Identifying frequent drug combinations associated with delirium in older adults: Application of association rules method to a case-time-control design

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Abstract

Background: Older adults are at an increased risk of delirium because of age, polypharmacy, multiple comorbidities, frailty, and acute illness. Although medication-induced delirium in older adults is well understood, limited population-level evidence is available, particularly on combinations of medications associated with delirium in older adults.

Objectives: We aimed to apply association rule analysis to identify drug combinations contributing to delirium risk in adults aged 65 and older using a case-time-control design.

Method: We sourced a nationwide representative sample of New Zealanders aged ≥65 years from the pharmaceutical collections and hospital discharge information. Prescription records (2005–2015) were obtained from New Zealand pharmaceutical collections (Pharms). Medication exposures were coded as binary variables (exposed vs. not exposed) at the individual drug level. All medications, including antimicrobials, antihistamines, diuretics, opioids, and nonsteroidal anti-inflammatory medications, were considered drugs of interest. The first-time coded diagnosis of delirium was extracted from the National Minimal Dataset (NMDS). A unique patient identifier linked the prescription dataset to the event dataset to set up a case-time-control cohort, indexed at the first delirium event. Association rules were then applied to identify frequent drug combinations in the case and the control periods (l-day with a 35-day washout period) that are statistically associated with delirium, and the association was tested by computing a time-trend adjusted matched odds-ratio (MOR) and its 95% confidence interval (CI).

Results: We identified 28 503 individuals (mean age 84.1 years) from 2005 to 2015 with delirium. Our combined association rule and case-time-control analysis identified several drug classes, including antipsychotics, benzodiazepines, opioids, and diuretics associated with delirium. Our analysis also identified frequently used drug combinations that are associated with delirium. Examples include combined exposures to quetiapine and furosemide (MOR = 6.17; 95%CIs = [2.05–18.54]), haloperidol (MOR = 4.81; 95%CIs = [3.16–6.69]), combined exposures to furosemide,
omeprazole, and lorazepam (MOR = 3.94; 95%CI = [3.03–5.10]), and fentanyl exposure (MOR = 3.46; 95%CI [2.05–9.21]).

**Conclusion:** The association rule method applied to a case-time-control design is a novel approach to identifying drug combinations contributing to delirium with adjustment for any temporal trends in exposures. The study provides new insight into the combination of medicines linked to delirium.

**KEYWORDS**
association rules, case-time-control design, delirium, older people, pharmacoepidemiology, pharmacovigilance

**Key Points**
- Older adults are at an increased risk of delirium because of age, polypharmacy, multiple comorbidities, and acute illness.
- The association rules method revealed that frequently used drug combinations associated with delirium are haloperidol, fentanyl, a combination of quetiapine and furosemide, a combination of furosemide, omeprazole, and lorazepam.
- The study provides new insight into the combination of medicines linked to delirium.

## 1 | INTRODUCTION

The association rules (AR) methodology is a data-mining algorithm that extracts from a big dataset frequent and statistically interesting item sets above a chosen frequency threshold. The AR method has been successfully used in pharmacoepidemiology and post-marketing surveillance to investigate frequent medication and medication combinations contributing to adverse drug events (ADEs). The AR method has also been used to illustrate the complex interactions of multimorbidity, depict common comorbidity patterns, and assess medication use complexity in community-dwelling older adults. The utility of the AR method has also been successfully extended to the field of bioinformatics to identify factors that control gene transcription.

We previously have demonstrated the AR method’s utility to investigate medication combinations associated with fracture and acute kidney injury in older adults. Our previous analyses were restricted to examining transient medication exposures during the time at risk of an acute event in line with the recommendation for implementing a case-crossover design. In this study, we used a case-time control design to adjust for time trends of medicine exposures.

Delirium is associated with higher morbidity, increased mortality, length of hospital stay, higher hospital costs, and greater cognitive impairment risk. Older adults are at an increased risk of delirium because of ageing, multiple comorbidities, frailty, and polypharmacy. Medication-induced delirium is a modifiable risk factor, and studies have shown several individual medications can contribute to delirium in older adults. Some of the most common medications classes associated with delirium include antimicrobials, antihistamines, antihypertensives, anticholinergics, antidepressants, antipsychotics benzodiazepines, diuretics, opioids, and nonsteroidal anti-inflammatory medications. Several studies have associated the drugs of interest from these medication classes with delirium; however, the mechanism and pathophysiology by which medicines induce delirium are not well understood.

There is limited population-level evidence available, particularly on combinations of medications associated with delirium in older adults.

This study chose to apply the AR method to a case-time-control design as it mitigates confounding from unknown time-invariant confounders. We followed all the recommendations to apply a case-time-control design to our analyses. The key assumptions met include that the occurrence of the event must be acute, and the exposure may vary over time.

The overarching aim of this case-time-control study was to apply the AR method to identify frequent medication combinations contributing to the risk of delirium in older adults aged 65 years and older.

## 2 | METHODOLOGY

We obtained ethical approval from the Human Ethics Research Committee, University of Bath (approval number EIRA1-5353).

### 2.1 | Data source

The New Zealand (NZ) Ministry of Health holds national collections of the community pharmacy dispensing, hospital discharge details and mortality data details. Pharms is the national collections of all prescription claims made by community pharmacists. It contains prescriptions of medicines funded by the Pharmaceutical Management Agency (PHARMAC). PHARMAC is the New Zealand government agency that decides which pharmaceuticals to fund in New Zealand publicly and provides funded access to pharmaceuticals for all New Zealanders. The National Minimum Data Set (NMDS) is a national collection of public and private hospital discharge information, including coded clinical data for inpatients and day patients. We have provided a detailed
description of both the datasets previously.\cite{7,8} We used unique encrypted National Health Index (NHI) identifiers to cross-match medication exposure data with hospital events data from NMDS.

We were interested in exploring the use of all PHARMAC-funded drugs and combinations of these at the population level, including mainly antimicrobials, antihistamines, antihypertensive drugs, anticholinergic drugs, antidepressant drugs, antipsychotics, benzodiazepines, diuretics, opioids, and nonsteroidal anti-inflammatory medications.\cite{2,3,19,23,27,30,31}

2.2 | Study subject

We identified from the NMDS all individuals aged 65 years and above. We used the ICD-10-AM (The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification) codes F050, F051, F058, and F059 to identify individuals with delirium.

2.3 | Case-time-control cohort

We created a case-time-control cohort for medication exposures, with two 1-day observation periods and two 5-week (35 days) washout periods, summed up to a 36-day study period (Figure 1). A case-time-control cohort consists of a “case” case-crossover subcohort, where individuals had experienced delirium at least once between January 01, 2005 and December 12, 2015; and a “control” case-crossover subcohort that was set up for mitigating the time-trend bias of varying exposure prevalence over time, where individuals had no delirium diagnosis between January 01, 2005 and December 12, 2015. In the case of subcohort, the index date is when the individual experienced delirium for the first time after January 01, 2005. For the control subcohort, each case subject was matched to up to 3 control subjects by sex, ethnicity, and age (at case subject’s index date, ±180 days), and the index dates of case subjects were taken as the index dates of the matched control subjects.

The case period is the day before the index date. The control period is the 1-day period 36 days before the index date. We chose two 5-week washout periods based on our previous study to avoid carrying over the effects of any medication exposures around the control period and to exclude prescriptions that are dated and unlikely to have effects within the observation period.\cite{8} We calculated the duration of each prescription by dividing the total dose supplied by the daily dose. We determined whether an individual had non-intermittent exposure to the drugs of interests within the case and control periods with the prescription dates.

2.4 | AR methodology and statistical analysis

We applied AR methodology in this study to identify exposures to drugs and drug combinations associated with an increased risk of delirium. In this study, drugs and drug combinations that individuals were exposed to with a frequency of at least one in every 200 individuals on the day before the event (i.e., within the case period) are the frequent itemsets. The interestingness statistics are the increased odds of delirium onset for each frequent drug combination due to the exposure.

We expressed the increased odds of delirium onset due to exposures as matched odds-ratio (MOR). We identified individuals with exposures to medication combinations in the case and the control periods from the case-time-control cohort. We counted the number of individuals, with delirium who were exposed to drugs of interest (exposures) within the case period but not the control period (N1), with delirium and with exposures in the control period but not the case period (N2), without delirium and with the exposures in the case period but not the control period. (N3), and without delirium and with the exposures in the control period but not the case period. (N4). Frequencies of individuals with delirium provide a background MOR due to variations in exposure prevalence over time. The unadjusted MOR of delirium was based on the case-crossover subcohort of individuals with delirium, $N_1/N_2$. The background MOR due to time-trend bias was based on the case-crossover subcohort of individuals without delirium, $N_3/N_4$. The MOR with time-trend adjustment can then be calculated as the ratio of the two MORs, $(N_1/N_2)/(N_3/N_4)$, or equivalently $(N_1 N_4)/(N_2 N_3)$, which is the same as the conventional odds-ratio, and the variance of the log (MOR) can be calculated as $(1/N_1) + (1/N_2) + (1/N_3) + (1/N_4)$.

We used heat maps to display the strength of the association between medication exposures and delirium. In the heat map, each row represents an exposure combination, and each column represents a medication that appears at least once in the set of exposure combinations. If a medication appears in a particular exposure combination, the corresponding grid is coloured. We then mapped the MOR calculations onto the heat map. Each row (i.e., each exposure combination) is proportional to the log(MOR) of delirium associated with this combination. The grid bordered with a blue colour in the heat map represents log(MOR) > 0 with a confidence level of 95%.

2.5 | Sensitivity analyses

We conducted sensitivity analyses to account for the carrying-over effects of drug exposures. We selected two other periods lengths, 3 and 7 days, for the case and control periods instead of 1 day. Case-time-control cohorts were re-created with those period lengths, then, the AR as mentioned above analyses were repeated.

A longer time window accounted for the possibility of carryover effect contributed by discontinuation closer to the observation period. When observation periods are longer than a day, we defined non-intermittent exposure to medication if prescribed for more than 80% of the days within the study period. The 80% cut-off is considered a standard measure for medication adherence in pharmacoepidemiological studies (i.e., the proportion of days covered ≥0.8).
The pharmaceutical collections (PHARMS) and NMDS data were made available as annual, CSV-formatted datasets. The filtering mentioned above and cohort-construction procedures were performed using a computer program written in R (3.4.2, R Core Team, 2016).

3 | RESULTS

We identified 28,503 individuals (mean age 84.1 years) from 2005 to 2015 with a recorded diagnosis of delirium. Of these, 24,814 had at least one prescription involving PHARMAC-funded drugs within the case period, the day before the delirium event. The number of individuals exposed to each of the 41 exposures mentioned above is shown in Table 1. For most combinations, the distribution of ages was slightly skewed towards the higher age group.

AR revealed 41 frequent exposure combinations that are associated with delirium with a confidence level of 95% and a MOR >3.0 (log(MOR) > 1.099) (Figure 2). Delirium is associated with combined exposures to aspirin, quetiapine and furosemide (MOR = 6.17; 95%CI = [2.05–18.54]), haloperidol exposure (MOR = 4.81; 95%CI = [1.93–4.07]), oxycodone hydrochloride (MOR = 2.81; 95%CI = [1.93–4.07]), nitrofurantoin (MOR = 2.66; 95%CI = [1.88–3.77]), norfloxacin (MOR = 2.66; 95%CI = [1.78–3.99]), roxithromycin (MOR = 2.18; 95%CI = [1.64–2.89]), co-trimoxazole (MOR = 2.17; 95%CI = [1.49–3.18]), sodium valproate (MOR = 2.15; 95%CI = [1.35–3.42]), clonazepam (MOR = 1.99; 95%CI = [1.49–2.65]), amoxycillin clavulanate (MOR = 1.97; 95%CI = [1.63–2.37]) (Supplementary Table S1).

The sensitivity analyses were repeated with (3-day) and weekly (7-day) case and control period windows (Supplementary Figure S1 and S2). With the use of 3-day windows (Supplementary Figure S1), delirium was associated with combined exposures to quetiapine and furosemide (MOR = 3.45; 95%CI = [1.68–7.11]) (Supplementary Figure S2), so was fentanyl exposure (MOR = 4.71; 95%CI = [2.33–9.52]). Also, haloperidol exposure (MOR = 3.74; 95%CI = [2.60–5.41]), and combined exposure to haloperidol, docusate and paracetamol (MOR = 6.06; 95%CI = [2.91–12.63]) were associated with delirium, with the use of 7-day windows (Supplementary Figure S2).
Discussion

In this study, we extended the AR method to a case-time-control matched cohort of older people to examine medications exposures frequently associated with delirium. AR identified several medication classes, including antipsychotics, loop diuretics, opioids, and benzodiazepines, which increase the risk of delirium in older adults. Delirium induced by the benzodiazepines class of medicines is supported by

| Drug combination                                                                 | 65–69 yr (n = 227) | 70–74 yr (n = 1735) | 75–79 yr (n = 4593) | 80–84 yr (n = 7016) | 85–89 yr (n = 8006) | 90 yr + (n = 6926) |
|----------------------------------------------------------------------------------|--------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Aspirin + Quetiapine + Furosemide                                               | 0                  | 9                   | 14                  | 39                  | 46                  | 45                  |
| Lorazepam + Omeprazole + Docusate sodium with sennosides                         | 2                  | 9                   | 24                  | 39                  | 32                  | 48                  |
| Haloperidol + Paracetamol + Docusate sodium with sennosides                       | 0                  | 13                  | 20                  | 40                  | 44                  | 45                  |
| Aspirin + Metoprolol succinate + Trimethoprim                                    | 0                  | 2                   | 13                  | 34                  | 44                  | 60                  |
| Metoprolol succinate + Trimethoprim                                              | 0                  | 5                   | 31                  | 59                  | 70                  | 89                  |
| Haloperidol                                                                       | 6                  | 42                  | 115                 | 145                 | 195                 | 163                 |
| Trimethoprim + Docusate sodium with sennosides                                   | 0                  | 3                   | 19                  | 33                  | 66                  | 82                  |
| Furosemide + Lorazepam + Omeprazole                                             | 2                  | 7                   | 8                   | 39                  | 39                  | 49                  |
| Fentanyl                                                                         | 2                  | 11                  | 36                  | 50                  | 44                  | 51                  |
| Metoclopramide hydrochloride + Morphine sulphate                                  | 5                  | 26                  | 42                  | 42                  | 37                  | 19                  |
| Haloperidol + Docusate sodium with sennosanes                                     | 0                  | 20                  | 42                  | 56                  | 65                  | 61                  |
| Lorazepam + Paracetamol + Omeprazole                                            | 3                  | 11                  | 24                  | 61                  | 56                  | 61                  |
| Erythromycin ethyl succinate                                                      | 1                  | 6                   | 24                  | 36                  | 49                  | 39                  |
| Furosemide + Trimethoprim                                                        | 0                  | 3                   | 22                  | 46                  | 68                  | 80                  |
| Quetiapine + Metoprolol succinate                                                 | 1                  | 19                  | 30                  | 65                  | 76                  | 60                  |
| Trimethoprim + Simvastatin                                                       | 0                  | 5                   | 28                  | 43                  | 56                  | 42                  |
| Morphine hydrochloride + Morphine sulphate + Paracetamol                          | 6                  | 18                  | 34                  | 36                  | 39                  | 25                  |
| Quetiapine + Docusate sodium with sennosanes                                     | 3                  | 13                  | 46                  | 80                  | 85                  | 74                  |
| Amoxicillin + Metoprolol succinate                                                | 0                  | 4                   | 23                  | 33                  | 44                  | 41                  |
| Haloperidol + Paracetamol                                                        | 3                  | 22                  | 47                  | 69                  | 102                 | 90                  |
| Metoprolol succinate + Sodium valproate                                          | 1                  | 18                  | 52                  | 45                  | 37                  | 22                  |
| Aspirin + Quetiapine + Omeprazole                                                | 0                  | 9                   | 18                  | 42                  | 49                  | 32                  |
| Quetiapine + Furosemide                                                          | 0                  | 11                  | 22                  | 61                  | 76                  | 72                  |
| Aspirin + Quetiapine + Metoprolol succinate                                      | 0                  | 12                  | 21                  | 43                  | 46                  | 38                  |
| Furosemide + Haloperidol                                                         | 0                  | 12                  | 31                  | 42                  | 56                  | 55                  |
| Haloperidol + Omeprazole                                                        | 2                  | 21                  | 39                  | 47                  | 68                  | 51                  |
| Trimethoprim                                                                     | 1                  | 19                  | 85                  | 170                 | 256                 | 267                 |
| Morphine sulphate + Zopiclone                                                    | 5                  | 21                  | 42                  | 44                  | 31                  | 30                  |
| Quetiapine + Paracetamol + Docusate sodium with sennosides                        | 1                  | 8                   | 22                  | 56                  | 45                  | 46                  |
| Morphine sulphate                                                                | 17                 | 110                 | 233                 | 277                 | 231                 | 167                 |
| Furosemide + Lorazepam + Paracetamol                                             | 1                  | 5                   | 12                  | 39                  | 46                  | 60                  |
| Morphine hydrochloride + Morphine sulphate                                       | 7                  | 28                  | 61                  | 56                  | 54                  | 33                  |
| Trimethoprim + Omeprazole                                                       | 1                  | 11                  | 30                  | 58                  | 101                 | 85                  |
| Aspirin + Lorazepam + Omeprazole                                                 | 2                  | 11                  | 26                  | 51                  | 43                  | 57                  |
| Aspirin + Metoprolol succinate + Paracetamol + Omeprazole + Isosorbide mononitrate | 1                 | 7                   | 25                  | 48                  | 57                  | 57                  |
| Amoxicillin clavulanate + Aspirin + Metoprolol succinate                          | 5                  | 12                  | 23                  | 37                  | 41                  | 39                  |
| Risperidone                                                                     | 2                  | 37                  | 122                 | 205                 | 285                 | 211                 |
| Aspirin + Furosemide + Lorazepam                                                | 1                  | 7                   | 15                  | 34                  | 44                  | 58                  |
| Lorazepam + Zopiclone                                                            | 2                  | 17                  | 38                  | 52                  | 61                  | 62                  |
| Aspirin + Trimethoprim                                                           | 0                  | 5                   | 30                  | 80                  | 124                 | 132                 |
| Amitriptyline + Aspirin + Simvastatin + Omeprazole                               | 1                  | 15                  | 30                  | 49                  | 40                  | 16                  |
evidence from a prospective cohort study conducted in older hospital inpatients. This study found that benzodiazepines accounted for one-third of delirium cases in patients with normal cognitive impairment.

The AR method also revealed loop diuretics increase the risk of delirium. The use of diuretics can be associated with fluid and electrolyte imbalance, including hyponatremia resulting in the onset of confusion and delirium. In a subgroup analysis (cohort size approximately 91,000) of a matched cohort study using electronic health records, calcium channel blockers were associated with less delirium than diuretics (OR 0.84 (0.79–0.90)).

The finding that fentanyl increases delirium risk in older adults is biologically plausible and congruent with evidence that links opioid use with delirium. The one postulated mechanism is that opioids

**FIGURE 2** Heat map shows medication-exposure combinations and the MOR of delirium due to case-period exposures (one-day time window) and the statistical significance [Colour figure can be viewed at wileyonlinelibrary.com]
induced delirium secondary to their central anticholinergic effects\textsuperscript{26,37} and directly acting on the opioid receptors. Pre-clinical studies conducted in rats have shown dose-dependent toxicity associated with fentanyl possibly mediated via binding to the brain’s muscarinic receptors.\textsuperscript{38} A case report also highlighted delirium risk in a 71-year-old elderly patient following fentanyl exposure.\textsuperscript{39}

Our study found a combination of furosemide, omeprazole and lorazepam increases the risk of delirium. There is a lack of well-designed studies addressing medication class combination associated with delirium. This study provides new insights into medication combinations that are linked with delirium. However, it should be noted from case reports that individually omeprazole,\textsuperscript{40} furosemide and lorazepam\textsuperscript{41} may increase the risk of delirium.

The finding that quetiapine is associated with delirium is interesting as antipsychotic medications are recommended to treat delirium.\textsuperscript{42} Antipsychotics are known to be associated with delirium, potentially mediated by their anticholinergic properties.\textsuperscript{43} Case reports have shown quetiapine and its metabolite norquetiapine have strong anticholinergic effects and may induce delirium in older adults.\textsuperscript{44} Case reports have also highlighted delirium associated with olanzapine secondary to its anticholinergic effects.\textsuperscript{26}

The sensitivity analyses repeated with (3-day) and weekly (7-day) time windows did not change the results for combined exposures to quetiapine and furosemide and fentanyl exposure. These time windows were chosen to align with the best practice recommendations for conducting a case-time-control study. The sensitivity analyses confirmed that haloperidol, lorazepam and fentanyl are associated with delirium in older adults.

AR method identified interesting but unexpected medication combinations linked with delirium. This study’s strength is that it has important implications for pharmacoepidemiology research, as it may facilitate the detection of interesting medication combinations linked to ADEs. Current pharmacovigilance methods do not report co-medication patterns and mainly investigate safety signals for single drug entities. Applying AR to a case-time-control cohort mitigates confounding from known and measurable confounders such as age, sex, genetic variability, and comorbidities.

However, the effects of time-varying confounders that change rapidly are difficult to adjust, which is a major limitation of this study. For example, acute health status changes, such as dehydration, may also increase delirium risk.\textsuperscript{45} We mitigated time-varying confounding by studying only the short, 72-day time period before the index date, but residual confounding remains a concern. The other limitation is protopathic bias; haloperidol and lorazepam are often recommended to treat delirium.\textsuperscript{56–49} Since we used pharmacy claims data, exposure misclassification due to lack of information on medication consumption, self-medication, and the use of over-the-counter drugs such as NSAIDs linked to delirium may have biased the findings.\textsuperscript{50} The NZ pharmacy claims data includes medications funded by PHARMAC and may differ from other countries’ drug formularies, and this limitation may affect the generalisability of the study findings.

We met the assumptions that the outcome of interest must be an acute event and not change over time; delirium is an acute event and is unlikely to change over the short study period employed in our study. However, we should be conscious of other important assumptions and limitations of the case-time-control design, including bias created by selecting the case and control windows, selecting a control group, and inadequate adjustment of time-varying confounders.\textsuperscript{29,51} We also acknowledge that persistent user bias cannot be eliminated by using case cross over designs studying chronic exposures as it may bias the findings (odds ratio) upwards.\textsuperscript{52} We applied a 5-week washout period universally for all exposures, and the differences in half-lives of individual medicines were not considered.

5 | CONCLUSION

The association rule method applied to a case-time-control design is a novel approach to identifying drug combinations contributing to delirium with adjustment for any temporal trends in exposures. The study provides new insight into the combination of medicines linked to delirium.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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

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