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ORIGINAL ARTICLE

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Identification of polypharmacy patterns in new-users of metformin using the Apriori algorithm: A novel framework for investigating concomitant drug utilization through association rule mining

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Abstract

Purpose: With increased concomitant chronic diseases in type 2 diabetes mellitus (T2DM), the use of multiple drugs increases as well as the risk of drug–drug interactions (DDI) and adverse drug reactions (ADR). Nevertheless, how medication patterns vary in T2DM patients across different sex and age groups is unclear. This study aims to identify and quantify common drug combinations in first-time metformin users with polypharmacy (≥5 co-medications).

Methods: New users of metformin were identified from the IQVIA Medical Research Data incorporating data from THIN, A Cegedim Database (2016–2019). A descriptive cohort study explored prescription patterns in patients with polypharmacy. The Apriori algorithm, used to find frequent item-sets in databases, was first-time applied to identify and quantify drug combinations of up to seven drugs to investigate potential harmful polypharmacy patterns.

Results: The cohort included 34 169 new-users of metformin, of which 20 854 (61.0%) received polypharmacy. Atorvastatin was the most frequently co-prescribed drug with metformin overall (38.7%), in women (34.3%) and men (42.6%). In the stratified analysis, a higher proportion of women received polypharmacy (65.6%) compared to men (57.4%). Moreover, the proportion of patients receiving polypharmacy increased with age (18–39 years = 30.4%, 40–59 years = 50.5%, 60–74 years = 70.9%, and ≥75 years = 84.3%).

Conclusion: This study is the first to identify and quantify commonly prescribed combinations of drugs compounds in patients with polypharmacy using the Apriori algorithm. The high polypharmacy prevalence at all strata indicates the need to optimize polypharmacy to minimize DDI and ADR.

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KEYWORDS

Apriori algorithm, diabetes mellitus type 2, drug interactions, drug utilization, polypharmacy, potentially inappropriate medications, prescription patterns

Key Points

- While prior studies have identified polypharmacy among patients with T2DM, this is the first study to provide information on the individual drugs that are commonly co-prescribed among patients with type 2 diabetes stratified by sex and age.
- The Apriori, a search algorithm to find frequent item-sets of different sizes in a database, was applied for the first time to identify and quantify common medication patterns on a drug compound level.
- Combinations of metformin + ≤6 drugs were identified and ranked based on the frequency of prescription to capture unique prescription patterns.
- A higher proportion of women had polypharmacy (65.6%) compared to men (57.4%), and women were more frequently receiving ≥20 drugs concomitantly.
- The high prevalence of polypharmacy (61%) at the start of anti-diabetic treatment indicates the need to optimize the drug therapies to minimize DDIs and ADR.

Plain Language Summary

Type 2 diabetes mellitus (T2DM) is a chronic condition that occurs when a person's blood glucose is too high. T2DM is associated with a higher number of co-existing diseases and the use of multiple drugs concurrently (i.e., polypharmacy). When multiple drugs are used together, there is a higher likelihood that harmful drug combinations could result in adverse health outcomes. As the particular drug combinations prescribed to patients with T2DM remain unclear, this study aimed to identify and quantify common combinations of drugs in patients starting metformin (i.e., antidiabetic medication). The study also aimed to identify if differences exist across sex and age groups. Patients were identified from a large primary care database between 2016 and 2019 and the Apriori algorithm (i.e., used to find frequent item-sets in a database) was first-time applied to identify and quantify drug combinations. Of the 34 169 patients, 61.0% received polypharmacy, with higher proportion of women and adults (≥75 years) receiving polypharmacy. Combinations of ≤7 drugs were identified and ranked based on the frequency of prescription to capture prescription patterns. The high proportion of polypharmacy at all age groups indicates the need to optimize the drug therapies to minimize adverse health outcomes.

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by high blood glucose levels, resulting from the body's inefficient use or production of insulin.[1–3] Management of individuals with T2DM is often complex due to the heterogeneity of the disease, and the coexistence of additional chronic conditions and complications of T2DM, which may result in complex prescription patterns.[4,5] Furthermore, to treat concomitant conditions, multiple drugs may be used at the same time, a problem that is also referred to as polypharmacy.

Polypharmacy is commonly defined as the simultaneous use of five or more drugs, and is common among patients with T2DM.[6] Polypharmacy is driven by the increasing prevalence of comorbidities (40% of adults with diabetes have at least three additional chronic conditions) and aging.[7,8] Moreover, it can be further increased by current T2DM treatment guidelines, which rarely offer guidance on how to treat patients with more than two additional chronic conditions.[9–11]

Medication errors, poor treatment adherence, and adverse drug reactions (ADR) are consequences of polypharmacy.[12] Importantly, polypharmacy increases the risk of several unintended adverse health outcomes due to harmful drug–drug interactions (DDIs).[13–16] The prevalence of potential DDIs in primary care is estimated to be higher than 60%,[17] with up to 12% being clinically significant,[17,18] with elevated morbidity and mortality and high healthcare costs.[19,20]

Despite increasing awareness of polypharmacy, specific drug combinations in diabetic patients receiving polypharmacy remain poorly characterized with the focus on the number of drugs rather than the individual drug combinations.[21,22] For example, a recent study revealed that 77.9% of patients with T2DM had polypharmacy, with an average of 7.7 drugs per patient.[23] Similarly, it was previously found that 60% of patients with T2DM aged ≥75 years receive ≥5 drugs.[21] Only a handful of studies have identified medication patterns at the drug compound level, but these studies only included a limited number of drug compounds in the analyses.[24–31]

Understanding polypharmacy patterns at a drug compound level is important as the occurrence of DDIs is not a problem related only to classes of drugs, but to single drug compounds. Therefore, this study aimed to use a novel approach in order to identify prescription patterns at the compound level among patients with T2DM receiving their first non-insulin antidiabetic drug (NIAD).

2 | METHODS

2.1 | Data source

We conducted a descriptive cohort study using the IQVIA Medical Research Data (IMRD; incorporating data from THIN, A Cegedim Database of anonymized electronic health records in the United Kingdom), between 2016 and 2019. IMRD is an extensive database containing longitudinal non-identified primary care medical records from over 18 million patients, of which ~2.9 million are currently active. IMRD has been shown to be generally representative of the United Kingdom and valid in terms of age and sex comparisons and a wide range of diseases.[32] The database comprises a range of information, including demographics (e.g., year of birth and sex), diagnosis, lab tests (e.g., estimated glomerular filtration rate [eGFR] and hemoglobin A1c [HbA1c]), drug prescriptions recorded by general practitioners (GPs), and other information (e.g., smoking status, pregnancy, and death). Medications were recorded in the database using the British National Formulary (BNF) classification, and then were mapped according to the international anatomical therapeutic codes (ATC) classification system. All diagnoses were recorded using Read codes.[33]

2.2 | Study population

Patients who received a first-ever metformin prescription and aged ≥18 years between January 2016 and December 2019 were included. Cohort entry (index date) was defined as the date of the first-ever metformin prescription. Patients with a previous NIAD treatment were excluded. Patients were allowed to have additional co-prescribed NIADs at the index date. All patients were required to have a minimum period of 1 year of database history and at least one GP visit prior to the index date. We only consider patients registered with a practice with a valid up-to-standard date and who had an acceptable patient flag. Patients diagnosed with gestational diabetes, polycystic ovary syndrome, or insulin therapy previous or at index date were excluded.

2.3 | Polypharmacy definition

We identified patients with polypharmacy at the start of metformin therapy, which was defined as the use of ≥5 different prescribed drug compounds (i.e., metformin + ≥4 additional unique ATC codes on the 5th level) on, or within 90 days before the index date. The average prescription length of drugs to treat chronic illnesses in the United Kingdom is 3 months, and therefore, we assumed that drugs prescribed in a 90-day period are deemed to be co-prescribed. Although treatments for acute illnesses (e.g., antibiotics and pain-killers) usually have shorter duration, we used sensitivity analyses with shorter prescription time frames to explore polypharmacy patterns with different exposure window lengths. Thus, polypharmacy was further defined as the prescription of ≥5 different drug compounds at: (i) the index date or within 30 days previous to index date; and (ii) index date or within 14 days around index date (i.e., 7 days ± index date). We only considered drugs and diagnosis (i.e., history of comorbidities) that had a valid flag in the database. Additional details on the selection of drugs for the polypharmacy analysis are available in Supporting Information.

2.4 | Statistical analysis

We describe patient characteristics at index date as a mean and standard deviation (SD) or median and interquartile range (IQR) or counts and proportions, as appropriate. Alcohol use and smoking were identified based on the most recent value recorded in the database (i.e., at or at any time before index date). Body mass index (BMI) was calculated using the value closest to the index date for the weight (i.e., at or before index date), nonetheless, as the height of an individual is not likely to vary significantly during adulthood, the closest value to the index date was considered regardless if recorded before, at, or after the index date. The mean HbA1c and eGFR were summarized using the most recently recorded values up to previous 6 months prior to the index date, and a history of comorbidities was assessed if ever registered in the database previous to index date. All characteristics are reported among those with and without polypharmacy, and stratified by sex.

To determine co-prescribed drugs, we performed association rule and frequent-set analysis using the Apriori algorithm.[34] This methodology represents a novel approach to identify prescription patterns in large databases when it is not computationally feasible to assess extremely high number of drug combinations (e.g., patients with up to 40 drugs, resulting in 1.1×10^{12} possible combinations). Additional details on the polypharmacy analysis using the Apriori and its metrics are included in Supporting Information and Table S1, respectively. In this study, the frequency and proportion of co-prescribed drugs in patients receiving polypharmacy were ranked by frequency of prescribing stratified by sex.

After identifying and quantifying the different sets of drugs, we ranked the combinations of metformin with one to up to six additional drugs based on the frequency of prescription. In this way, we captured unique prescription patterns prescribed in patients with T2DM. Moreover, quantifying the "at least" particular combinations of drugs is important for knowing all patients exposed to any given combination of drugs.

Within each stratum (i.e., sex), we assessed the top five most frequently occurring drug combinations in patients receiving polypharmacy. If >1 drug combination shared the same position in the rank, we presented all combinations with the same frequency. In the secondary analysis, we repeated the analysis stratified by age groups.

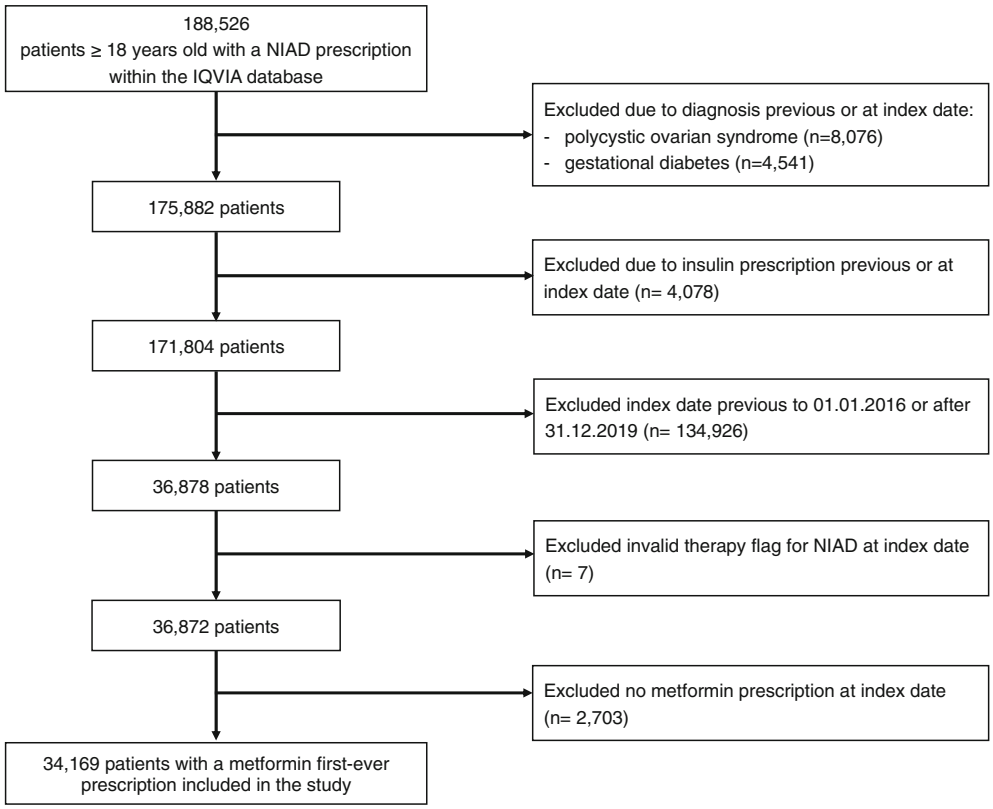

FIGURE 1 Flow diagram of patient selection. NIAD, non-insulin antidiabetic drug

Numbers fewer than seven are suppressed according to data use agreement with IMRD. All analyses were performed using the R version (4.1.2).

3 | RESULTS

3.1 | Patients' characteristics at metformin first-ever prescription

We identified 34 169 metformin initiators between 2016 and 2019 (Figure 1). The demographic characteristics at index are provided in Table 1, stratified by sex and polypharmacy status. Overall, 20 854 (61.0%) received ≥4 additional drugs in addition to metformin at index date or within 90 days before index date, and were categorized as having polypharmacy. The mean age of individuals with polypharmacy was 63.1, while for individuals with no polypharmacy was 53.7. Patients with polypharmacy had a higher prevalence of comorbidities than those without. When stratified by sex, there was a higher proportion of women receiving polypharmacy (65.6%) compared to men (57.4%), and women were more frequently receiving ≥20 drugs concomitantly (women = 2.0%; men = 0.9%). Moreover, women with polypharmacy were more often obese and had a lower eGFR, while men had higher levels of HbA1c and received more frequently combined antidiabetic pharmacotherapy (i.e., additional NIAD at metformin first prescription).

The demographics characteristics for the secondary analysis stratified by age groups is provided in Table S2. The proportion of patients receiving polypharmacy increased with age (18–39 years = 30.4%, 40–59 years = 50.5%, 60–74 years = 70.9%, and ≥75 years = 84.3%). The most prevalent concomitant condition among patients with polypharmacy aged ≥40 years was hypertension (40–59 years = 43.9%, 60–74 years = 65.3%, and ≥75 years = 71.8%), while depression was most the prevalent concomitant condition in 18–39 years old (38.3%) with polypharmacy. Additionally, patients younger than 60 years had more often a diagnosis for asthma, depression, and were more likely to be obese. On the other hand, patients aged ≥60 years had more often a diagnosis of cardiovascular diseases, osteoarthritis, hypothyroidism, and cancer.

The sensitivity analysis using shorter exposure windows to identify concomitant drugs are available in the Supporting Information (Tables S3 and S4 for exposure window at index date and within 30 days previous to index date, and Tables S5 and S6 for 14 days exposure window around the index date). Overall, the proportion of patients receiving polypharmacy declined from 61.0% in the primary analysis to 43.8% with a 30 days window and 20.9% with a 14 days window. Similarly, the mean number of drugs prescribed declined from 9.0 in the primary analysis to 8.1 and 7.7 with a 30 and 14 days window, respectively.

3.2 | Drug prescription patterns in patients receiving polypharmacy

Table 2 shows the proportions of patients prescribed each of the top five most co-prescribed drugs and combinations of up to six drugs additional to metformin overall patients with polypharmacy and stratified by sex. Atorvastatin was the most frequently co-prescribed drug

TABLE 1 Baseline characteristics of metformin new-users, stratified by sex

Characteristic	Overall study patients ($N = 34\,169$)		Women ($N = 14\,964$)		Men ($N = 19\,205$)	
	No polypharmacy	Polypharmacy	No polypharmacy	Polypharmacy	No polypharmacy	Polypharmacy
N (%)	13 315 (39.0%)	20 854 (61.0%)	5141 (34.4%)	9823 (65.6%)	8174 (42.6%)	11 031 (57.4%)
Mean age (SD)	53.7 (13.3)	63.1 (12.7)	52.1 (15.2)	62.8 (13.6)	54.7 (11.9)	63.4 (12.0)
Median number of drugs (IQR)	3 (2–4)	8 (6–11)	3 (2–4)	8 (6–11)	3 (2–4)	8 (6–10)
Mean number of drugs (SD)	2.6 (1.1)	9.0 (3.9)	2.7 (1.1)	9.4 (4.2)	2.6 (1.1)	8.6 (3.6)
Distribution of drugs *n* (%)						
1 (only metformin)	2532 (7.4%)	-	953 (6.4%)	-	1579 (8.2%)	-
2–4	10 783 (31.6%)	-	4188 (28.0%)	-	6595 (34.3%)	-
5–9	-	13 635 (39.9%)	-	6002 (40.1%)	-	7633 (39.7%)
10–19	-	6742 (19.7%)	-	3517 (23.5%)	-	3225 (16.8%)
≥20	-	477 (1.4%)	-	304 (2.0%)	-	173 (0.9%)
Max no of drugs	-	40	-	40	-	38
Number of NIADs prescribed at index date *n* (%)						
≥2	410 (3.1%)	696 (3.3%)	99 (1.9%)	284 (2.9%)	311 (3.8%)	412 (3.7%)
Smoking status[a], *n* (%)						
Current	2282 (17.1%)	3757 (18.0%)	792 (15.4%)	1820 (18.5%)	1490 (18.2%)	1937 (17.6%)
Never	7348 (55.2%)	9175 (44.0%)	3206(62.4%)	4938 (50.3%)	4142 (50.7%)	4237 (38.4%)
Former	3576 (26.9%)	7832 (37.6%)	1092 (21.2%)	3017 (30.7%)	2484 (30.4%)	4815 (43.6%)
Unknown/missing value	109 (0.8%)	90 (0.4%)	51 (1.0%)	48 (0.5%)	58 (0.7%)	42 (0.4%)
Alcohol use[a], *n* (%)						
Current	9147 (68.7%)	13 463 (64.5%)	3086 (60.0%)	5637 (57.4%)	6061 (74.1%)	7826 (71.0%)
Never (Lifelong teetotaler)	2616 (19.6%)	5155 (24.7%)	1381 (26.9%)	3168 (32.3%)	1235 (15.1%)	1987 (18.0%)
Former	409 (3.1%)	1303 (6.2%)	154 (3.0%)	542 (5.5%)	255 (3.1%)	761 (6.9%)
Unknown/missing value	1143 (8.6%)	933 (4.5%)	520 (10.1%)	476 (4.8%)	623 (7.6%)	457 (4.1%)
BMI[b], *n* (%)						
Obese (BMI ≥30.0 kg/m^2)	7969 (59.8%)	13 884 (66.6%)	3169 (61.6%)	6849 (69.7%)	4800 (58.7%)	7035 (63.8%)
Overweight (BMI 25.0–29.9 kg/m^2)	3627 (27.2%)	5036 (24.1%)	1182 (23.0%)	2034 (20.7%)	2445 (29.9%)	3002 (27.2%)
Normal/Underweight (BMI < 25.0 kg/m^2)	1167 (8.8%)	1456 (7.0%)	576 (11.2%)	715 (7.3%)	591 (7.2%)	741 (6.7%)
Missing value	552 (4.2%)	478 (2.3%)	214 (4.2%)	225 (2.3%)	338 (4.1%)	253 (2.3%)
History of disease, *n* (%)						
Hypertension	3674 (27.6%)	12 282 (58.9%)	1273 (24.7%)	5653 (57.6%)	2401 (29.4%)	6629 (60.1%)
Coronary heart disease	174 (1.3%)	3936 (18.9%)	32 (0.6%)	1138 (11.6%)	142 (1.7%)	2798 (25.4%)
Heart failure	17 (0.2%)	1007 (4.8%)	<7	325 (3.3%)	18 (0.2%)	682 (6.2%)
Cerebrovascular disease	208 (1.6%)	1822 (8.7%)	51 (1.0%)	743 (7.6%)	157 (1.9%)	1079 (9.8%)
Chronic kidney disease	25 (0.2%)	244 (1.2%)	14 (0.3%)	111 (1.1%)	11 (0.1%)	133 (1.2%)
Chronic liver disease	294 (2.2%)	883 (4.2%)	102 (2.0%)	455 (4.6%)	192 (2.4%)	428 (3.9%)
COPD	140 (1.1%)	2151 (10.3%)	49 (1.0%)	972 (9.9%)	91 (1.1%)	1179 (10.7%)
Asthma	1214 (9.1%)	4088 (19.6%)	538 (10.5%)	2367 (24.1%)	676 (8.3%)	1721 (15.6%)
Diabetic retinopathy	292 (2.2%)	736 (3.5%)	95 (1.9%)	328 (3.3%)	197 (2.4%)	408 (3.7%)

TABLE 1 (Continued)

Characteristic	Overall study patients ($N = 34\,169$)		Women ($N = 14\,964$)		Men ($N = 19\,205$)	
	No polypharmacy	Polypharmacy	No polypharmacy	Polypharmacy	No polypharmacy	Polypharmacy
Sleep disorders	629 (4.7%)	1959 (9.4%)	196 (3.8%)	870 (8.9%)	433 (5.3%)	1089 (9.9%)
Depression	2088 (15.7%)	6024 (28.9%)	1103 (21.5%)	3603 (36.7%)	985 (12.1%)	2421 (22.0%)
Alzheimer/Dementia	23 (0.2%)	344 (1.7%)	12 (0.2%)	195 (2.0%)	11 (0.1%)	149 (1.4%)
Hypothyroidism	564 (4.2%)	2449 (11.7%)	387 (7.5%)	1856 (18.9%)	177 (2.2%)	593 (5.4%)
Osteoarthritis	1258 (9.5%)	5365 (25.7%)	561 (10.9%)	2967 (30.2%)	697 (8.5%)	2398 (21.7%)
Osteoporosis	71 (0.5%)	702 (3.4%)	56 (1.1%)	559 (5.7%)	15 (0.2%)	143 (1.3%)
Cancer	545 (4.1%)	1985 (9.5%)	275 (5.4%)	1014 (10.3%)	270 (3.3%)	971 (8.8%)
Characteristic	**Overall study patients ($N = 34\,169$)**		**Women ($N = 14\,964$)**		**Men ($N = 19\,205$)**	
	No polypharmacy	**Polypharmacy**	**No polypharmacy**	**No polypharmacy**	**Polypharmacy**	**No polypharmacy**
Lab values						
Most recent HbA1c measurement 6 months prior to index date *n* (%)[c]						
<6.5% (48 mmol/mol)	545 (4.1%)	754 (3.6%)	320 (6.2%)	439 (4.5%)	225 (2.8%)	315 (2.9%)
6.5–7.4% (48–57 mmol/mol)	2956 (22.2%)	6410 (30.7%)	1263 (24.6%)	3137 (31.9%)	1963 (20.7%)	3273 (29.7%)
7.5–8.5% (58–69 mmol/mol)	2486 (18.7%)	5142 (24.7%)	878 (17.1%)	2383 (24.3%)	1608 (19.7%)	2759 (25.0%)
>8.5% (69 mmol/mol)	5418 (40.7%)	6334 (30.4%)	1559(30.3%)	2722 (27.7%)	3859 (47.2%)	3612 (32.7%)
Missing value	2858 (14.3%)	2214 (10.6%)	1121 (21.8%)	1142 (11.6%)	789 (9.6%)	1072 (9.7%)
Most recent eGFR measurement (ml/min/1.73 m^2) 6 months prior to index date *n* (%)[c]						
<30	<7	19 (0.1%)	<7	12 (0.1%)	<7	7 (0.1%)
30–59	487 (3.7%)	2400 (11.5%)	227 (4.4%)	1314 (13.4%)	260 (3.2%)	1086 (9.8%)
≥60	8652 (65.0%)	12 874 (61.7%)	3009 (58.5%)	5812 (59.2%)	5643 (69.0%)	7062 (64.0%)
Missing value	4173 (31.3%)	561 (26.7%)	1904 (37.0%)	2685 (27.3%)	2269 (27.8%)	2876 (26.1%)

Note: A history of comorbidities was assessed if ever registered in the database previous to or at index date. Numbers fewer than seven are suppressed according to data use agreement with IMRD.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, Estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IQR, interquartile range; NIAD, non-insulin antidiabetic drug; SD, standard deviation.

[a]Identified values closest to the index date (i.e., at or before index date).

[b]BMI was assessed using the most recently recorded value for weight (at or at any time before index date) and height (at or at any time before or after index date).

[c]The most recent value (at index date and previous 6 months) registered in the database with a valid unit was considered.

with metformin overall (38.7%), in women (34.3%), and men (42.6%), with a higher proportion of men receiving the medication. Overall, frequently prescribed drugs and drug combinations mainly treat manifestations of metabolic syndrome.

We repeated the analysis of drug prescription patterns stratifying by age groups (Table 3). Atorvastatin was the most co-prescribed drug in addition to metformin in adults ≥40 years old with polypharmacy (40–59 years [37.6%]; 60–74 years [42.6%]; ≥75 years [37.2%]). A second statin (simvastatin) was among the most prescribed drugs in patients aged ≥60 years (60–74 years [26.5%]; ≥75 years [28.9%]). On the other hand, salbutamol was often prescribed in 40–59 years old (20.6%), and sertraline (13.5%) among adults <40 years.

In the sensitivity analyses, similar results were obtained for overall patients with polypharmacy and stratified by sex and age using a 30 days window (Tables S7 and S8, respectively) and 14 days window (Tables S9 and S10, respectively), as compared to our primary and secondary analyses.

4 | DISCUSSION

This population-based study explored prescription patterns in patients with new-onset T2DM receiving multiple medications. This is the first study to identify polypharmacy patterns at the drug compound level,

TABLE 2 Rank of co-prescribed drug compounds and combinations of up to six drugs (excl. metformin) by frequency of prescribing in overall new metformin users receiving polypharmacy at index date and within 90 days before index date, and stratified by sex

Sex (*N*)	No of drugs	Rank	*N* (%)	Drug compound
Overall (20854)	1	1	8064 (38.7%)	Atorvastatin
		2	5798 (27.8%)	Omeprazole
		3	4808 (23.1%)	Amlodipine
		4	4713 (22.6%)	Simvastatin
		5	4650 (22.3%)	Ramipril
	2	1	2437 (11.7%)	Aspirin, atorvastatin
		2	2388 (11.5%)	Amlodipine, atorvastatin
		3	2263 (10.9%)	Ramipril, atorvastatin
		4	2185 (10.5%)	Omeprazole, atorvastatin
		5	2139 (10.3%)	Bisoprolol, atorvastatin
	3	1	1220 (5.9%)	Aspirin, bisoprolol, atorvastatin
		2	924 (4.4%)	Aspirin, ramipril, atorvastatin
		3	857 (4.1%)	Bisoprolol, ramipril, atorvastatin
		4	845 (4.1%)	Aspirin, bisoprolol, ramipril
		5	708 (3.4%)	Amlodipine, ramipril, atorvastatin
	4	1	577 (2.8%)	Aspirin, bisoprolol, atorvastatin, ramipril
		2	334 (1.6%)	Omeprazole, aspirin, bisoprolol, atorvastatin
		3	325 (1.6%)	Lansoprazole, aspirin, bisoprolol, atorvastatin
		4	300 (1.4%)	Aspirin, glyceryl trinitrate, bisoprolol, atorvastatin
		5	260 (1.2%)	Aspirin, amlodipine, bisoprolol, atorvastatin
	5	1	159 (0.8%)	Lansoprazole, aspirin, bisoprolol, ramipril, atorvastatin
		2	152 (0.7%)	Aspirin, glyceryl trinitrate, bisoprolol, ramipril, atorvastatin
		3	144 (0.7%)	Aspirin, bisoprolol, ramipril, atorvastatin, omeprazole
		4	95 (0.5%)	Aspirin, bisoprolol, ramipril, atorvastatin, amlodipine
		5	89 (0.4%)	Aspirin, isosorbide mononitrate, bisoprolol, atorvastatin, ramipril
	6	1	41 (0.2%)	Lansoprazole, aspirin, glyceryl trinitrate, bisoprolol, atorvastatin, ramipril
		2	39 (0.2%)	Ticagrelor, aspirin, glyceryl trinitrate, bisoprolol, atorvastatin, ramipril
		3	38 (0.2%)	Aspirin, omeprazole, glyceryl trinitrate, bisoprolol, atorvastatin, ramipril
		4	37 (0.2%)	Lansoprazole, aspirin, clopidogrel, bisoprolol, atorvastatin, ramipril
		5	34 (0.2%)	Lansoprazole, aspirin, ticagrelor, bisoprolol, atorvastatin, ramipril
		5	34 (0.2%)	Glyceryl trinitrate, furosemide, bisoprolol, ramipril, atorvastatin, aspirin
Women (9823)	1	1	3365 (34.3%)	Atorvastatin
		2	2955 (30.1%)	Omeprazole
		3	2176 (22.2%)	Salbutamol
		4	2014 (20.5%)	Co-codamol
		5	2009 (20.5%)	Simvastatin
	2	1	992 (10.1%)	Omeprazole, atorvastatin
		2	881 (9.0%)	Amlodipine, atorvastatin
		3	751 (7.6%)	Ramipril, atorvastatin
		4	750 (7.6%)	Aspirin, atorvastatin

TABLE 2 (Continued)

Sex (*N*)	No of drugs	Rank	*N* (%)	Drug compound
		5	723 (7.4%)	Salbutamol, omeprazole
	3	1	314 (3.2%)	Prednisolone, salbutamol, amoxicillin
		2	313 (3.2%)	Aspirin, bisoprolol, atorvastatin
		3	253 (2.6%)	Prednisolone, salbutamol, omeprazole
		4	251 (2.6%)	Aspirin, omeprazole, atorvastatin
		5	236 (2.4%)	Aspirin, ramipril, atorvastatin
	4	1	124 (1.3%)	Aspirin, bisoprolol, ramipril, atorvastatin
		2	115 (1.2%)	Prednisolone, salbutamol, amoxicillin, omeprazole
		3	104 (1.1%)	Omeprazole, aspirin, bisoprolol, atorvastatin
		4	96 (1.0%)	Prednisolone, salbutamol, amoxicillin, atorvastatin
		5	84 (0.9%)	Prednisolone, salbutamol, doxycycline, omeprazole
Sex (*N*)	**No of drugs**	**Rank**	***N* (%)**	**Drug compound**
Women (9823)	5	1	41 (0.4%)	Omeprazole, aspirin, ramipril, bisoprolol, atorvastatin
		2	36 (0.4%)	Prednisolone, salbutamol, amoxicillin, co-codamol, omeprazole
		3	34 (0.3%)	Aspirin, bisoprolol, ramipril, atorvastatin, glyceryl trinitrate
		4	32 (0.3%)	Prednisolone, salbutamol, amoxicillin, omeprazole, paracetamol
		5	31 (0.3%)	Prednisolone, salbutamol, amoxicillin, tiotropium bromide, omeprazole
	6	1	14 (0.1%)	Prednisolone, doxycycline, salbutamol, amoxicillin, montelukast, atorvastatin
		2	13 (0.1%)	Furosemide, prednisolone, doxycycline, salbutamol, paracetamol, tiotropium bromide
		2	13 (0.1%)	Prednisolone, salbutamol, atorvastatin, lansoprazole, amoxicillin, tiotropium bromide
		3	12 (0.1%)	Prednisolone, amoxicillin, salbutamol, paracetamol, tiotropium bromide, omeprazole
		3	12 (0.1%)	Prednisolone, amoxicillin, salbutamol, tiotropium bromide, omeprazole, carbocisteine
		3	12 (0.1%)	Omeprazole, aspirin, bisoprolol, ramipril, atorvastatin, glyceryl trinitrate
		4	11 (0.1%)	Prednisolone, doxycycline, salbutamol, tiotropium bromide, carbocisteine, atorvastatin
		4	11 (0.1%)	Prednisolone, amoxicillin, salbutamol, clarithromycin, co-codamol, omeprazole
		4	11 (0.1%)	Prednisolone, amoxicillin, salbutamol, atorvastatin, formoterol and budesonide, tiotropium bromide
		4	11 (0.1%)	Prednisolone, vitamins with minerals, alendronic acid, salbutamol, tiotropium bromide, omeprazole
		4	11 (0.1%)	Prednisolone, doxycycline, salbutamol, atorvastatin, salmeterol and fluticasone, tiotropium bromide
		4	11 (0.1%)	Furosemide, prednisolone, amoxicillin, salbutamol, omeprazole, tiotropium bromide
		4	11 (0.1%)	Prednisolone, amoxicillin, co-codamol, salbutamol, atorvastatin, tiotropium bromide
		4	11 (0.1%)	Omeprazole, prednisolone, paracetamol, salbutamol, tiotropium bromide, atorvastatin
		4	11 (0.1%)	Furosemide, prednisolone, amoxicillin, paracetamol, salbutamol, omeprazole
		4	11 (0.1%)	Prednisolone, amoxicillin, co-codamol, salbutamol, omeprazole, amitriptyline
		4	11 (0.1%)	Lansoprazole, prednisolone, amoxicillin, co-codamol, salbutamol, atorvastatin
		5	10 (0.1%)	Furosemide, prednisolone, doxycycline, tiotropium bromide, salbutamol, carbocisteine
		5	10 (0.1%)	Prednisolone, paracetamol, salbutamol, tiotropium bromide, carbocisteine, omeprazole
		5	10 (0.1%)	Prednisolone, paracetamol, salbutamol, tiotropium bromide, carbocisteine, atorvastatin
		5	10 (0.1%)	Omeprazole, prednisolone, salbutamol, tiotropium bromide, carbocisteine, atorvastatin
		5	10 (0.1%)	Amlodipine, prednisolone, doxycycline, salbutamol, atorvastatin, montelukast
		5	10 (0.1%)	Lansoprazole, prednisolone, amoxicillin, salbutamol, atorvastatin, montelukast
		5	10 (0.1%)	Lansoprazole, prednisolone, amoxicillin, salbutamol, atorvastatin, formoterol and budesonide
		5	10 (0.1%)	Prednisolone, doxycycline, salbutamol, atorvastatin, formoterol and beclometasone, tiotropium bromide

(Continues)

TABLE 2 (Continued)

Sex (*N*)	No of drugs	Rank	*N* (%)	Drug compound
		5	10 (0.1%)	Prednisolone, amoxicillin, sabutamol, tiotropium bromide, omeprazole, formoterol and beclometasone
		5	10 (0.1%)	Prednisolone, omeprazole, sabutamol, tiotropium bromide, formoterol and beclometasone, atorvastatin
		5	10 (0.1%)	Prednisolone, alendronic acid, vitamins with minerals, paracetamol, salbutamol, omeprazole
		5	10 (0.1%)	Furosemide, prednisolone, alendronic acid, paracetamol, salbutamol, tiotropium bromide
		5	10 (0.1%)	Prednisolone, amoxiciliin, salbutamol, tiotropium bromide, omeprazole, salmeterol and fluticasone
		5	10 (0.1%)	Lansoprazole, prednisolone, doxycycline, salbutamol, tiotropium bromide, atorvastatin
		5	10 (0.1%)	Prednisolone, levothyroxine sodium, amoxicillin, salbutamol, tiotropium bromide, omeprazole
		5	10 (0.1%)	Predisolone, amoxicillin, paracetamol, salbutamol, tiotropium bromide, atorvastatin
		5	10 (0.1%)	Omeprazole, prednisolone, amoxicillin, co-codamol, tiotropium bromide, salbutamol
		5	10 (0.1%)	Furosemide, bisoprolol, prednisolone, paracetamol, tiotropium bromide, salbutamol
		5	10 (0.1%)	Furosemide, omeprazole, prednisolone, paracetamol, tiotropium bromide, salbutamol
		5	10 (0.1%)	Prednisolone, paracetamol, tiotropium bromide, salbutamol, atorvastatin, amitriptyline
		5	10 (0.1%)	Prednisolone, omeprazole, tiotropium bromide, salbutamol, atorvastatin, amitriptyline
		5	10 (0.1%)	Aspirin, bisoprolol, ramipril, atorvastatin, co-codamol, omeprazole
Sex (*N*)	**No of drugs**	**Rank**	***N* (%)**	**Drug compound**
Men (11031)	1	1	4699 (42.6%)	Atorvastatin
		2	3053 (27.7%)	Aspirin
		3	2940 (26.7%)	Amlodipine
		4	2929 (26.6%)	Ramipril
		5	2843 (25.8%)	Omeprazole
	2	1	1687 (15.3%)	Aspirin, atorvastatin
		2	1512 (13.7%)	Ramipril, atorvastatin
		3	1507 (13.7%)	Amlodipine, atorvastatin
		4	1450 (13.1%)	Bisoprolol, atorvastatin
		5	1398 (12.7%)	Bisoprolol, aspirin
	3	1	907 (8.2%)	Aspirin, bisoprolol, atorvastatin
		2	688 (6.2%)	Aspirin, ramipril, atorvastatin
		3	661 (6.0%)	Aspirin, bisoprolol, ramipril
		4	648 (5.9%)	Atorvastatin, bisoprolol, ramipril
		5	491 (4.5%)	Amlodipine, ramipril, atorvastatin
	4	1	453 (4.1%)	Aspirin, bisoprolol, ramipril, atorvastatin
		2	248 (2.2%)	Lansoprazole, aspirin, bisoprolol, atorvastatin
		3	230 (2.1%)	Omeprazole, aspirin, bisoprolol, atorvastatin
		4	222 (2.0%)	Aspirin, bisoprolol, atorvastatin, glyceryl trinitrate
		5	198 (1.8%)	Aspirin, bisoprolol, atorvastatin, amlodipine
	5	1	131 (1.2%)	Lansoprazole, aspirin, ramipril, bisoprolol, atorvastatin
		2	118 (1.1%)	Aspirin, glyceryl trinitrate, bisoprolol, ramipril, atorvastatin
		3	103 (0.9%)	Aspirin, bisoprolol, ramipril, atorvastatin, omeprazole
		4	75 (0.7%)	Aspirin, amlodipine, bisoprolol, atorvastatin, ramipril
		5	72 (0.7%)	Aspirin, isosorbide mononitrate, bisoprolol, atorvastatin, ramipril
	6	1	37 (0.3%)	Lansoprazole, aspirin, glyceryl trinitrate, bisoprolol, ramipril, atorvastatin
		2	31 (0.3%)	Lansoprazole, aspirin, clopidrogrel, bisoprolol, ramipril, atorvastatin
		3	30 (0.3%)	Glyceryl trinitrate, aspirin, ticagrelor, bisoprolol, atorvastatin, ramipril

TABLE 2 (Continued)

Sex (N)	No of drugs	Rank	N (%)	Drug compound
		4	27 (0.2%)	Isosorbide mononitrate, aspirin, lansoprazole, bisoprolol, atorvastatin, ramipril
		4	27 (0.2%)	Clopidogrel, aspirin, glyceryl trinitrate, bisoprolol, atorvastatin, ramipril
		5	26 (0.2%)	Lansoprazole, aspirin, ticagrelor, bisoprolol, ramipril, atorvastatin
		5	26 (0.2%)	Omeprazole, aspirin, glyceryl trinitrate, bisoprolol, atorvastatin, ramipril

which is essential when investigating the potential for DDIs. Additionally, this is the first study to use the Apriori algorithm in a large prescription database to overcome the computational challenges of assessing an extremely high number of drug combination. The Apriori algorithm computes frequent combinations of drugs per patient, including the combinations prescribed to no patient in the data. This methodology allowed us to precisely identify and quantify polypharmacy patterns at a compound level, particularly challenging in patients receiving extremely high number of medications, moving away from the existing knowledge of polypharmacy based on drug classes.[23,30,35]

We identified that 61.0% of patients initiating metformin received ≥4 additional drugs at index date or within 90 days before index date, and polypharmacy was more prevalent among women and patients aged ≥75 years. For example, it was previously found that 77.9% of patients with T2DM in an Asian population received polypharmacy (i.e., the use of ≥5 drugs in a day), of which 60.4% are women.[23] Moreover, this study identified an average of 7.7 different drugs taken per patient, with a mean age of 62.8 years. Similarly, it was estimated that adults with T2DM receive an average of 8.4 different drugs within the same day in Germany.[35]

We pinpointed several examples of potential DDIs in our study. For instance, a pharmacokinetic interaction between atorvastatin (metabolized by the cytochrome P450 [CYP] 3A4) and CYP3A4 substrates, inhibitors, and inducers (i.e., bisoprolol, ticagrelor, and lansoprazole). This drug combination is highly prevalent in overall and adults aged 40–59 years. While the individual use of weak CYP3A4 inhibitors has minimal effect on statin plasma levels,[36] it is unclear whether the use of multiple drugs affecting CYP3A4 in many ways and, thus, atorvastatin metabolism may increase the risk of DDIs and ADR in those patients. An additional example of drug combination that may result in hypoglycemia is discussed in Supporting Information.

Although most drugs identified in our study prevent diabetes complications and are likely important drugs that cannot be de-prescribed, it is essential to consider individual characteristics of drugs (e.g., CYP enzyme interactions) in patients receiving multiple drug treatments. For instance, statins are commonly prescribed in diabetic patients with cardiovascular risk,[6] and some members of this class are CYP3A4-metabolized (e.g., simvastatin and atorvastatin), while others are non-CYP3A4 metabolized (e.g., rosuvastatin). When CYP3A4-metabolized statins are used concomitantly with the antidiabetic drug glyburide, the maximum plasma concentration (C_{max}) and the area under the curve (AUC) of the antidiabetic drug may increase by up to 20%, increasing the risk for ADE. Moreover, additional drugs affecting CYP3A4 activity may be co-prescribed, adding to the risk of a multi-drug interaction with clinical significance. Therefore, the particular combination of glyburide and a CYP3A4-metabolized statin may be inappropriate in diabetic patients with T2DM receiving polypharmacy, and replacement by a non-CYP3A4 metabolized statin should be considered.

4.1 | Strengths and limitations

A key strength of this study is the first-time use of the Apriori algorithm in a large prescription database, which allowed to assess an extremely high number of drug combinations at a compound level. Apriori and other algorithms used to find frequent item-sets (e.g., Toivonen's and PCY algorithms) are efficient approaches for finding frequent patterns in large databases. Thus, we moved beyond polypharmacy quantification at a drug class level as seen in previous studies.[22,26,37] These analyses failed to consider the omission of potentially harmful medications at a pharmaceutical ingredient level, as DDIs is not a problem related only to classes of drugs but to single drug compounds. IMRD allowed studying a large number of patients starting a metformin treatment who are representative of the United Kingdom population, where GPs usually manage T2DM.[38] Moreover, most of the results of our primary analysis remained consistent in the sensitivity analyses.

Our study also has some limitations. First, the IMRD only captures drug prescriptions, and therefore, we would not identify over-the-counter drugs.[39] Second, the use of primary care data means that prescriptions made in secondary care are not available, as well as medications required in hospital administration, special safety monitoring, or expensive drugs are often not fully captured (e.g., biologic disease-modifying antirheumatic drugs, methotrexate, atypical antipsychotics, and cancer treatments). Therefore, we might have underestimated actual drug utilization and interactions. However, as the GP acts as the gatekeeper, chronic diseases and prescriptions are often monitored by the physician. Thus, we do not expect this limitation to greatly influence the interpretation of the results. Similarly, this study did not consider variations in dosages, formulation types, or between drugs within the same therapeutic class. Nevertheless, we believe this constraint has not interfered with the study's primary objective.

Third, we acknowledge that the concomitant use of drugs may have been overestimated as, in some cases, the prescription length

TABLE 3 Rank of co-prescribed drug compounds and combinations of up to six drugs (excl. metformin) by frequency of prescribing stratified by age in new metformin users receiving polypharmacy at index date and within 90 days before index date

Age (*N*)	No of drugs	Rank	*N* (%)	Drug compound
18–39 years (862)	1	1	213 (24.7%)	Omeprazole
		2	210 (24.4%)	Salbutamol
		3	153 (17.7%)	Co-codamol
		4	123 (14.3%)	Amoxicillin
		5	116 (13.5%)	Sertraline
	2	1	59 (6.8%)	Amoxicillin, salbutamol
		1	59 (6.8%)	Beclomethasone, salbutamol
		2	48 (5.6%)	Co-codamol, omeprazole
		3	47 (5.5%)	Prednisolone, salbutamol
		4	44 (5.1%)	Omeprazole, salbutamol
		5	42 (4.9%)	Omeprazole, naproxen
	3	1	28 (3.2%)	Prednisolone, amoxicillin, salbutamol
		2	16 (1.9%)	Amoxicillin, beclometasone, salbutamol
		3	14 (1.6%)	Prednisolone, salbutamol, omeprazole
		3	14 (1.6%)	Aspirin, bisoprolol, atorvastatin
		4	13 (1.5%)	Doxyclycline, prednisolone, salbutamol
		4	13 (1.5%)	Prednisolone, salbutamol, beclometasone
		4	13 (1.5%)	Amoxicillin, salbutamol, co-codamol
		4	13 (1.5%)	Omeprazole, amoxicillin, salbutamol
		5	12 (1.4%)	Amlodipine, ramipril, atorvastatin
		5	12 (1.4%)	Omeprazole, diazepam, amitriptyline
		5	12 (1.4%)	Omeprazole, co-codamol, salbutamol
	4	1	10 (1.2%)	Omeprazole, prednisolone, amoxicillin, salbutamol
		2	9 (1.0%)	Aspirin, bisoprolol, ramipril, atorvastatin
		2	9 (1.0%)	Indapamide, amlodipine, atorvastatin, ramipril
		3	8 (0.9%)	Prednisolone, amoxicillin, beclometasone, salbutamol
		3	8 (0.9%)	Prednisolone, doxycycline, amoxicillin, salbutamol
		3	8 (0.9%)	Prednisolone, amoxicillin, salbutamol, co-codamol
		4	7 (0.8%)	Aspirin, glyceryl trinitrate, bisoprolol, atorvastatin
		4	7 (0.8%)	Aspirin, glyceryl trinitrate, ramipril, atorvastatin
		4	7 (0.8%)	Amoxicillin, salbutamol, predinisolone, clarithromycin
40–59 years (7007)	1	1	2635 (37.6%)	Atorvastatin
		2	2003 (28.6%)	Omeprazole
		3	1635 (23.3%)	Ramipril
		4	1451 (20.7%)	Amlodipine
		5	1441 (20.6%)	Salbutamol
	2	1	813 (11.6%)	Ramipril, atorvastatin
		2	700 (10.0%)	Omeprazole, atorvastatin
		3	692 (9.9%)	Amlodipine, atorvastatin
		4	664 (9.5%)	Aspirin, atorvastatin
		5	618 (8.8%)	Bisoprolol, atorvastatin
	3	1	408 (5.8%)	Aspirin, bisoprolol, atorvastatin
		2	318 (4.5%)	Aspirin, ramipril, atorvastatin
		3	305 (4.4%)	Bisoprolol, ramipril, atorvastatin
		4	301 (4.3%)	Aspirin, bisoprolol, ramipril
		5	240 (3.4%)	Amlodipine, ramipril, atorvastatin

TABLE 3 (Continued)

Age (*N*)	No of drugs	Rank	*N* (%)	Drug compound
	4	1	227 (3.2%)	Aspirin, bisoprolol, ramipril, atorvastatin
		2	121 (1.7%)	Aspirin, glyceryl trinitrate, bisoprolol, atorvastatin
40–59 years (7007)	4	3	111 (1.6%)	Lansoprazole, aspirin, bisoprolol, atorvastatin
		4	105(1.5%)	Omeprazole, aspirin, bisoprolol, atorvastatin
		5	90 (1.3%)	Lansoprazole, aspirin, ramipril, atorvastatin
	5	1	66 (0.9%)	Lansoprazole, aspirin, ramipril, bisoprolol, atorvastatin
		2	61 (0.9%)	Aspirin, glyceryl trinitrate, bisoprolol, ramipril, atorvastatin
		3	58 (0.8%)	Aspirin, bisoprolol, ramipril, atorvastatin, omeprazole
		4	47 (0.7%)	Aspirin, ticagrelor, bisoprolol, atorvastatin, ramipril
		5	39 (0.6%)	Lansoprazole, aspirin, glyceryl trinitrate, bisoprolol, atorvastatin
	6	1	19 (0.3%)	Aspirin, ticagrelor, glyceryl trinitrate, bisoprolol, ramipril, atorvastatin
		2	18 (0.3%)	Lansoprazole, aspirin, glyceryl trinitrate, bisoprolol, ramipril, atorvastatin
		2	18 (0.3%)	Lansoprazole, aspirin, bisoprolol, ramipril, atorvastatin, clopidogrel
		3	16 (0.2%)	Lansoprazole, aspirin, ticagrelor, bisoprolol, atorvastatin, ramipril
		4	15 (0.2%)	Clopidogrel, aspirin, glyceryl trinitrate, bisoprolol, atorvastatin, ramipril
		5	13 (0.2%)	Lansoprazole, aspirin, bisoprolol, ramipril, atorvastatin, isosorbide mononitrate
60–74 years (9073)	1	1	3861 (42.6%)	Atorvastatin
		2	2516 (27.8%)	Omeprazole
		3	2407 (26.5%)	Amlodipine
		4	2401 (26.5%)	Simvastatin
		5	2375 (26.2%)	Aspirin
	2	1	1264 (13.9%)	Aspirin, atorvastatin
		2	1258 (13.9%)	Amlodipine, atorvastatin
		3	1062 (11.7%)	Ramipril, atorvastatin
		4	1058 (11.7%)	Omeprazole, atorvastatin
		5	1044 (11.5%)	Bisoprolol, atorvastatin
	3	1	604 (6.7%)	Aspirin, bisoprolol, atorvastatin
		2	440 (4.8%)	Aspirin, ramipril, atorvastatin
		3	408 (4.5%)	Aspirin, bisoprolol, ramipril
		4	402 (4.4%)	Bisoprolol, ramipril, atorvastatin
		5	400 (4.4%)	Amlodipine, aspirin, atorvastatin
	4	1	261 (2.9%)	Aspirin, bisoprolol, ramipril, atorvastatin
		2	167 (1.8%)	Omeprazole, aspirin, bisoprolol, atorvastatin
		3	159 (1.8%)	Lansoprazole, aspirin, bisoprolol, atorvastatin
		4	146 (1.6%)	Aspirin, bisoprolol, atorvastatin, glyceryl trinitrate
		4	146 (1.6%)	Aspirin, bisoprolol, atorvastatin, amlodipine
		5	120 (1.3%)	Aspirin, amlodipine, ramipril, atorvastatin
	5	1	73 (0.8%)	Lansoprazole, aspirin, ramipril, bisoprolol, atorvastatin
		2	71 (0.8%)	Aspirin, glyceryl trinitrate, bisoprolol, ramipril, atorvastatin
		3	58 (0.6%)	Omeprazole, aspirin, bisoprolol, ramipril, atorvastatin
		4	54 (0.6%)	Aspirin, bisoprolol, amlodipine, ramipril, atorvastatin
		5	47 (0.5%)	Aspirin, bisoprolol, atorvastatin, glyceryl trinitrate, isosorbide mononitrate
	6	1	20 (0.2%)	Lansoprazole, aspirin, glyceryl trinitrate, bisoprolol, ramipril, atorvastatin
		2	17 (0.2%)	Aspirin, glyceryl trinitrate, bisoprolol, ramipril, atorvastatin, isosorbide mononitrate

(Continues)

TABLE 3 (Continued)

Age (*N*)	No of drugs	Rank	*N* (%)	Drug compound
		2	17 (0.2%)	Amlodipine, aspirin, bisoprolol, ramipril, atorvastatin, glyceryl trinitrate
		2	17 (0.2%)	Omeprazole, aspirin, glyceryl trinitrate, bisoprolol, ramipril, atorvastatin
		3	16 (0.2%)	Glyceryl trinitrate, aspirin, bisoprolol, ramipril, atorvastatin, furosemide
		3	16 (0.2%)	Lansoprazole, clopidogrel, aspirin, bisoprolol, ramipril, atorvastatin
		4	15 (0.2%)	Furosemide, prednisolone, doxycycline, tiotropium bromide, salbutamol, carbocisteine
		4	15 (0.2%)	Aspirin, prednisolone, salbutamol, tiotropium bromide, atorvastatin, carbocisteine
		4	15 (0.2%)	Aspirin, omeprazole, glyceryl trinitrate, isosorbide mononitrate, bisoprolol, atorvastatin
		4	15 (0.2%)	Lansoprazole, aspirin, furosemide, bisoprolol, ramipril, atorvastatin
Age (*N*)	**No of drugs**	**Rank**	***N* (%)**	**Drug compound**
60–74 years (9073)	6	5	14 (0.2%)	Aspirin, ticagrelor, bisoprolol, ramipril, atorvastatin, glyceryl trinitrate
		5	14 (0.2%)	Lansoprazole, aspirin, ticagrelor, bisoprolol, atorvastatin, ramipril
		5	14 (0.2%)	Prednisolone, amoxicillin, salbutamol, omeprazole, tiotropium bromide, salmeterol and fluticasone
		5	14 (0.2%)	Aspirin, glyceryl trinitrate, isosorbide mononitrate, bisoprolol, atorvastatin, omeprazole
		5	14 (0.2%)	Glyceryl trinitrate, aspirin, bisoprolol, ramipril, atorvastatin, salbutamol
		5	14 (0.2%)	Aspirin, prednisolone, doxycycline, salbutamol, atorvastatin, amoxicillin
		5	14 (0.2%)	Omeprazole, atorvastatin, prednisolone, doxycyline, amoxicillin, salbutamol
		5	14 (0.2%)	Aspirin, prednisolone, salbutamol, atorvastatin, amoxicillin, bisoprolol
		5	14 (0.2%)	Omeprazole, amlodipine, ramipril, atorvastatin, aspirin, bisoprolol
≥75 years (3912)	1	1	1455 (37.2%)	Atorvastatin
		2	1130 (28.9%)	Simvastatin
		3	1114 (28.5%)	Aspirin
		4	1066 (27.2%)	Omeprazole
		5	1009 (25.8%)	Bisoprolol
	2	1	493 (12.6%)	Aspirin, atorvastatin
		2	454 (11.6%)	Bisoprolol, atorvastatin
		3	409 (10.5%)	Amlodipine, atorvastatin
		4	399 (10.2%)	Omeprazole, atorvastatin
		5	381 (9.7%)	Aspirin, simvastatin
	3	1	194 (5.0%)	Aspirin, bisoprolol, atorvastatin
		2	155 (4.0%)	Aspirin, ramipril, atorvastatin
		3	150 (3.8%)	Omeprazole, aspirin, atorvastatin
		4	140 (3.6%)	Furosemide, bisoprolol, atorvastatin
		4	140 (3.6%)	Bisoprolol, ramipril, atorvastatin
		5	134 (3.4%)	Aspirin, amlodipine, atorvastatin
	4	1	80 (2.0%)	Aspirin, bisoprolol, ramipril, atorvastatin
		2	57 (1.5%)	Omeprazole, aspirin, bisoprolol, atorvastatin
		3	52 (1.3%)	Lansoprazole, aspirin, bisoprolol, atorvastatin
		4	51 (1.3%)	Omeprazole, aspirin, ramipril, atorvastatin

TABLE 3 (Continued)

Age (*N*)	No of drugs	Rank	*N* (%)	Drug compound
		5	45 (1.2%)	Aspirin, bisoprolol, atorvastatin, furosemide
	5	1	24 (0.6%)	Omeprazole, aspirin, ramipril, bisoprolol, atorvastatin
		2	21 (0.5%)	Warfarin, digoxin, furosemide, bisoprolol, atorvastatin
		3	18 (0.5%)	Lansoprazole, aspirin, bisoprolol, ramipril, atorvastatin
		3	18 (0.5%)	Prednisolone, amoxicillin, salbutamol, furosemide, atorvastatin
		4	16 (0.4%)	Furosemide, aspirin, ramipril, bisoprolol, atorvastatin
		5	15 (0.4%)	Aspirin, bisoprolol, ramipril, atorvastatin, isosorbide mononitrate
		5	15 (0.4%)	Warfarin, digoxin, furosemide, paracetamol, bisoprolol
		5	15 (0.4%)	Warfarin, furosemide, bisoprolol, paracetamol, atorvastatin
	6	1	8 (0.2%)	Omeprazole, aspirin, isosorbide mononitrate, bisoprolol, ramipril, atorvastatin
		2	7 (0.2%)	Lansoprazole, warfarin, digoxin, furosemide, bisoprolol, atorvastatin
		2	7 (0.2%)	Warfarin, digoxin, furosemide, bisoprolol, atorvastatin, paracetamol

may be shorter than 90 days, and, thus, patients will have stopped one drug before starting another. Moreover, drug exposure was defined based on unique ATC codes on the fifth level, and therefore, the concomitant use of drugs may have been underestimated when one ATC code combined >1 active pharmaceutical ingredient. Since all prescriptions are considered "exposures" through the entire window length (i.e., 90, 30, or 14 days), longer windows increased the mean drug exposure counts, and thus the frequency (i.e., ranking) of prescriptions with short durations (e.g., antibiotics or pain-killers) was increased. Thus, the extent of polypharmacy decreased when we shortened the exposure window in which we may have missed many of the repeated prescriptions for drugs treating chronic diseases, where the mode of prescriptions is a 90 days' supply in the United Kingdom. Nevertheless, the prescription patterns are consistent over different exposure windows. Thus, we believe that it plausibly reflects prescribed polypharmacy. As for most data sources on drug utilization, whether patients actually consumed the medications remains a limitation. Finally, although the potential DDIs identified in this study were conceivable, no adverse health events were assessed.

5 | CONCLUSION

This study is the first to precisely identify and quantify polypharmacy patterns at a drug compound level by assessing the frequency of item-sets. The use of Apriori is efficient for finding frequent patterns in large databases and allowed us to assess an extremely high number of drug combinations at a compound level, moving away from the existing knowledge of polypharmacy based on drug classes. Polypharmacy was identified in 61% of metformin new-users, with a higher proportion of women and adults (≥75 years). The high prevalence of polypharmacy at all age strata indicates the need to optimize drug therapies to minimize DDI and ADR. Most drugs identified in our study were not relevant for drug deprescribing, however, they highlight the importance of considering the characteristics of individual drug compounds (e.g., CYP enzyme interactions) in patients receiving polypharmacy. While potential clinically relevant DDIs and drug combinations were identified, results should be interpreted cautiously, and longitudinal studies will be needed to investigate causal associations.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

The study protocol was approved by the THIN scientific research council (study reference number: 20SR062). IMRD is an anonymized electronic healthcare record database and hence further ethics approval is not required.

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