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Perspective

Polypharmacy in older adults: Association Rule and Frequent-Set Analysis to evaluate concomitant medication use

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ABSTRACT

The aim of this study was to apply Association Rule and Frequent-Set analysis, and novel means of data visualisation to ascertain patterns of medication use and medication combinations contributing to medication group clusters according to geriatric syndrome status in older adults. Participants were community-dwelling men (aged ≥70 years, n = 1686), Sydney, Australia. Medication exposure was categorised at medication class level and data were analysed according to geriatric syndrome status (presence of at least one syndrome including frailty, falls, cognitive impairment and urinary incontinence). Association Rule and Frequent-Set analysis were performed to identify "interesting" patterns of medication combinations that occur together. This analysis involves advanced computer algorithms that investigated all possible combinations of medications in the dataset in order to identify those which are observed more or much less frequently than expected. Frequent-Set Analysis demonstrated one unexpected medication combination, antiulcer and antidiabetic medications (3.5% of participants) in the overall population (n = 1687). Frequency of medication combinations was similar in participants with (n = 666) and without (n = 1020) geriatric syndromes. Among participants with geriatric syndromes, the most frequent combinations included antigout with lipid-lowering agents (5.7%) followed by angiotensin II and diuretics combination (22%). This novel methodology can be used to detect common medication combinations overall by data visualisation, and against specific adverse drug reactions such as geriatric syndromes. This methodology may be a valuable pharmacovigilance approach to monitor large databases for the safety of medications.

1. Introduction

To ensure the safety of pharmacological treatments, pharmacovigilance reporting systems have been established internationally to monitor adverse events associated with use of marketed pharmaceutical products. However, the process of screening and monitoring of adverse drug events (ADEs) can be extremely resource-intense and often relies predominantly on spontaneous reports of adverse events to a central health agency; however data quality is often poor, and the expected frequency of signals can be small. To mitigate some of these challenges, there has been growing interest in applying novel analytic techniques such as a network sciences approach [1] when analysing medication prescription data in routinely collected administrative databases to monitor for ADEs. Comprehensive analyses from spontaneous reports, administrative claims databases and pharmacoepidemiological studies are vital to generate high-quality data on risks and benefits of pharmacological treatments [2].

Among the available methods, Association Rule analysis may be a useful technique for monitoring for complexity of medicine utilisation patterns, and identifying scientific questions for subse-

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quent pharmacoepidemiological studies [1]. This method may also be applied to characterise the complexity of medication utilisation patterns including medication combinations, and drug interactions at participant and population level [3]. Association Rule analysis has been used to determine strong and frequent directional associations in marketing between jointly purchased items [4] and in medicine using gene expression data [5]. Moreover, the application of Association Rule analysis to generate evidence on medication safety has been recently proposed for monitoring the safety of vaccine use [6]. A number of studies have used this technique to characterise the complex interactions of multi-morbidity [7], and more recently to identify risk factors for early childhood caries [8] and adverse drug reactions signals due to confounding observed in observational studies [9]. We have also shown the utility of Association Rule analysis with network analysis to determine common comorbidity patterns in community-dwelling older adults [10].

While this potential pharmacovigilance methodology may be important for all patient groups because clinical trials are not large enough to detect rare ADEs, it is particularly important for older adults, due to their increased risk of ADEs. As multi-morbidity is common in older adults it follows that polypharmacy is frequent. However, standard statistical methods are limited in their capacity to ascertain the combinations of medications older adults take. In older individuals, the risk of ADEs is increased by changes in pharmacokinetics and pharmacodynamics, reduced physiologic reserve, hyperpolypharmacy (≥10 medications), multi-morbidity, geriatric syndromes and health care professionals' prescribing practices [11,12]. Geriatric syndromes (e.g. frailty, falls, cognitive impairment and urinary incontinence) are of particular interest because they are common in older people but there is conflicting information about the role of medications and medication combinations as risk factors for their occurrence. Therefore, we need pharmacoepidemiology and pharmacovigilance data on medication utilisation and safety to guide safe prescribing for older people [2].

To our knowledge, no study to date has investigated the application of Association Rule analysis to describe the complexity of medication use in older people. This methodology may be helpful in detecting patterns of concurrent medication use, which may be a useful pharmacovigilance approach to monitor the safety of pharmacological treatments. Therefore, the aim of this study is to apply Association Rule and the closely related Frequent-Set analysis, and novel means of data visualisation 'Support Grids' to ascertain patterns of medication use. Specifically, we investigate common medication combinations on person-level within clusters, and medication combinations contributing to medication group clusters according to geriatric syndrome status in community-dwelling older men.

2. Methods

2.1. Study population

Participants were community-dwelling men enrolled in the Concord Health and Ageing in Men Project (CHAMP), Sydney, Australia. Eligible participants were those aged ≥70 years and living in the study region recruited between January 2005 and June 2007 [13]. Participants living in residential aged care facilities were excluded. The electoral roll was used to identify men eligible for the study (n = 2815), who were then contacted by phone or mail resulting in a 54% participation (n = 1511). An additional 194 men living in the study area heard about the study from friends or the local media and were recruited before receiving an invitation letter, giving a final sample of 1705 participants. For the current study, analysis was restricted to 1686 participants with complete data. Participants underwent baseline assessments, which comprised a self-completed study questionnaire and a clinical assessment that consisted of physical performance measures, neuropsychological testing, and medication inventory [14]. The study was approved by the Sydney Local Health District Human Research Ethics Committee Concord Repatriation General Hospital, Sydney, Australia.

2.2. Medication assessment

A medication inventory was conducted on each participant by trained personnel during the baseline clinic visit. Participants were instructed to bring all prescription and over-the-counter medications they were taking to the clinic visit for review. Participants were asked whether they had taken any prescription or non-prescription medications during the past month. Details of all medications and prescription pattern were recorded. Reported medications were coded using the Iowa Drug Information Service code numbers. For this analysis, we used data on prescription medications (regular and on as needed basis) and have categorised medication exposure at medication class level (yes versus no). We have limited the analysis to medication classes (n = 24) reported by at least 50 participants. The analysis was conducted at the medication class level as we were interested to explore co-administration of most common medication classes.

2.3. Geriatric syndrome assessment

Data were obtained for four geriatric syndromes, frailty, falls, urinary incontinence and cognitive impairment, using assessment methods previously described and validated [15]. For frailty, similar criteria were used as in the Cardiovascular Health Study (CHS). This involved objectively assessing participants for weight loss/shrinking, weakness, exhaustion, slowness and low physical activity [16]. Participants were considered frail if they met criteria for three or more of the five components. For weakness (defined as the lowest sample quintile for grip strength) and slowness (defined as the lowest sample quintile for walking speed), the same criterion used in the CHS was employed. However, weight loss (defined as current weight lower by ≥15% than the highest self-reported lifetime weight), exhaustion (assessed using the 12-item Short Form Health Survey) [17] and low activity (defined as being in the lowest quartile of activity using the Physical Activity Scale for the Elderly) [18] were assessed using an adapted criteria. This was due to the unavailability of some measurements in our study that were used in the CHS methodology.

Participants were screened for cognitive impairment and at the end of the screening and clinical assessments, participants were categorised as having dementia, mild cognitive impairment (MCI) or being cognitively intact. Those participants with a diagnosis of dementia or MCI were classified as cognitively impaired [19]. The International Consultation of Incontinence Questionnaire (ICIQ) self-administered questionnaire was used to assess the presence of urinary incontinence. Men were classified as incontinent if they reported leaking urine at least twice a week in the past four weeks [20]. Participants who had two self-reported falls in the previous 12-months at the baseline interview were considered fallers. Lastly, a participant was classified as part of the 'combined geriatric syndrome' subgroup if they had at least one of the previously mentioned four geriatric syndromes. Participants (n = 11) with missing data for more than two of the geriatric syndromes were excluded.

2.4. Statistical analysis

The main feature of the statistical methods used in this study is the application of data mining techniques known as Association Rule or Frequent Set analysis. These methods are designed

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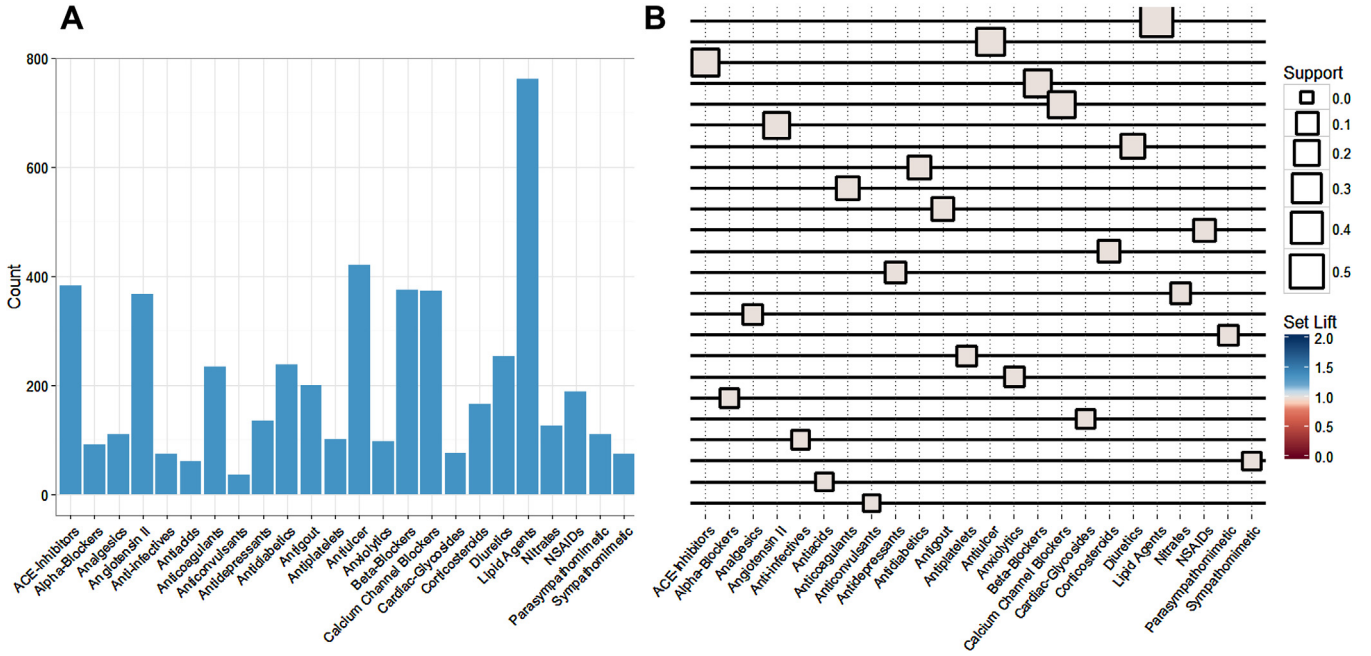

Fig. 1. Histogram showing the prevalence of medication classes (A) and Frequent-Set Analysis of individual medications displayed in a Support Grid (B) in the total study population. Each horizontal row in the Support Grid represents a separate item set. The size of squares represents frequency (support) of individual medications. Abbreviations: angiotensin converting enzyme (ACE)-inhibitors; non-steroidal anti-inflammatory drugs (NSAIDs).

to quickly traverse big datasets to identify combinations of items that co-occur. This analysis identified associations between the selected medication classes in the entire sample. Next, comparisons between sub-groups defined by clinical characteristics were performed (e.g. with and without geriatric syndromes). Association Rule and Frequent-Set analysis were undertaken using R (version 3.1.0, R Core Team, 2015) and the library "arules" (version 1.1-6).

The Frequent-Set analysis considers all combinations of medications and calculates several statistics for visualisation and inspection. The goal of this analysis is to identify combinations of medication classes that occur together more often than would be expected by chance, i.e. more often than we would expect under statistical independence. A total of 24 different medication classes were considered in this analysis. This means there are a total of $2^{24} = 16{,}777{,}216$ possible combinations of medications that

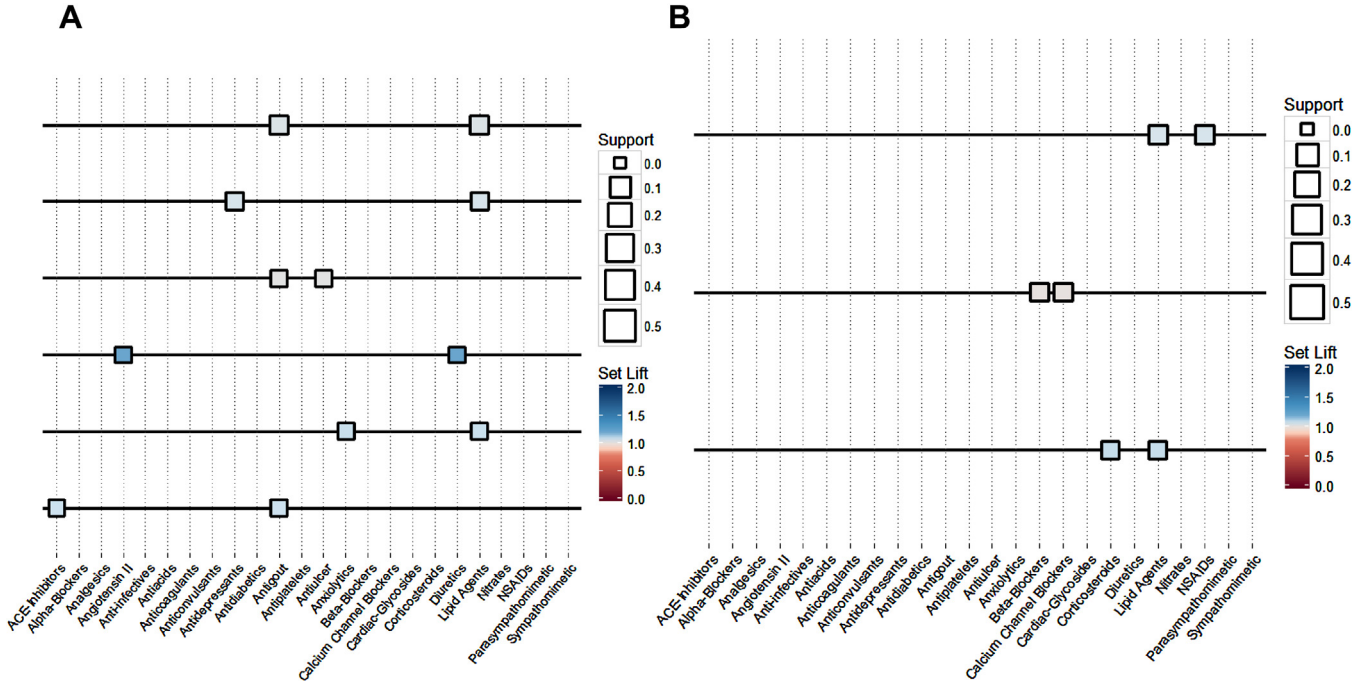

Fig. 2. Support Grids for Frequent-Set analysis of medication classes in participants with (A) and without (B) geriatric syndromes. Each row represents a different combination or "item-set" of medications. Set Lift quantifies how much more frequently two sets of items occur together compared to how often would be expected under statistical independence. Support is the prevalence of an item set. Abbreviations: angiotensin converting enzyme (ACE)-inhibitors; non-steroidal anti-inflammatory drugs (NSAIDs).

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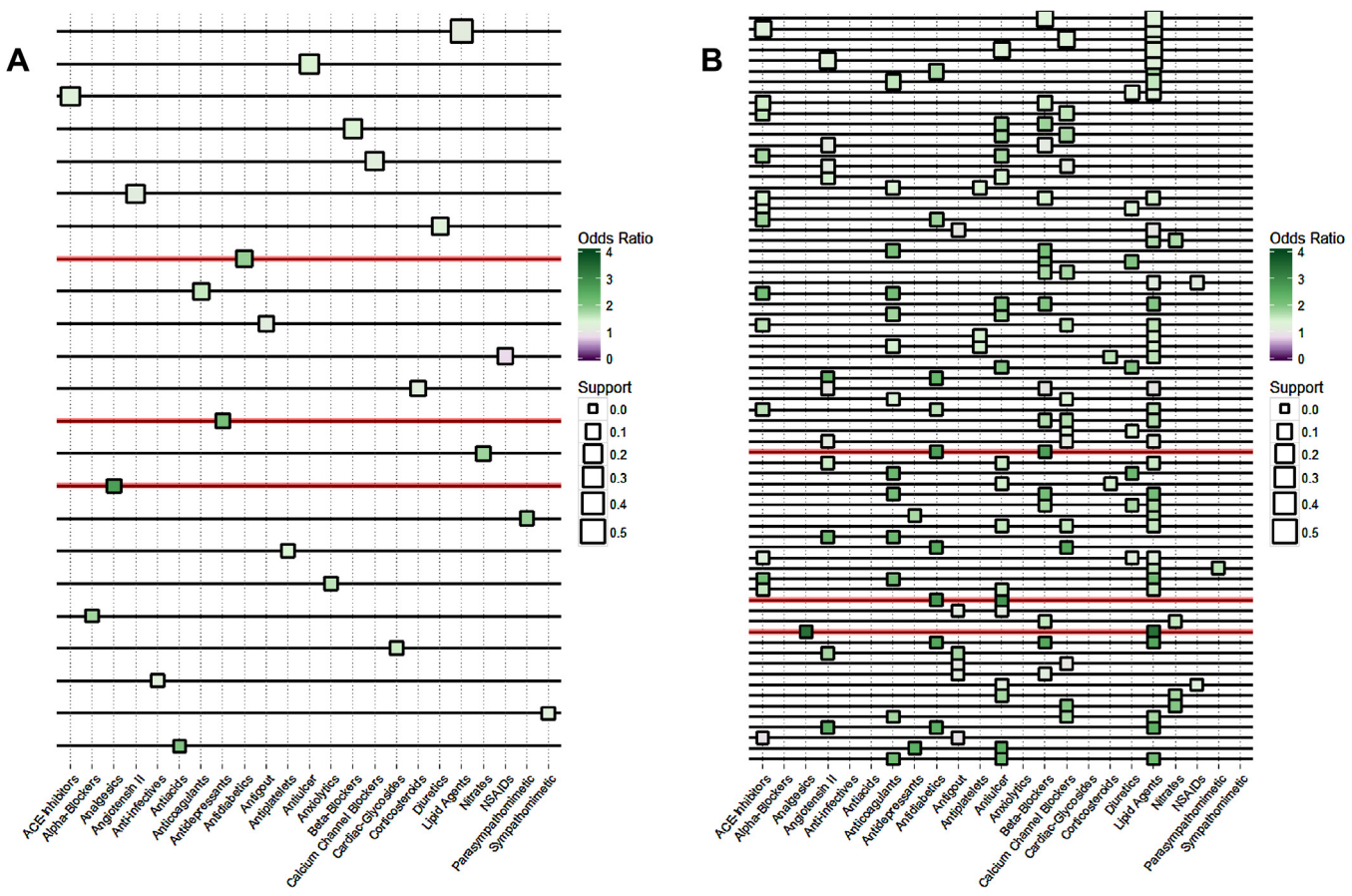

Fig. 3. Support Grids for Frequent-Set analysis for comparisons of individual medications (A) and medication combinations (B) displaying the odds ratios of participants with geriatric syndromes relative to those without geriatric syndromes. Colour codes (i.e. highest value) represent the odds ratios while size is the frequency of an item set in the entire sample. For the subgroup analysis, people without geriatric syndromes are the reference group. Abbreviations: angiotensin converting enzyme (ACE)-inhibitors; non-steroidal anti-inflammatory drugs (NSAIDs).

need to be considered. The following terminology is applied in the Frequent-Set analysis: (1) combinations of medications are referred to as an 'item set'; (2) the prevalence of an item set is called 'support'; (3) 'lift' quantifies how much more frequently two sets of items occur together compared to how often would be expected under statistical independence; we apply this concept of lift to individual item sets, by comparing the support of the set with the product of support of the items it contains; (4) item-sets that show high support and high-lift simultaneously are labelled as "interesting", which is technical term from the data mining literature, as previously published [10]. Odds ratios (ORs) for each comparison and tests for significance were adjusted with Holm correction for multiple testing. In contrast to Association Rules, Frequent-Set analysis does not imply a directionality of associations between sets of items. For this reason Frequent-Set analysis is more suitable in this context.

To limit the number of reported item sets, we defined minimum threshold for support (prevalence). This threshold quantifies what can be considered as "*interesting*" by selecting only those combinations above that are observed with sufficient frequency within the population. There are no universal standards for selecting these thresholds. Throughout this analysis our default threshold for minimum support is 3%. This threshold is specific to this data set. It was chosen manually with the objective to identify "interesting" combinations, while at the same time setting a barrier high enough to exclude combinations that may have occurred by chance. We used the 'eclat' algorithm in R [21] to efficiently go through all possible combinations of medication classes and identify those that are above this threshold. The findings are presented graphically, using "Support Grids". Support Grids are customised data visualisations used to identify and compare the patterns identified as "interesting".

As an introduction, we present a traditional bar chart together with a Support Grids (Fig. 1A). The Support Grid encodes the same information as the bar chart, but it uses the size of squares instead of height of bars to represent frequency (support) of individual items. Each horizontal row in the Support Grid represents a separate item set. In this case we have limited the selection to sets that contain only one item, equivalent to the bar chart. These are the smallest possible item sets. In Fig. 2 we have depicted item sets with more than one item, which are represented as more than one square in the same row. Using a separate visual channel, colour coding is used to convey the sets' "interestingness". The measure of interest (i.e. lift in Figs. 1 and 2 or OR in Fig. 3) is shown as a colour gradient where off-white in the centre stands for "not interesting" with lift or odds ratio very close to one. Positive and negative deviations from this central point are then represented through increasing colour intensity. Theoretically this could be a scale from 0 (much less frequent than expected) to infinity (much more frequent than expected), but the colour scale is set to cover all graphs in the analysis here.

Our analysis is descriptive, showcasing the potential of data mining and visualisation in exploring the patterns in of medication complexity. There is a wide range of possible criteria to quantify the "interestingness" of an item set besides lift and ORs [22]. Yet all reduce the number of reported item sets to those of outstanding rel-

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evance or "interestingness". In comparisons of item sets between two sub-populations, we tested the difference in proportions to additionally assess "interestingness" through odd ratio tests. These tests are conservative and identify only those item sets that have an odds ratio that is so extreme it would be expected by chance in at most 5% of the time. We calculated OR tests for all items sets above a minimum support value of 3%, using two-sided hypothesis tests with Holm correction for multiple testing [23].

3. Results

3.1. Patterns in the entire study population

Of 1686 participants, 60.5% (n = 1020) were classified as having geriatric syndromes, while 39.5% (n = 666) had no geriatric syndromes. The prescription frequency for individual medication classes for the entire study population is visualised in Fig. 1A and B. In this study population, lipid-lowering medications were reported by 45.2% of the population, followed by antiulcer (24.9%), angiotensin converting enzyme (ACE)-Inhibitors (22.7%) and beta-blockers (22.2%). The results of Frequent Set Analysis showed that there is just one combination of co-administered medications (antiulcer and antidiabetic medications) that met our minimum thresholds to display "interestingness". This combination surpassed our thresholds with 58 observed cases equal to 3.5% of the sample and a lift of 1.02 (data not shown). This lift was very low and indicates that there are no combinations of medications that are used together in a systematic way that would deviate from the overall prevalence of each medication across the study population.

3.2. Patterns in participants with and without geriatric syndromes

Among participants with geriatric syndromes, there were six combinations of two medication classes (as illustrated with two boxes on six individual rows) that were utilised together more frequently than would be expected if these classes were statistically independent (Fig. 2A). The most frequent combination was antigout with lipid-lowering agents, observed in 5.7% (n = 38) of participants with a lift of 1.04. The combination of angiotensin II agents with diuretics was found to have the highest lift, at 1.22, making these medications appear together 22% times more frequently than would be expected if they were independent. In the sample without geriatric syndromes (Fig. 2B), there were only three combinations of two medication classes (as illustrated with two boxes on three individual rows) that meet our inclusion criteria for "interestingness" including lipid lowering-agents in combination with corticosteroids (support = 3.7%, lift = 1.09), lipid lowering-agents in combination with non-steroidal anti-inflammatory drugs (NSAIDs) (support = 4.9%, lift = 1.06), and beta-blockers and calcium channel blockers combination (support = 4.1%, lift = 1.01).

Using ORs, we compared the groups of participants with and without geriatric syndromes for individual medications (Fig. 3A) and for medication combinations (Fig. 3B). The colour coding indicates how different the odds are in the group with geriatric syndromes versus without geriatric syndromes. There were three individual medication classes that showed an OR of a magnitude that can be attributed to non-independence with more than 95% certainty. These include analgesics (OR = 2.69), antidepressants (OR = 2.06) and antidiabetics (OR = 1.85). These rows are highlighted in red. A number of medication combinations frequently used together reached the minimum prevalence threshold of 3% in either of the two sub-populations. The combination with the highest significant OR of 3.37 was lipid-lowering agents and analgesics. Other combinations with particularly high ORs included beta-blockers and antidiabetics (OR = 2.68) and antiulcer with antidiabetics (OR = 2.70).

4. Discussion

This study involved secondary analysis of the data obtained from the CHAMP study using the novel data-mining methodologies including the Association Rule and Frequent-Set analysis. These novel methodologies can be used to detect combinations of medications, and drug–drug interactions according to underlying clinical characteristics for high risk groups, such as older adults. These methodologies provide a unique opportunity to regularly monitor the complexity of medicine utilisation patterns in large populations of older adults, and other patient groups to inform safe prescribing in real-word setting.

In our study population of community-dwelling older men, the Frequent-Set analysis revealed one "interesting" and unexpected medication combination, antiulcer and antidiabetic combination. While co-prescription of these medications may be clinically justified, studies suggest that diabetes is an independent risk factor for peptic ulcer bleeding [24], therefore this may in part explain co-prescription of antiulcer and antidiabetic medications in our population. Another clinical scenario might be the use of certain antidiabetic agents, such as metformin leading to gastrointestinal adverse effects and subsequent antiulcer treatment [25]. Interestingly, the Frequent-Set analysis demonstrated similar frequency of medications, with some significant differences in medication combinations, among participants with and without geriatric syndromes. This is somewhat unexpected as studies have consistently reported that people with geriatric syndromes use more medications, and have higher hyperpolypharmacy exposure. However, we have previously found in this cohort that the prevalence of optimal medical therapy (antiplatelet, beta-blocker, renin angiotensin system blocker and statin therapy) for secondary prevention in coronary heart disease is similar in participants with and without geriatric syndromes [26].

Most "interesting" medication combinations did differ according to geriatric syndrome status. Among men with geriatric syndromes, antigout with lipid-lowering agents and the combination of angiotensin II agents with diuretics were observed more frequently than would be expected if they were independent. Studies have shown that cardiovascular medications are the most commonly used pharmacological group in older people regardless of the presence or absence of geriatric syndromes [27]. While the combination of angiotensin II with diuretic is commonly used to manage hypertension, there are potential harms associated with the use of these agents, including risk of falls, should be of concern in this patient population [27]. In participants without geriatric syndromes three medication combinations met inclusion criteria for "interestingness" including lipid lowering-agents in combination with corticosteroids and NSAIDs, and beta-blockers and calcium channel blockers combination. There is evidence that the use of corticosteroids agents, such as prednisone, may lead to hyperlipidaemia, and subsequent use of lipid-lowering medications. The combination of beta-blockers and calcium channel blockers is synergistic and is considered beneficial in the treatment of hypertension and heart disease. Serious adverse effects may occur with incorrect dosing and inadequate monitoring (e.g. significant drop in heart rate and blood pressure), especially problematic in older people with polypharmacy and multi-morbidity [27]. However, it should be noted that these associations are not causal and future studies are warranted to investigate the potential mechanisms.

Our study demonstrates the utility of Association Rule and Frequent-Set analysis to detect common medication combinations and to interpret the complexity of medication patterns in

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older people according to geriatric syndrome status. The method can also be applied to other clinical scenarios, such as analyses of large and complex biomedical datasets and social media for assessing medication safety [28]. Other opportunities also include the application of Association Rule analysis to clinical pharmacology research as pharmacoepidemiology and pharmacogenomics research is increasingly being driven by bioinformatics-associated discovery. Additionally, this methodology can be used to monitor compliance with clinical guideline recommendations.

This study has several important strengths. Validated tools were used to assess geriatric syndromes, and a careful and systematic medication inventory was performed by checking all medications, thereby minimising exposure misclassification. Data were obtained from a large sample of community-dwelling older men. We have applied novel methods of data presentation and visualisation. The main limitation associated with this work is the cross-sectional study design and the fact that Association Rules analysis can only be used to identify medication combinations that warrant further investigation. Patterns of medication combinations are limited to this study population, which includes medication data collected a decade ago and medication exposures identified in this sample. Other patterns may be detected in other datasets or study settings. However, despite these limitations, there are opportunities to utilise this technique with the current pharmacovigilance approaches to rapidly generate post-marketing surveillance data on safety of medicines used in the real-word setting. Another limitation is that our data could not be used to determine the appropriateness of treatments for individual participants. Future studies should aim to incorporate data on diseases and whether individual medications have at least one clinical indication. This methodology could also be expanded to investigate the temporal changes in medication combination and associations with clinical outcomes, geriatric syndromes, and patient-centred outcomes such as self-reported health or disability over time. The study's generalisability may be limited given that this sample comprised community-dwelling older men living in a defined geographic location. Participation in the study was voluntary, and clinical characteristics of participants may have differed from those of non-participants, which may have biased the sample.

5. Conclusions

These novel methodologies provide a translational approach for investigating medication combinations and potential drug interactions, and it provides complementary methods to traditional pharmacoepidemiology and pharmacovigilance research. These methodologies may be particularly important for studies of older people who have polypharmacy, multiple medication combinations and atypical presentations of adverse drug reactions.

Conflicts of interest

The authors declare that they have no competing interests.

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