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Network analysis as a tool to illustrate the population-level complex prescribing to community-dwelling people living with dementia

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Abstract

Introduction

Prescribing for people living with dementia can be challenging. Emerging research methods present an opportunity to learn about complex patterns of medication use and leverage this understanding to optimize care.

Objective

We describe network analysis, an unsupervised machine learning method, to understand population-level prescribing in older adults living with dementia.

Methods

We included community-dwelling adults aged 67 and older, newly ascertained as having dementia between April 1, 2014, and March 31, 2016 in Ontario, Canada. Using medication dispensation data, we created network graphs at ascertainment and five years later. Each node represented a medication subclass; subclasses concurrently dispensed to the same individual were considered linked by an edge. Attributes of networks were used to characterize prescribing across individuals: nodes, edges (including network density), and node centrality metrics.

Results

We identified 99,064 individuals with incident dementia, of which 15,222 were alive and not living in a nursing home after five years. Network graphs visually demonstrated trends at the subclass level, such as a high prevalence of cardiovascular medications, and showed changes between times, such as an increase in dispensation of central nervous system active medications, particularly cholinesterase inhibitors (15.5% at index compared to 26.4% at five years). Co-dispensing (edge width) remained mostly consistent over time. Metrics derived from the networks highlighted differences, such as increased density (proportion of co-dispensed medication subclasses of all possible pairs) at five years compared to at ascertainment. Node centrality established frequently prescribed medication subclasses (statins, proton pump inhibitors, and beta blockers) as important within networks in this population.

Conclusions

This study offered an introductory review of the fundamental aspects of network analysis and demonstrated the complexity of prescribing patterns in people with incident dementia at the population-level. This showed that networks analysis can be used in future studies to compare population-level prescribing patterns across patient subgroups, prescribers, settings of care and regions to identify important differences.

Keywords

network analysis; population cohort; administrative health data; unsupervised machine learning; dementia

Key points

- Network graphs and associated metrics offer a novel way of summarizing complex prescribing data across populations and may allow the discovery of important medication differences over time, between patient subgroups, and across prescribers.
- For older adults living with dementia in the community, medication network graphs were highly connected and showed a high prevalence of cardiovascular in addition to central nervous system medications.
- Corresponding network graph metrics supported these findings quantitatively and showed increased density at five years compared to at ascertainment.

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Introduction

Older adults living with dementia in community settings have approximately three times the odds of being prescribed five or more medications (polypharmacy) or ten or more medications (hyperpolypharmacy) compared to those without dementia [1]. The risk of adverse events due to drug-drug and drug-disease interactions [2, 3] may be amplified in older adults living with dementia due to a high number of comorbidities [4], increased frailty [5], and pharmaceutical management of symptoms. Cognitive impairment can make it difficult to manage multiple medications with varying prescribing regimens and challenges articulating adverse effects [6, 7]. Inappropriate prescribing can also exacerbate cognitive decline [8]. Understanding medication prescribing and use in this population is a research priority [9] and could inform strategies to reduce polypharmacy and support deprescribing initiatives.

Polypharmacy and hyperpolypharmacy in older adults have been extensively explored [10–19]. The use of cross-sectional studies and binary exposures (e.g., yes/no having polypharmacy) have been highlighted as limitations in current studies examining medication-related adverse events [20]. These approaches may not capture complexity contributing to medication related adverse events adequately, and do not account for changes in prescribing patterns over time or disease progression. There is an opportunity to build on current methods using unsupervised machine learning to characterize prescribing.

Network analysis is a graphical method, frequently applied in social science and ecology [21–23], where a network is a set of objects, called nodes, with connections among them, called edges or links [24]. This method can be applied to medication data, where medications are considered nodes and medications an individual uses concurrently are linked through edges. Network analysis graphs can be used to map medications, providing a visualization of prescribing patterns. Networks can be summarized quantitatively using metrics associated with the number of nodes, size of edges among nodes, and measures of node importance (i.e., centrality). These measures have been used to compare complexity of different ecological systems [21, 25], the strength of connections within groups (e.g., genres) [26], and highlight important “players” within a network [27]. These measures can all be applied in the context of medication networks to compare the medications prescribed to different subgroups (for example, of different patient and prescriber characteristics), to examine the strength of co-prescribing patterns and, possibly, to identify key medications contributing to polypharmacy. A small number of studies have applied network analysis in a pharmacoepidemiology context [28–30]; however, analysis of medication networks has not yet been applied to the context of community-dwelling older adults with dementia.

The goal of this paper was to conduct a network analysis of dispensed medications of community-dwelling people living with dementia across two time points to illustrate this method and its advantages in understanding population-level prescribing.

Methods

Study design

This paper describes multiple networks, drawn cross-sectionally from a population-based cohort derived from health administrative databases in Ontario, Canada.

Data sources

Ontario Drug Benefit (ODB) Plan claims, which record prescription medications dispensed to all people aged ≥ 65 years or those receiving social assistance, were used to capture over 4,400 medications covered by the ODB. Reliability and validity of these data have been established in prior studies [15, 31–34]. Additional databases, such as the Registered Persons Database and Ontario Health Insurance Plan, were used (Supplementary Table 1). These datasets were linked using unique encoded identifiers and analyzed at ICES. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The use of the data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board, although Research Ethics Board approval from University of Toronto was acquired.

Study population

Community-dwelling residents of Ontario, aged ≥ 67 years, with an incident case of dementia between April 1, 2014, and March 31, 2016, were ascertained using a validated algorithm [35] (Supplementary Table 2). The algorithm identifies one hospital billing or three physician claims in two years separated by at least 30 days (ICD-9 (46.1, 290.0, 290.1, 290.2, 290.3, 290.4, 294.x, 331.0, 331.1, 331.5, 331.82); ICD-10 (F00.x, F01.x, F02.x, F03.x, G30.x); OHIP (290, 331)) or one prescription filled for a cholinesterase inhibitor subclass. The case ascertainment date (index date) is the first health system encounter where a diagnosis code for dementia was recorded using the algorithm. This cohort was followed for five years from the index date, censoring for date of death, admission to nursing home, or end of data follow up (March 31, 2021).

Statistical analysis

A medication was considered dispensed when a course of drug therapy (dispensing date + number of days supplied) overlapped the two time points of interest (that is, either the index date or the date of five years following index). Medications were grouped into subclasses using IQVIA's Uniform System of Classification [36]. Multiple medications of the same subclass were counted once for each individual. Pairs of medication subclasses were considered concurrently dispensed when both medications were dispensed to the same individual on the same date. Medication subclasses were grouped into larger categories according to the organ or system they act upon using the Anatomical Therapeutic Chemical (ATC) system [37], represented graphically by colour.

In the network graphs, medication subclasses were represented as nodes, and concurrently dispensed medication subclasses were linked by edges. Network graphs were first plotted using all possible medication subclasses dispensed (referred to as “complete networks”) at index and at five years following index. Network graphs were also restricted to the top 25 most frequently dispensed medications at index and at five years following index, due to the complexity of initial graphs (referred to as “restricted networks”). Subsequently, networks were limited to central nervous system (CNS) active medications (referred to as “CNS-specific networks”) to highlight how the visualizations can be useful to explore subgroups of medications. The networks were mapped using R packages *sna* and *network*. The network graphs were plotted using the Fruchterman-Reingold force-directed layout [38, 39], where nodes sharing more connections are mapped closer together.

Following the creation of graphs, the attributes of the networks – nodes, edges, and centrality metrics – were examined for each of the six network graphs produced. The size of node represents the proportion of the cohort dispensed the medication subclass. Each concurrently dispensed medication subclass pair was plotted with a line (edge) between the corresponding nodes. The width of the edge between nodes is proportional to the number of times subclasses were concurrently dispensed in the population; thus, the line between two medications frequently concurrently dispensed appears thicker than the line between two medications infrequently concurrently dispensed to the same individual.

Metrics were compared between complete networks at index and at five years. First, the total number of nodes (i.e., number of unique medication subclasses dispensed) and average node size (i.e., mean number of individuals to which medication subclasses were dispensed) were reported and standardized to the cohort size. Standardized, a larger number of nodes would indicate a higher mean number of unique medication subclasses, while a larger average node size would suggest a higher mean proportion of dispensed medication subclasses. Next, edges were examined at a network level. The mean width of all edges in the network represents the average number medication pairs concurrently dispensed. Density represents the ratio of the number of edges (medication subclass pairs concurrently dispensed) to the number of edges that could possibly exist at that timepoint, with values closer to 1 indicating more concurrent co-dispensations.

Following examination of metrics summarizing the network, metrics at the node level were examined, again for the complete networks at index and at five years. Three common [40] measures of centrality (betweenness, degree, and eigenvector) were calculated for each of the medication subclasses at index and at five years. Each measure provides a score of how important a specific node is within a network, though the way importance is defined and calculated differs for each measure. A path is the connection between nodes and can be a single edge (if the two medication subclasses were concurrently dispensed at least once) or multiple edges (if two medication subclasses were not concurrently dispensed at least once together, and can only be connected through other nodes). The betweenness centrality score is calculated by measuring the number of shortest paths passing through each specific node. Nodes with high betweenness centrality

act as connectors in networks, bridging from one cluster to another [41]. In medication networks, nodes with high betweenness centrality may connect clusters that contribute to polypharmacy. Degree centrality is the extent to which one node is involved in direct links, that is, the number of other nodes a specific node is connected to [41]. For this study, a node with high degree centrality is commonly concurrently dispensed with other medications. Eigenvector centrality, an extension of degree centrality, measures the number of other nodes that each node is connected to, and considers whether those nodes have high centrality with the theory that more interactions with important nodes indicates more meaningful connections [41]. As eigenvector centrality must be calculated on a symmetric matrix (which can be used in undirected networks – meaning the direction between nodes is mutual and bidirectional), closeness and betweenness centrality were also calculated on a symmetric matrix [40]. The nodes of the top 25 largest centrality measures (and their betweenness, degree, and eigenvector centralities) were displayed.

Results

We identified 99,064 individuals living with incident dementia, and 15,222 were alive and not living in a nursing home after five years ($n=35546$ [36%] dying during follow-up and $n=48,278$ [49%] being admitted to long term care during follow-up). At index, the mean age was 83.1 years and 57.7% of the cohort were female. More than half (53.6%) had over five chronic conditions, including hypertension (82.5%), history of cancer (56.8%), and coronary heart disease (37.2%). (Supplementary Table 3)

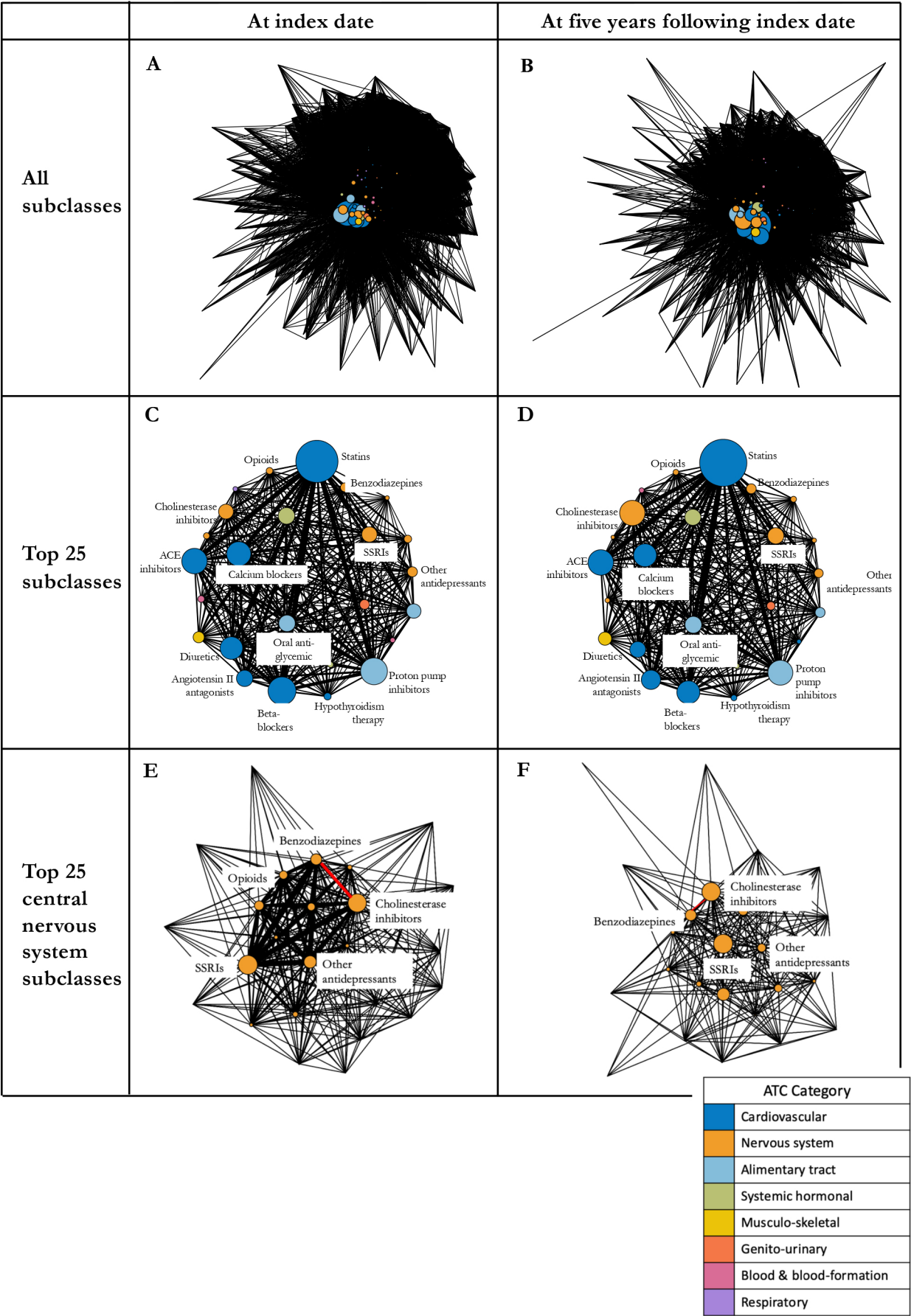
Exploring medication frequency through nodes

Graphs of the complete networks at index (Figure 1A) and at five years (Figure 1B) were visually challenging to interpret as there were 187 unique medication subclasses dispensed at index and 165 subclasses dispensed at five years. Frequently dispensed medication subclasses (large nodes) were clustered in the centre of the graph, with many infrequently dispensed medication subclasses (small nodes) as outliers. Node colour, designated according to the ATC categories at the organ/system level, showed *Cardiovascular System* medications were the most dispensed category with *Nervous System* and *Alimentary Tract* classes following. These patterns were more clearly visible within restricted networks of the top 25 medications (Figure 1C & 1D). Changes between dispensing frequency at index (Figure 1C) and five years later (Figure 1D) were visually apparent by node size differences. For example, cholinesterase inhibitors were prescribed to proportionally more individuals over time (15.5% at index compared to 26.4% at five years).

Exploring concurrent medication use through edges

At index, 5,790 unique medication subclass pairs were concurrently dispensed and plotted. Edge widths were difficult to differentiate in the complete networks (Figure 1A & 1B). The visualizations for restricted networks (Figure 1C & 1D)

Figure 1: Network graphs for complete (all medication subclasses) and restricted (top 25 most common, top 25 most common central nervous system active) groups at index and at five years in community-dwelling older adults living with incident dementia between 2014 and 2016 in Ontario, Canada



showed more frequent concurrent dispensing (thicker edges) between statins and proton pump inhibitors, statins and ACE inhibitors, and statins and beta blockers, respectively. This was consistent with calculated concurrent dispensing frequencies and proportions for this network (Supplementary Table 4). In the CNS-specific networks, the most frequent concurrently dispensed CNS-active medication subclasses included cholinesterase inhibitors and selective serotonin reuptake inhibitors (SSRIs) (2.7%), benzodiazepines and SSRIs (2.8%), and other antidepressants and SSRIs (2.7%) (Figure 1E & 1F), again consistent with calculated frequencies and proportions (Supplementary Table 5). To demonstrate how networks are a tool to highlight specific concurrent dispensing patterns, the connection between opioids and benzodiazepines was highlighted in red in Figure 1E & 1F. This represented 1.6% of individuals being dispensed both opioids and benzodiazepines at index (one of the potentially inappropriate prescribing pairs noted by the Beers criteria [42]).

Exploring differences over time through network metrics including node centrality

In complete networks, there were 187 unique medication subclasses dispensed at index and 165 subclasses dispensed at five years. However, standardized to the population size ($n=99,046$ at index and $n=15,222$ at five years), there were more unique medication subclasses dispensed at five years. The mean number of times a pair of medication subclasses was concurrently dispensed (represented by mean edge width) was 156.7 at index and 36.4 at five years. Standardized to sample size, the cohort at five years were dispensed medication pairs more frequently (i.e., there was more concurrent prescribing): density was 0.6 at index and 0.8 at five years. Decreased mean centrality at a network level between index and five years (degree: 80.9 and 47.2, eigenvector: 0.1 and 0.1, and betweenness: 45.5 and 43.6, at index and five years, respectively) suggested on average that the medication subclasses were less connected at five years (Table 1). However, certain medication subclasses showed increasing importance between index and five years, as described below.

In the complete networks, the medication subclasses with the highest betweenness centrality were statins (461), proton pump inhibitors (459), and angiotensin II antagonists (341) (Table 2), indicating these subclasses most often connect many other medication subclasses (i.e., are frequently present in concurrent dispensations). Betweenness is used to indicate a bridge between clusters, but no distinct clusters on the network graphs were visually apparent. Statins had the highest betweenness centrality at five years and increased in absolute value (641). As with dispensed frequency and visible node size, the betweenness centrality of cholinesterase inhibitors also increased over time (226 at index compared to 477.0 at five years). The medication subclasses with the highest degree centrality were statins (182), proton pump inhibitors (179), and calcium blockers (173). At five years, the maximum degree centrality decreased for statins (149), proton pump inhibitors (143), and oral anti-glycemics (140) (Table 2). This suggests the number subclasses that these

medications were concurrently dispensed with at least once decreased at five years, likely due to the absolute number of medication subclasses decreasing because of a smaller cohort size. Eigenvector centrality was similar across nodes at index (all approximately 0.1), and similarly established statins, proton pump inhibitors, and oral anti-glycemic as important nodes according to this measure. This increase in centrality means the number of other important medication subclasses connected to the statins, proton pump inhibitors, and oral anti-glycemics increased. Despite a decrease in the overall number of medication subclasses concurrently dispensed for statins, proton pump inhibitors, and oral anti-glycemics (i.e., decrease in their degree centrality), the subclasses they were concurrently dispensed with were more connected and important. This potentially reflects a decrease in concurrent dispensation of rare (e.g. lower eigenvector centrality) medications at five years and increased concurrent dispensation of the more common medication subclasses.

Discussion

It is well-known that patterns of medication use can be complex in individuals living with dementia [1, 6, 14, 43–45]. This study offered an introduction to the fundamental aspects of network analysis by examining dispensed medications in a cohort of individuals with incident dementia who were examined at two cross-sectional time points. We used network graphs and associated metrics to explore how this method can be used to characterise and compare prescribing when diagnosis is ascertained in the health administrative data and five years after. The most frequently dispensed medications, primarily those used to treat and manage cardiovascular disease, remained at similar proportions at index and at five years. There were changes in some CNS-active medications through time. Medication networks after five years were denser, which could suggest medication use became more complex through dementia progression, although our findings also suggest selection in who remains living in the community over time. Node-level measures of centrality highlighted frequently prescribed medication subclasses, such as statins, proton pump inhibitors, and beta blockers, as well as CNS-active medication like SSRIs and other antidepressants.

One of the main strengths of network analysis for understanding population prescribing patterns are the visual graphs. In a network graph, key frequencies and concurrent dispensing were identifiable. For example, graphs showed high usage of cardiovascular medications. This medication class is often overlooked in research considering potentially inappropriate prescribing in older adults because of the strong safety and tolerance profile of cardiovascular medications [46]. Despite lower risk profiles relative to CNS-active medications, a narrative review found up to 50% of medication-related harms in older adults may be attributable to cardiovascular medications that is often under-recognized in clinical practice [46]. The appropriateness of cardiovascular medication may change over time in older adults with dementia, and a review highlighted the need for additional research [47]. The role of cardiovascular medications needs to be considered in drug-drug interactions, drug-disease interactions, and polypharmacy at a population-level and in individual medication reviews,

Table 1: Metrics of medication subclass networks at index and at five years in community-dwelling older adults living with incident dementia between 2014 and 2016 in Ontario, Canada

Definition	At index date		At five years following index date*		
	N=99,046 individuals		N=15,222 individuals		
	Per 1,000 individuals ^a		Per 1,000 individuals ^a		
Nodes					
Total unique nodes	Total number of unique medication subclasses	187	1.9	165	10.8
Mean node size (SD)	Mean frequency of dispensed medication subclass	2,492 (6076)	25.2 (61.4)	413 (998)	27.13 (65.6)
Median node size (IQR)	Median frequency of dispensed medication subclasses	181 (20.8–1205.8)	1.83 (0.2-12.2)	35 (6.0–320.3)	2.30 (0.4–21.0)
Edges					
Mean number of edges	Mean number of times a pair of medication subclasses was concurrently dispensed	156.7	1.6	36.4	2.4
Median number of edges (IQR)	Median number of times a pair of medication subclasses was concurrently dispensed	8 (2–44)	0.08 (0.0-0.4)	4 (1–17)	0.26 (0.1–1.1)
Minimum edge width	Minimum number of times a pair of medication subclasses was concurrently dispensed	0	0	0	0
Maximum edge width	Maximum number of times a pair of medication subclasses was concurrently dispensed	17,786	179.6	2,714	178.3
Network density	Ratio of the number of edges (medication subclasses that are concurrently dispensed) that exist to the number of concurrently dispensed medication subclass pairs that could exist	0.6		0.8	
Measures of centrality					
Mean degree	Average degree centrality denotes the extent medication subclasses are more involved in direct connections than others.	80.9		47.6	
Mean betweenness	Average betweenness centrality summarizes the extent medication subclasses are on short pathways between other pairs of medication.	45.5		43.8	
Mean eigenvector	Average eigenvector centrality demonstrates the extent medication subclasses are connected to other medication subclasses with high eigenvector scores.	0.1		0.1	

*For those still surviving in the community (excludes those who have entered nursing homes or are deceased).

^a Values were standardized to show values per 1,000 individuals (by dividing by the N at index, and at 5 years, respectively, and multiplying by 1,000), where appropriate. Measures of density and centrality are not based on the weight of nodes or edges and thus do not need to be standardized.

because of their high prevalence of use in community-dwelling older adults living with dementia [48, 49]. Thus, the graphical aspect of network analyses can complement traditional frequentist statistical approaches as it demonstrates the complexity of prescribing. For example, the information included in the graph representing the top 25 medications reflects a 25 by 25 matrix of the number of co-prescriptions between each medication subclass, a frequency list for 25 medication subclasses, and the ATC classification for each of the 25 medications.

Another important benefit of plotting the medication subclasses as nodes was being able to readily compare two graphs across populations – in our example, medication use at two different timepoints. Many of the CNS-active medication subclasses were more frequently prescribed at five years, which was seen in the increased node size, consistent with CNS-active medication use increasing through disease progression in people living with dementia [6, 50]. Previous studies have also used networks to highlight comparisons across groups. For example, networks stratified by age and sex found differences in patterns between females and males aged 30 to 60 years,

but not in other age groups [29]. Networks for females were more interconnected which authors suggested may be due to a larger number of pathologies and higher pathophysiological complexity [29].

When there are many nodes with multiple connections there is limited utility to the visualization produced when mapping all nodes and edges in a single graph. Network graphs are often used to plot more sparsely connected nodes, such as social networks or in ecology [25, 26]. Restricting the networks, either by frequency to the most common nodes or by ATC category, made the visualizations understandable. In our study, medications were grouped into subclasses because networks at the drug name (i.e., generic medication) level would have been even more dense and less interpretable. Many of the documented (e.g., American Geriatric Society Beers criteria [42]) potentially inappropriate prescribing patterns occur at the drug therapy level, so that when investigating drug-drug interactions, producing networks at this more granular level may be necessary.

Networks are more than a graphical representation of relationships in data. Attributes of the networks – such as

Table 2: Measures of node centrality at index (N=99,046 individuals) and at five years (N=15,222 individuals) for the top 25 most central* subclasses in community-dwelling older adults newly identified as living with dementia between 2014 and 2016 in Ontario, Canada

Medication subclass	Degree ^a		Betweenness ^b		Eigenvector ^c	
	At index	At five years	At index	At five years	At index	At five years
Statins	182	149	461.0	641.0	0.109	0.131
Proton pump inhibitors	179	143	459.2	521.0	0.109	0.129
Calcium blockers	173	135	311.2	360.0	0.108	0.128
Beta-blockers and combinations	172	138	273.6	409.0	0.108	0.128
Diuretics	171	131	272.7	297.2	0.108	0.127
Selective serotonin reuptake inhibitors (SSRIs)	171	132	328.8	284.7	0.108	0.127
Angiotensin II antagonists (ARB)	171	135	340.8	275.5	0.108	0.129
Hypothyroidism therapy	170	127	283.4	212.2	0.107	0.126
Cathartics, laxatives, and stool softeners	169	133	243.1	324.2	0.108	0.127
Oral anti-glycemics	168	140	222.7	383.2	0.108	0.130
Angiotensin-converting enzyme (ACE) inhibitors	168	137	257.4	419.8	0.107	0.128
Other antidepressants	167	128	220.5	213.9	0.107	0.126
Benzodiazepines	167	126	259.3	285.2	0.107	0.124
Cholinesterase inhibitors	166	137	226.1	477.0	0.107	0.129
Bisphosphonates	166	132	276.3	348.8	0.107	0.125
Opioids	164	125	210.6	255.8	0.107	0.124
Corticosteroids	162	121	205.4	166.1	0.106	0.123
Analgesics and antipyretics	160	109	164.3	91.8	0.106	0.117
Prostatic hyperplasia medications	160	116	194.4	150.0	0.105	0.118
Adenosine diphosphate inhibitors	157	107	183.4	82.5	0.105	0.116
Anti-cholinergics	154	107	143.7	103.1	0.104	0.116
Anticonvulsants	154	112	143.5	160.2	0.104	0.116
Antipsychotic agents	154	110	144.4	140.7	0.104	0.117
Gamma-aminobutyric acid (GABA) derivatives	153	107	144.6	112.6	0.104	0.115
Selective beta 2 – adrenergic agonists	151	107	127.4	73.2	0.103	0.117

*After calculating node-level centrality, nodes were sorted from highest (most central) to lowest (least central) by all three measures of centrality evaluated and the top 25 most central are displayed here. ^aDegree centrality denotes the extent medications are more involved in many direct ties (connections) than other nodes. ^bBetweenness centrality summarizes the extent medications are on short pathways between other pairs of medication. ^cEigenvector centrality demonstrates the extent medication subclasses are connected to other medication subclasses with high eigenvector scores.

metrics about nodes, edges, and centrality – can provide insights when applied to medication data and used to make comparisons across patient subgroups, prescribers, health care settings (i.e., nursing homes) and regions. In our example, metrics derived from the network changed between time periods, suggesting more complex prescribing

to those still surviving in the community at five years. Edge metrics in medications networks may be of particular interest when the co-prescribed pairs themselves are important, as in the example above when investigating medication pairs constituting potentially inappropriate prescribing for older adults or those living with dementia [42, 51, 52]. In very dense

and highly clustered medication networks in older adults in Italy [28], proton pump inhibitors were more frequently co-prescribed than expected with other proton pump inhibitors [28], especially since these prescriptions often do not have a clear clinical indication in this population [53].

There were limitations to the practical utility of metrics in our example, but which may be more useful to other research studies applying this method. For our population, there was relatively little difference in the dispensation of medication subclasses between index and 5 years, and thus limited changes in the associated metrics. However, differences in those who remained in the cohort (i.e., alive and not living in a nursing home after five years) likely contribute to this. Several other studies have examined the change in medication use over time in people with dementia, and reported increased, decreased, or no change in proportion of medication subclasses being dispensed. For example, Gnjidic et al examined the impact of dementia diagnosis on potentially inappropriate prescribing, finding an 11% increase in number of medications one year following diagnosis – leading to a 1.2 higher odds of a potentially inappropriate medication [44]. Other studies found minimal changes or no changes in medication subclass use [48], increase in drug-drug interactions or potentially inappropriate prescribing [48] or association between polypharmacy or hyperpolypharmacy with a trajectory of cognitive decline [54] after a dementia diagnosis. This purpose of this study was to examine the usefulness of networks when describing population-level dispensing in older adults with dementia, and thus we did not delve deeply into the clinical appropriateness of medication pairs.

High node-level centrality highlighted medications that were frequently dispensed. Although this validates these network measures in their ability to select important nodes, it suggests complicated calculations of centrality scores may be less useful for densely connected networks if the same information can be obtained from frequency tables. Additionally, in highly connected networks, nodes often have highly associated betweenness, degree, and eigenvector centrality scores [40], suggesting researchers can choose one centrality score that is appropriate for the research question and interpretable for their data. In our study, medication subclasses with high degree centrality are frequently concurrently dispensed with other medications and may be important to highlight in medication reviews. Although not seen in our example, in networks with multiple distinct clusters (also called communities), medications with high betweenness centrality could indicate areas for clinical intervention to reduce polypharmacy. Similar “bridges” have been identified in studies of infectious disease transmission using network analysis [25] where intervention could stop or limit outbreaks. The clusters which could show groups of medications more likely to be prescribed together (i.e., more than medication pairs) were not clear in the commonly prescribed medications, which is consistent with densely connected networks.

Network analysis can be used to reveal both well-known and under-recognized prescribing patterns occurring at a population-level, demonstrate changes over time and/or between subgroups, and might suggest areas to optimize prescribing across populations. This study showed how this method can compare multiple aspects of prescribing

simultaneously, such as the percentage of cohort being prescribed a medication, the strength of co-prescribing, and the overall complexity of prescribing. There are extensions of the method, such as community detection, not explored in this paper, that may be useful in future applications. Continued exploration of techniques novel to pharmacoepidemiology are important for the advancement of our understanding of prescribing in those living with dementia in the community, and in turn, improving medication use in this population.

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Statement of conflict of interest

The authors do not have any financial or personal conflicts of interest to disclose.

Data sharing agreement

The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Ethics approval

The use of the data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board, however we acquired Research Ethics Board approval from University of Toronto.

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Supplementary Table 1: Databases used in cohort creation and for variables used in study

Database name	Database description	Use in current study
Ontario Dementia Database (Dementia)	ICES derived data cohort, based on algorithm which discerns dementia diagnosis in the health administrative data Algorithm*: 1 hospitalization or same-day surgery for dementia <i>and/or</i> 3 physician visits for dementia within 2 years (each at least 30 days apart) <i>and/or</i> filled prescription for a cholinesterase inhibitor (Se=79.3%, Sp=99.1%, PPV=80.4%, NPV=99.0%)	Cohort creation: used to define a cohort of individuals with dementia Case ascertainment date (earliest of the dates described left) used as index date
Ontario Drug Benefit Claims (ODB)	Contains prescription drug claims, received under the Ontario Drug Benefit program, which mostly includes individuals aged ≥ 65	Captures medication use (at the generic, subclass, and class level), including the specific days a prescription was “filled” over
Registered Persons Data Base (RPDB)	Basic demographic information about Ontarians (who have received an Ontario health card)	Basic demographics used as covariates and to describe the cohort over time
Discharge Abstract Database (DAD)	Contains patient data about acute, rehab, chronic and day surgery institutions in Ontario	Used to describe health service use prior to entering the cohort and to define the outcome of fall-related hospitalizations
Ontario Health Insurance Plan (OHIP)	Contains claims paid for by the Ontario Health Insurance Plan	Used to define specific characteristics (such as comorbidities)
Continuing Care Reporting System (CCRS)	Contains clinical and demographic information on residents receiving facility based continuing care services (long-term care [nursing] homes)	Used to define censoring dates (admission to long-term care [nursing] homes) and apply initially exclusion
Census Area Profiles (Census)	Contains demographic information and income information from the Census	Used to define neighbourhood income level and urban/rural residence as covariates

*RL Jaakkimainen et al., “Identification of physician-diagnosed Alzheimer’s disease and related dementias in population-based administrative data: A validation study using family physicians’ electronic medical records”, *Journal of Alzheimer’s Disease*, vol. 54, no. 1, pp. 337–349, Aug. 2016, <https://doi.org/10.3233/JAD-160105>.



Supplementary Table 2: Detailed description of the algorithm used to define incident dementia cases

Description of algorithm used	ICD-9 billing codes and specific prescriptions	Health administrative databases derived from	Sensitivity	Specificity	PPV	NPV
One hospital billing or three physician claims in 2 years separated by at least 30 days or one prescription filled	ICD-9 (46.1, 290.0, 290.1, 290.2, 290.3, 290.4, 294.x, 331.0, 331.1, 331.5, 331.82); ICD-10 (F00.x, F01.x, F02.x, F03.x, G30.x); OHIP (290, 331). Prescription drug reimbursement records were examined for reference to the cholinesterase inhibitor subclass including donepezil (Aricept), galantamine (Reminyl, Reminyl ER, Razadyne, Razadyne ER), rivastigmine (Exelon), tacrine (Cognex), and memantine (Ebixa, Namenda).	Canadian Institute for Health Information hospital Discharge Abstract Database (CIHI-DAD), Ontario Health Insurance Plan (OHIP), National Ambulatory Care Reporting System (NACRS), Ontario Drug Benefit (ODB)	79.3	99.1	80.4	99

*Results of sensitivity, specificity, PPV and NPV from Jaakkimainen, R. L., Bronskill, S. E., Tierney, M. C., Herrmann, N., Green, D., Young, J., Ivers, N., Butt, D., Widdifield, J., & Tu, K. (2016). Identification of Physician-Diagnosed Alzheimer's Disease and Related Dementias in Population-Based Administrative Data: A Validation Study Using Family Physicians' Electronic Medical Records. *Journal of Alzheimer's Disease*, 54(1), 337–349. <https://doi.org/10.3233/JAD-160105>.



Supplementary Table 3: Clinical and demographic characteristics in community-dwelling older adults with incident dementia between 2014 and 2016 in Ontario, Canada at index and at five years

	At index N = 99046	At five years N = 15222
Age		
Mean (SD)	83.1 (7.2)	78.9 (6.4)
67-74	13853 (14.0)	4156 (27.3)
75-84	40586 (41.0)	7950 (52.2)
85+	44607 (45.0)	3116 (20.5)
Female	57143 (57.7)	9046 (59.4)
Urban location	86549 (87.6)	13809 (90.8)
Neighbourhood Income Quintile		
Lowest (1)	23790 (24.1)	3006 (19.8)
2	22345 (22.6)	3224 (21.2)
3	18869 (19.1)	2893 (19.1)
4	17009 (17.2)	2844 (18.7)
Highest (5)	16738 (17.0)	3216 (21.2)
Number of chronic conditions		
0-1	5349 (5.4)	1039 (6.8)
2	8584 (8.7)	1672 (11.0)
3	14108 (14.2)	2482 (16.3)
4	17958 (18.1)	3035 (19.9)
5+	53047 (53.6)	6992 (45.9)
Prevalence of specific chronic conditions		
AMI	7751 (7.8)	732 (4.8)
Asthma	14185 (14.3)	2244 (14.7)
Cancer	56260 (56.8)	8295 (54.5)
Arrhythmia	22305 (22.5)	2599 (17.1)
Coronary heart disease	36859 (37.2)	4695 (30.8)
COPD	13724 (13.7)	1267 (8.3)
CHF	17168 (17.3)	1265 (8.3)
Diabetes	34326 (34.7)	4653 (30.6)
Hypertension	81740 (82.5)	11633 (76.4)
Mood disorders	53712 (54.2)	8882 (58.4)
Mental health	23406 (23.6)	3821 (25.1)
Osteoarthritis	72203 (72.9)	11141 (73.2)
Osteoporosis	16605 (16.8)	2795 (18.4)
Renal	12882 (13.0)	1061 (7.0)
Rheumatoid arthritis	3007 (3.0)	401 (2.6)
Stroke	11493 (11.6)	1254 (8.2)
Have at least one of health system visit in year prior		
Home care	31765 (32.1)	2244 (14.7)
Mental health hospitalizations	269 (0.3)	39 (0.3)
Rehabilitation stays	2147 (2.3)	181 (1.2)
Hospitalization	16697 (16.9)	1763 (11.6)
Complex continuing care	827 (0.8)	44 (0.3)
Emergency department	35599 (35.9)	4573 (30.0)
Number of medications		
Median (IQR)	4 (2-7)	4 (2-6)
0-1	17265 (17.4)	2501 (16.4)
2-4	33024 (33.3)	5888 (38.7)
5-9	40929 (41.3)	5924 (38.9)
=>10	7828 (7.9)	909 (6.0)

Supplementary Table 4: Common medication pairs concurrently dispensed in community-dwelling older adults with incident dementia between 2014 and 2016 in Ontario, Canada at index (N = 99,046) and at five years following (N = 15,222)

Medication dyad	Frequency (%)	
	At index	At five years
STATINS + BETA-BLOCKERS	17786 (18.0)	2444 (16.1)
STATINS + ACE INHIBITORS	16285 (16.4)	2714 (17.9)
STATINS + PROTON PUMP INHIBITORS	15912 (16.1)	2456 (16.1)
STATINS + CALCIUM BLOCKERS	13995 (14.1)	2234 (14.7)
STATINS + DIURETICS	12949 (13.1)	1579 (10.3)
STATINS + ORAL ANTI-GLYCEMICS	12397 (12.5)	2079 (13.7)
BETA-BLOCKERS + DIURETICS	11088 (11.2)	979 (6.4)
PROTON PUMP INHIBITORS + BETA-BLOCKERS	11021 (11.1)	1249 (8.2)
BETA-BLOCKERS + ACE INHIBITORS	10467 (10.6)	1323 (8.7)
STATINS + ANGIOTENSIN II ANTAGONIST	9873 (10.0)	1957 (12.9)
BETA-BLOCKERS + CALCIUM BLOCKERS	9303 (9.4)	1187 (7.8)
PROTON PUMP INHIBITORS + DIURETICS	8975 (9.1)	845 (5.6)
PROTON PUMP INHIBITORS + CALCIUM BLOCKERS	8826 (8.9)	1154 (7.6)
CALCIUM BLOCKERS + ACE INHIBITORS	8665 (8.8)	1234 (8.10)
STATINS + HYPOTHYROIDISM THERAPY	8619 (8.7)	1393 (9.2)

*ACE = Angiotensin-converting enzyme.

Supplementary Table 5: Common central nervous system-active medication pairs concurrently dispensed in community-dwelling older adults with incident dementia between 2014 and 2016 in Ontario, Canada at index (N=99,046) and at five years following (N = 15,222)

Medication dyad	Frequency (%)	
	At index	At five years
SSRIs + CHOLINESTERASE INHIBITORS	2665 (2.7)	693 (4.5)
ANTIPSYCHOTIC AGENTS + SSRIs	2031 (2.1)	281 (1.8)
BENZODIAZEPINE DERIVATIVES + SSRIs	1804 (1.8)	493 (3.2)
ANALGESICS & ANTIPYRETICS + ANTIDEPRESSANTS	1645 (1.7)	128 (0.8)
ANTIDEPRESSANTS + CHOLINESTERASE INHIBITORS	1644 (1.7)	377 (2.5)
ANTIDEPRESSANTS + SSRIs	1614 (1.6)	399 (2.6)
OPIOIDS + SSRIs	1614 (1.6)	218 (1.4)
OPIOIDS + ANTIDEPRESSANTS	1574 (1.5)	198 (1.3)
ANTIPSYCHOTIC AGENTS + ANTIDEPRESSANTS	1459 (1.5)	183 (1.2)
BENZODIAZEPINE DERIVATIVES + CHOLINESTERASE INHIBITORS	1442 (1.5)	453 (2.9)
ANALGESICS & ANTIPYRETICS + CHOLINESTERASE INHIBITORS	1269 (1.3)	243 (1.6)
OPIOIDS + ANALGESICS & ANTIPYRETICS	1166 (1.2)	75 (0.4)
LEVODOPA + CHOLINESTERASE INHIBITORS	1067 (1.1)	143 (0.9)
ANTIPSYCHOTIC AGENTS + CHOLINESTERASE INHIBITORS	1044 (1.1)	219 (1.4)

*SSRI = selective serotonin reuptake inhibitors.