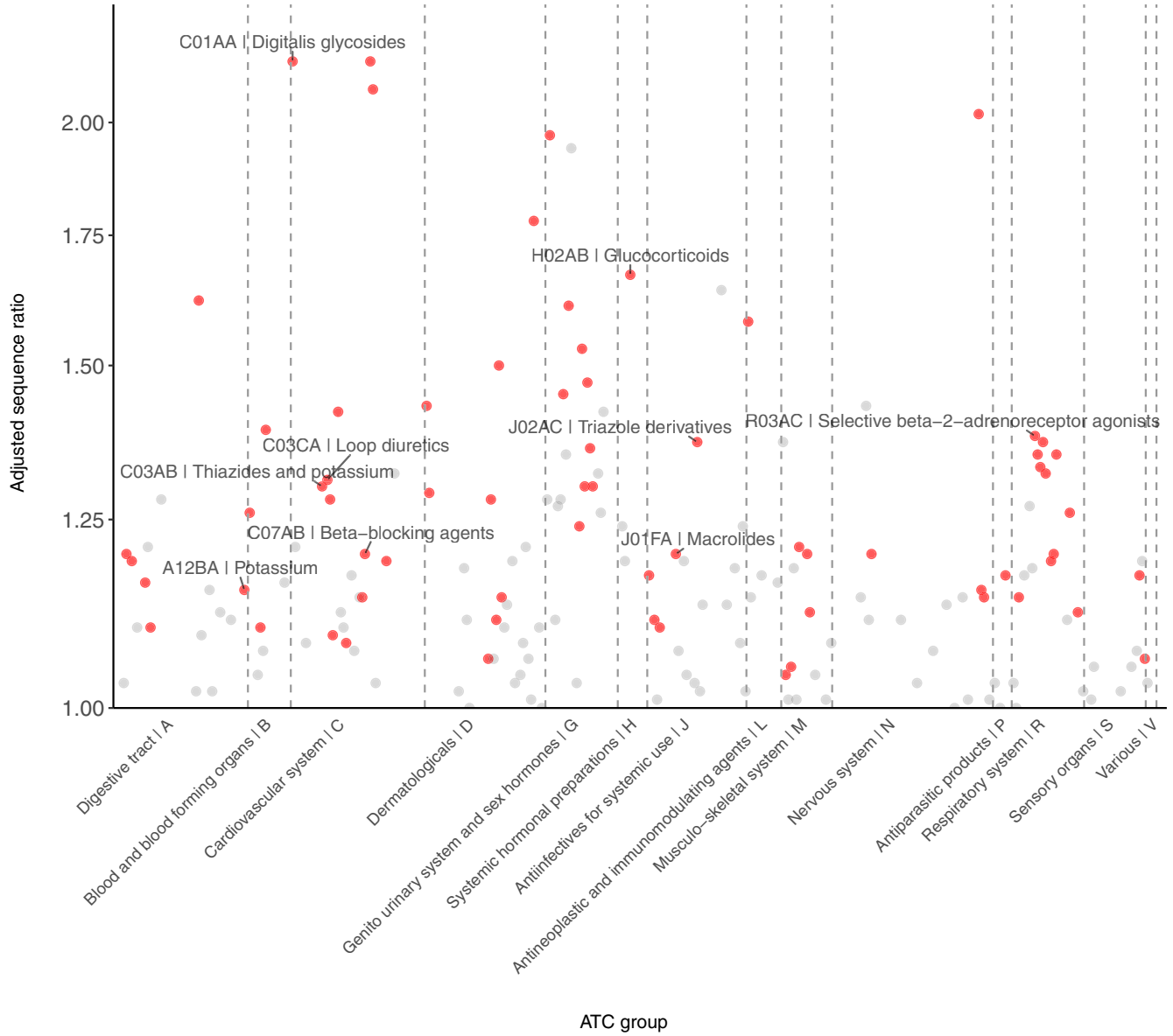
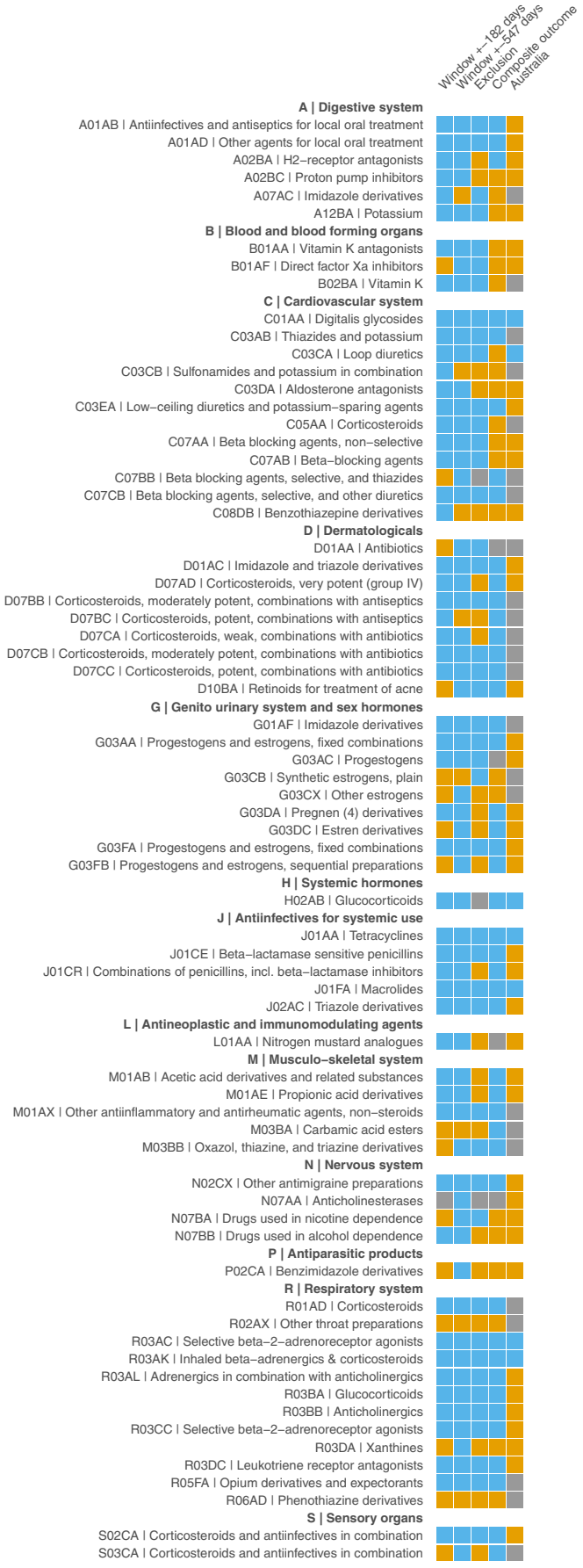


FIGURE 4 Scatter plot of the strength of drug-diabetes associations grouped according to the first digit of ATC code. Estimates with confidence intervals including 1.00 are shaded grey, while safety signals (lower bound of the 95% confidence interval >1.00) are in red. ATC, anatomical therapeutical classification

or patients suspecting and reporting an adverse event to be related to the initiation of new medication.

The main limitation of our study is the lack of adjustment for time varying confounding, in particular protopathic bias[25] and step-wise treatment initiation, for example, if guidelines specify that a given treatment should be initiated before antidiabetic medication. Presenting symptoms of diabetes, for example, superficial fungal infections or urinary tract infections,[26] may be treated before antidiabetic glucose-lowering therapy is initiated, leading to an abundance of the sequence antifungal or antibacterial treatment → antidiabetic medication, although the association is not causal. This limitation can be overcome by comparing a given drug or drug class SR to another drug class that is used on the same indication,[27] for example, macrolides (SR 1.20, 95% CI 1.16-1.24) and penicillinase-sensitive penicillins (SR 1.11, 95% CI 1.08-1.14) or tetracyclines (SR 1.17, 95% CI 1.09-1.24), as it could be considered unlikely that all three of these drug classes are diabetogenic, given their pharmacological diversity. Approximately one-tenth of the potential signals identified in the Danish data were replicated in Australia, when filtering on whether the 95% CI includes 1.00. This may be partly explained by a smaller study population and henceforth lower precision the Australian data source. Another limitation of the validation efforts in the Australian data source was that important clinical characteristics, such as body weight, were unmeasured in both data sources. Therefore, we could not assess whether the two populations were comparable regarding these variables. While the case-only design mitigates potential confounding from these factors, differences



in results between the two data sources could potentially be attributed to effect modification by such unmeasured variables. Furthermore, we could not elucidate whether a given signal, or absence of it, could be attributable to drug-drug interactions. In general, our study is by design limited to identifying associations, not causality. The results from our study must therefore be viewed as being possible hypotheses, that is, drug safety signals, that should be investigated further in studies specifically designed to investigate each given association before any firm conclusions can be made.

Regarding findings in relation to other studies, we reproduced multiple known drug-diabetes associations, for example, systemic and topical glucocorticoids,[28] thiazides and β-blockers.[29] Known diabetogenic drugs[3] that could not be investigated were immunosuppressants (calcineurin inhibitors and mammalian target of rapamycin inhibitors), tyrosine kinase inhibitors, highly active antiretroviral therapy and androgen deprivation therapy, as these drugs are rarely dispensed from community pharmacies in Denmark and thus poorly covered by our data.[30] Surprisingly, statins and selected atypical antipsychotics were inversely associated with initiating antidiabetic medication (SR <1.00), while the existing literature suggests these drugs to be diabetogenic.[31,32] Treatment with atypical antipsychotics may be withheld in individuals at a moderate to high risk of diabetes or typical antipsychotics may be preferred in these patients, reducing the occurrence of the sequence atypical antipsychotics → antidiabetic medication. Furthermore, diabetes is an indication for treatment with statins in patients with pre-existing dyslipidaemia, leading to an excess of the sequence diabetes → statins.

Of the signals classified as new, the strongest association was found for digitalis glycosides (SR >2). In Denmark, the only digitalis glycoside in clinical use is digoxin. Digoxin has been shown to increase blood glucose levels in an animal model,[33] but blood glucose levels are unaffected in healthy adults.[34] Four case reports about a possible diabetogenic effect of digitalis glycosides have been published[35,36] and one observational study has reported this association.[37] At best, the current evidence can be classified as equivocal. On visual inspection, the distribution of sequences shows a clear asymmetry, not unlike glucocorticoids (Figure 3). Still, confounding in relation to increased biochemical monitoring and diagnostic activity following a diagnosis of atrial

FIGURE 5 Overview of whether signals identified in the main analysis persisted in sensitivity analyses. Each column indicates a sensitivity analysis. First column, window size reduced to ±182 days. Second column, window size increased to ±547 days. Third column, exclusion of individuals initiating glucocorticoids before or during the observation period. Fourth column, use of a composite outcome of a first diabetes diagnosis or initiation of antidiabetic medication. Fifth column, replication of the main analysis in the Australian data source. Blue squares indicate that the lower bound of the 95% confidence interval was >1.0, while orange squares indicate a lower bound below 1.0. Grey square indicates that results could not be reported due to data privacy regulation and/or a drug class not being marketed in Australia. Drugs are listed in descending order according to the number of attributable cases, calculated as the numerical difference between the two sequences

fibrillation or heart failure may apply to this signal. However, we did not find signals of similar magnitude for drugs that are common alternatives to digoxin in the frequency control of atrial fibrillation, such as β-blockers and verapamil. Overall, this signal warrants further investigation.

Drugs used to treat infections in the community setting produced multiple signals, for example, penicillinase-sensitive penicillins and macrolides were associated with the initiation of antidiabetic medication (Figure 2). Even though antibiotics have previously been reported to increase the risk of type 2 diabetes,[38] protopathic bias would probably be an explanation for these signals, as further studies accounting for important lifestyle factors could not reproduce the association.[39] Furthermore, a diagnosis of diabetes may be prompted by individuals with as of yet undiagnosed diabetes seeking medical attention for an infection, as individuals with diabetes are at an increased risk of infections.[26] Finally, the inflammatory response to a serious infection may increase blood glucose levels[40] and lead to subsequent glucose-lowering therapy in individuals with prediabetes, that is, individuals with elevated blood glucose levels that fall below the threshold for the initiation of antidiabetic treatment.

Multiple drugs used in the treatment of obstructive airway diseases produced signals of moderate strength, which persisted after the exclusion of corticosteroid users (Table S7), for example, inhaled short-acting β2 agonists, inhaled corticosteroids, combinations of inhaled short-acting β2 agonists and corticosteroids, inhaled anticholinergics, cough suppressants and leukotriene receptor agonists (Figure 2). These drugs may be used to treat early symptoms of chronic obstructive pulmonary disease, of which type 2 diabetes mellitus is a frequent comorbidity.[41] Therefore, we consider it probable that these findings are either related to confounding by indication or an increased diagnostic activity in individuals with pre-existing comorbidity.

Overall, it is reassuring, that we mostly identified known signals and few hitherto unknown signals, which could indicate that most drugs with the potential to cause diabetes have already been identified. It is out of the scope of this work to investigate whether the hitherto unknown associations represent causal effects. This could be further investigated using targeted epidemiological analyses, such as active comparator, new user cohort studies[42] or analyses comparing haemoglobin A1c levels before and after initiation of a given drug. In the future, repeated screening analyses for outcomes of interest could be used in the safety surveillance of newly marketed drugs.

5 | CONCLUSION

In this study, many known or postulated associations between specific drugs and diabetes were reproduced. The strongest new signals were found for digoxin and macrolides. Targeted epidemiological or clinical studies are needed to confirm or refute these associations.

AUTHOR CONTRIBUTIONS

LCL, PHJ and JH designed and conceived the study. LCL, JH and NP analysed the data. LCL and JH drafted the original manuscript. LCL, PHJ, MA, AP, NP and JH critically revised the manuscript. LCL and JH had full access to the Danish raw data used in the study. NP had full access to the Australian raw data used in the study. All authors had full access to all results and aggregated data that was generated in each country. LCL is the guarantor and confirms that this manuscript is an accurate, transparent and honest account of the study that has been conducted.

CONFLICT OF INTEREST

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PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14982.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicy due to Danish and Australian privacy regulations. Danish data are available to authorized researchers after application to the Danish health data authority (https://sundhedsdatastyrelsen.dk). Australian data can be requested from Services Australia (https://www.servicesaustralia.gov.au/organisations/about-us/reports-and-statistics/statistical-information-and-data).

ETHICS APPROVAL

The institutional data protection board at the University of Southern Denmark (application number 10.113) and the Danish Health Data Authority (project number 00003747) approved the research project. Services Australia, External Request Evaluation Committee approved the publication of the Australian data (approval number RMS1942). According to Danish law, studies based entirely on registry data do not require approval from an ethics review board.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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