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Epidemiology

Patterns of multimorbidity and pharmacotherapy: a total population cross-sectional study

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Abstract

Background: Treatment of multimorbid patients can be improved. Development of patient-centred care of high-quality requires context-bound understanding of the multimorbid population's patterns of demographics, co-morbidities and medication use.
Objective: The aim of this study was to identify patterns of multimorbidity in the total population of Region Stockholm, Sweden, by exploring demographics, claimed prescription drugs, risk of mortality and non-random association of conditions.
Methods: In this cross-sectional descriptive population-based cohort study, we extracted data from the Swedish VAL database (*N* = 2 323 667) including all consultations in primary and specialized outpatient care, all inpatient care and all prescriptions claimed during 2017. We report number of chronic conditions and claimed prescription drugs, physical and mental co-morbidity, and 1-year mortality. We stratified the analyses by sex. We examined non-random associations between diseases using cluster analysis.
Results: In total, 21.6% had multimorbidity (two or more chronic conditions) and 24.1% had polypharmacy (more than five claimed prescription drugs). Number of claimed drugs, co-occurrence of mental and physical conditions, and 1-year mortality increased as multimorbidity increased. We identified seven multimorbidity clusters with clinically distinct characteristics. The smallest cluster (7% of individuals) had prominent cardiovascular disease, the highest 1-year mortality rate, high levels of multimorbidity and polypharmacy, and was much older. The largest cluster (27% of individuals) was younger and heterogenous, with primarily mental health problems.
Conclusions: Individuals with chronic conditions often show clinical complexity with both concordant and discordant conditions and polypharmacy. This study indicates that clinical guidelines addressing clustering of conditions may be one strategy for managing complexity.

Key words: Chronic disease, frailty, multimorbidity, phamacology/drug reactions, population health, primary health care

Key Messages

- Multimorbidity present in 22% of individuals in the Stockholm region.
- Increased multimorbidity associated with high prevalence of sedatives.
- Clinical multimorbidity management guidelines should address clustering of conditions.

Introduction

As multimorbidity, defined as two or more chronic health conditions, becomes the norm, patients are increasingly complex in primary care where most consultations take place (1–4). Degree of multimorbidity has been shown to be highly correlated with health care resource use and costs in a variety of contexts (5–8). Multimorbidity leads to polypharmacy, increased hospitalization and non-adherence, and increased potentially inappropriate medication (9,10). Despite this, evidence-based management guidelines for common chronic conditions are usually based on a single-disease paradigm and seldom take into account co-morbidities or patient complexity (11,12). The NICE guidelines and comprehensive review of the literature published 2016 recommend a shift in primary care towards systematic identification of patients with multimorbidity who need individually tailored management (13).

High-quality patient-centred care requires context-bound understanding of the multimorbid population's patterns of demographics, co-morbidities and medication use (14). In Sweden, there is a national impetus to improve care of individuals with multimorbidity (15). The Swedish Study on Aging and Care in Kungsholmen (SNAC-K), following a cohort of individuals aged 60+ in central Stockholm, indicated that some constellations of multimorbidity and trajectories of development are likely to lead to decreased function and cognitive ability (16–18). However, population-based patterns of multimorbidity, medication and increased risk for mortality have yet to be described.

The aim of this study was to identify patterns of multimorbidity in the total population of Region Stockholm, Sweden, by exploring demographics, claimed prescription drugs, risk of mortality and non-random association of conditions.

Material and methods

In this cross-sectional descriptive population-based cohort study, we used the Swedish VAL database to identify the entire population of Region Stockholm 31 December 2017 (N = 2 323 667).

Database and study sample

Region Stockholm (Stockholm city and surrounding suburban and rural areas) has 2.3 million residents, ~20% of the total population of Sweden. In Sweden, all necessary medical care is funded by public health insurance covering all legal residents. Services are provided by region, either at public facilities or by private providers under contractual agreement with the region. Providers are obligated to record diagnoses and file reports, including information on health care utilization, reasons for hospitalizations and consultations in primary and specialist care, all diagnosis codes, data on prescriptions and socio-demographics. In Region Stockholm, this information is automatically collated in the comprehensive health administration VAL database used for health care planning, practice remuneration and quality assessment. All living residents of Region Stockholm are registered in VAL. Date of death as well as migration in and out of the region are included in VAL. The VAL database is described in more detail elsewhere (19).

In this study, we included data from all consultations in primary care, all consultations in specialized outpatient care, all inpatient care and all prescriptions claimed during 2017. All extracted data were anonymized.

Variable identification

Chronic conditions and multimorbidity

As we wanted to investigate multimorbidity separately from pharmacotherapy, we revised a definition based on 40 chronic health conditions identified as internationally clinically important (2) using only ICD codes (Supplementary Table 1). We define multimorbidity as two or more chronic health conditions across the 40 listed chronic conditions. We report degree of multimorbidity using the intervals 0–1, 2–4, 5–9 and 10+ diagnoses, based on current literature indicating that 5+ and 10+ diagnoses reflect clinically relevant cut points (2).

Pharmacotherapy

We collected the Anatomical Therapeutic Chemical (ATC) Classification System codes for all the individual's claimed prescription drugs during 2017. Each ATC code was counted as one claimed prescription in the analysis to avoid overcounting because of drug iteration. We report number of claimed prescription drugs in the intervals 0–4, 5–9, 10–14 and 15+, using accepted previous definitions of polypharmacy (20), and the current literature indicating that 15+ medications compared with less than five medications substantially increases risk for adverse events (21).

Analyses

All descriptive data are reported as frequencies. For the 40 chronic conditions, we described median age, median number of co-morbidities, median number of medications and 1-year mortality. We identified the top 12 most common multimorbid conditions as those with the highest median number of co-morbidities and the largest number of individuals. For each degree of multimorbidity, we reported sex, age group (10-year intervals), number of claimed prescription drugs, frequency of physical–mental health co-morbidity, frequency for the top 12 conditions and 1-year mortality rate, calculated using mortality data from 1 January until 31 December 2018. For graphical display we defined age groups in 20-year intervals.

We stratified data for sex and repeated frequency calculations. Relative risk was calculated for women compared with men for age group (10-year intervals), number of claimed prescription drugs, frequency of physical–mental health co-morbidity, frequency of the top 12 conditions and 1-year mortality rate.

We use percentages and graphical display to describe the proportions of the top 25 co-morbidities and the proportions of the top 25 claimed medications for the top 12 conditions.

To examine non-random associations between diseases in individuals, we identified individuals with at least two conditions and conducted a cluster analysis. To find the optimum number of clusters the data was initially grouped into 50 clusters using the FASTCLUS k-means procedure with 100 iterations. We used the CLUSTER procedure using the centroid method to determine the optimal number

of clusters. The Cubic Clustering Criterion, Pseudo *F* and Pseudo *T*-Squared statistics all suggested seven clusters which was deemed appropriate after clinical analysis. Last, individuals were grouped into seven clusters using the *k*-means procedure with 100 iterations.

Data analyses were performed with SAS EG 7.1. Due to the nature of the database, there was no missing data.

Results

Table 1 shows demographics, multimorbidity and pharmacotherapy characteristics, and 1-year mortality rate of all 2 323 667 individuals residing in the Stockholm region during 2017. 21.6% had multimorbidity. The top 12 conditions associated with multimorbidity were heart failure, chronic kidney disease, coronary heart disease, atrial fibrillation, COPD, stroke/TIA, dementia, peripheral vascular disease, hypertension, diabetes and cancer (Supplementary Table 2). One-year all-cause mortality increased as number of diagnoses increased (from 0.1% to 19.3%). There was 2.7%, absolute 1-year risk of mortality in multimorbid patients, but these deaths represented most deaths in the total population (>85%). In the total population, 24% had more than five claimed prescription drugs and number of drugs increased as the number of diagnoses increased. Of individuals with >10 diagnoses, 80% had >15 medications. Co-occurrence of mental and physical conditions increased with number of diagnoses (24.1–58.5%).

With age, the proportion of individuals with multimorbidity and number of co-morbidities increased (Fig. 1a), as did number of claimed prescription drugs (Fig. 1b). Multimorbidity increased after age 50, existed in more than half of the population at age 70, and in >80% over age 80. A similar age-related pattern was seen in the proportion of individuals with >5, 10 and 15 claimed prescription drugs. However, after the age of 90, the population showed decreased multimorbidity and polypharmacy.

Disease patterns differed between the sexes (Table 2, Supplementary Table 3). Under 60, women were more likely than men to have multimorbidity, with elevated risk of 10+ conditions

Table 1. Demography, pharmacotherapy, common multimorbid diseases, physical–mental health co-morbidity and 1-year mortality by number of diagnoses

Number of diagnoses					
	All	0–1	2–4	5–9	10+
N (%)	2 323 667 (100%)	1 822 056 (78.4%)	424 489 (18.3%)	75 305 (3.2%)	1817 (0.1%)
Sex					
Female	1 162 569 (50.0%)	884 840 (48.6%)	238 850 (56.3%)	38 089 (50.6%)	790 (43.5%)
Male	1 161 098 (50.0%)	937 216 (51.4%)	185 639 (43.7%)	37 216 (49.4%)	1027 (56.5%)
Age					
0–9	295 754 (12.7%)	286 529 (15.7%)	9204 (2.2%)	21 (0.03%)	0 (0%)
10–19	258 750 (11.1%)	241 006 (13.2%)	17 538 (4.1%)	206 (0.3%)	0 (0%)
20–29	320 453 (13.8%)	289 557 (15.9%)	29 946 (7.1%)	950 (1.3%)	0 (0%)
30–39	350 272 (15.1%)	312 669 (17.2%)	36 113 (8.5%)	1481 (2.0%)	9 (0.5%)
40–49	327 025 (14.1%)	2781 13 (15.3%)	46 153 (10.9%)	2742 (3.6%)	17 (0.9%)
50–59	289 043 (12.4%)	215 439 (11.8%)	66 978 (15.8%)	6560 (8.7%)	66 (3.6%)
60–69	219 562 (9.5%)	123 922 (6.8%)	82 976 (19.6%)	12 450 (16.5%)	214 (11.78)
70–79	174 220 (7.5%)	60 800 (3.3%)	89 295 (21.0%)	23 563 (31.3%)	562 (30.9%)
80–89	70 159 (3.0%)	11 903 (0.7%)	37 139 (8.8%)	20 383 (27.1%)	734 (40.4%)
90–99	17 963 (0.8%)	2042 (0.1%)	8904 (2.1%)	6803 (9.0%)	214 (11.8%)
100+	466 (0.0%)	76 (0.0%)	243 (0.06%)	146 (0.2%)	1 (0.06%)
Number of medications					
0–4	1 762 514 (75.9%)	1 607 117 (88.2%)	152 043 (35.8%)	3337 (4.4%)	17 (0.9%)
5–9	365 566 (15.7%)	180 121 (9.9%)	167 089 (39.4%)	18 288 (24.3%)	68 (3.7%)
10–14	125 794 (5.4%)	27 816 (1.5%)	72 501 (17.1%)	25 200 (33.5%)	277 (15.2%)
15+	69 793 (3.0%)	7002 (0.4%)	32 856 (7.7%)	28 480 (37.8%)	1455 (80.1%)
Common multimorbid diseases					
Heart failure	36 444 (1.6%)	574 (0.03%)	12 621 (3.0%)	21 905 (29.1%)	1344 (74.0%)
Chronic renal disease	25 443 (1.1%)	1303 (0.07%)	10 417 (2.5%)	12 816 (17.0%)	907 (49.9%)
Coronary heart disease	63 778 (2.7%)	3292 (0.2%)	32 842 (7.7%)	26 382 (35.0%)	1262 (69.5%)
Atrial fibrillation	58 841 (2.5%)	3997 (0.2%)	28 064 (6.6%)	25 582 (33.0%)	1198 (65.9%)
COPD	48 620 (2.1%)	5406 (0.3%)	25 644 (6.0%)	16 613 (22.1%)	957 (52.7%)
Stroke/TIA	42 027 (1.8%)	2826 (0.2%)	21 260 (5.0%)	17 067 (22.7%)	874 (48.1%)
Dementia	18 202 (0.8%)	1329 (0.07%)	9497 (2.2%)	7050 (9.4%)	326 (17.9%)
Peripheral vascular disease	14 220 (0.6%)	1896 (0.1%)	6633 (1.6%)	5326 (7.1%)	365 (20.1%)
Bronchiectasis	2411 (0.1%)	282 (0.02%)	1269 (0.3%)	801 (1.1%)	59 (3.3%)
Hypertension	334 935 (14.4%)	69 061 (3.8%)	201 517 (47.5%)	62 623 (83.2%)	1734 (95.4%)
Diabetes	105 534 (4.5%)	13 141 (0.7%)	63 300 (14.9%)	27 997 (37.2%)	1096 (60.3%)
Cancer	98 369 (4.23%)	20 068 (1.1%)	54 844 (12.9%)	22 590 (30.0%)	867 (47.7%)
Physical–mental health co-morbidity	133 942 (5.8%)	0 (0%)	102 069 (24.1%)	30 810 (40.9%)	1063 (58.5%)
Anxiety disorders	131 088 (5.6%)	41 659 (2.3%)	75 458 (17.8%)	13 516 (18.8%)	455 (25.0%)
Depression	72 286 (3.1%)	14 165 (0.8%)	46 662 (11.0%)	11 061 (14.7%)	398 (21.9%)
Alcohol problems	60 671 (2.6%)	17 441 (1.0%)	33 347 (7.9%)	9529 (12.7%)	354 (19.5%)
Substance misuse	30 591 (1.3%)	7434 (0.4%)	18 035 (4.3%)	4888 (6.5%)	234 (12.9%)
1-Year mortality	15 842 (0.7%)	2315 (0.1%)	7122 (1.7%)	6054 (8.0%)	351 (19.3%)

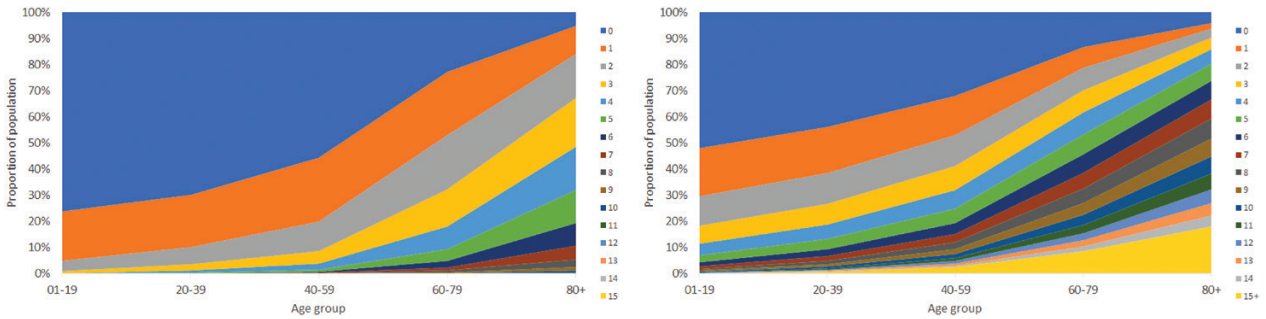

Figure 1. Proportion of the population in 2017 (N = 2 323 667) with (A) number of *diagnoses* per age group and (B) numbers of claimed prescription drugs per age group.

in age groups 30–39 and 40–59 [relative risk (RR) 4.55 and 4.23, respectively]. After 60, there were more women than men that were healthy or had only one condition (RR 1.15) and this likelihood increased with increasing age (to RR 3.54 at age 90–99). Women were more likely than men to have polypharmacy. Men suffered multimorbidity due to cardiovascular disease, kidney disease and diabetes to a higher degree than women. Women had higher prevalence of multimorbidity including lung disease and dementia. Compared with men, women were more likely to have both physical and mental health conditions.

For individuals with the top 12 conditions, 6 of the top 10 drugs were medications aimed at improvement of cardiovascular health (Table 3). There was high prevalence of potentially inappropriate medications: hypnotics and sedatives were prescribed to between 19.8% (diabetes) and 33.5% (dementia); anxiolytics to between 10% (diabetes) and 27% (dementia); proton-pump inhibitors to between 23.3% (hypertension) and 35.2% (heart failure). Additionally, opioids were the 14th most prescribed drug and were prescribed to between 16.5% (hypertension) and 25.6% (heart failure). Antidepressants were claimed by between 15% (hypertension, cancer) and 41% (dementia).

In the top 12 conditions, we identified the 25 most common co-morbidities (Supplementary Table 4). Hypertension was the most common, found in 44–81%, followed by diabetes (11–32%), hearing loss (10–16%) and thyroid disorders (12–16%). Anxiety disorders and depression were associated with all 12 common conditions, but at low rates (5–8% and 5–7%, respectively).

Cluster analysis examining non-random associations between diseases in the 501 611 individuals with at least two conditions, resulted in seven clusters (Table 4). The largest cluster included the 27% of individuals with multimorbidity not in other clusters. This cluster was characterized by lower median age, number of co-morbidities and number of drugs compared to the other clusters. No single disease was dominant, but in this group, 40% had anxiety, 26% depression, 17% alcohol problems and 14% had irritable bowel syndrome (IBS). The second largest cluster consisted of individuals with hypertension but *without* diabetes, cancer, thyroid disorders or hearing loss, and with a low degree of other cardiovascular disease, followed by a cluster of individuals with hypertension and diabetes. The fourth cluster consisted of individuals with cancer and hypertension. In the fifth cluster, thyroid disorders, 18% had anxiety, 10% had depression, 38% had hypertension and 9% had IBS. In the sixth cluster, hearing loss, there was a broad spectrum of conditions with hypertension and anxiety disorders most common. The smallest cluster, 7% of individuals, was characterized by hypertension in combination with one or several other cardiovascular diseases and to some extent diabetes. This cluster had a higher median age, number of co-morbidities and number of drugs, and higher 1-year mortality rate compared with the other clusters.

Discussion

Summary of the findings

In this total population study, the proportion of individuals with multimorbidity and polypharmacy increased with age until age 90, after which multimorbidity and polypharmacy decreased drastically. Multimorbid individuals had a low absolute 1-year risk of mortality but represented most deaths in the total population. Increased number of conditions was associated with increased risk for concomitant physical–mental disease. The top 12 conditions associated with multimorbidity were heart failure, chronic kidney disease, coronary heart disease, atrial fibrillation, COPD, stroke/TIA, dementia, peripheral vascular disease, hypertension, diabetes and cancer, all associated with high prevalence of multiple co-morbid conditions and high prevalence of prescribed medication, including potentially inappropriate medications. Women were more likely than men to have multimorbidity before age 60, less likely to have multimorbidity after age 80 and more likely than men to have lung disease, dementia and co-morbid physical and mental conditions. We identified seven clinically distinct non-randomly clustered conditions: a mental health cluster; a thyroid disease cluster; a cancer cluster; a hearing loss cluster; and a hypertension cluster, a hypertension-metabolic cluster and a cardiovascular cluster.

Relationship with previous research

Our study population resembles other cohorts. In a cross-sectional study of individuals registered at medical practices in Scotland, 23.2% had multimorbidity (2). As in the current study, prevalence increased with increasing age and prevalence of mental health disorders increased as the number of physical co-morbidities increased (2). In a retrospective cohort study of a random sample of primary care attenders in England, 16% of individuals had multimorbidity (22). Prevalence of multimorbidity in a population-based study in Ontario, Canada was 24.3% and patterns of concurrent disease were complex, similar to our study (3). No previous study has reported both the patterns of multimorbidity and polypharmacy on a population level.

The top 12 conditions identified in our study population overlap with clinically relevant conditions collated in a systematic review (23), but also include chronic kidney disease, dementia and peripheral vascular disease, while depression and arthritis do not make our

Table 2. Relative risk proportion of women compared to men for demography, pharmacotherapy, common multimorbid diseases, physical–mental health co-morbidity and 1-year mortality by number of diagnoses

	All	0–1	2–4	5–9	10+
Relative risk proportion of women versus men	N/A	0.94 (0.94-0.94)	1.29 (1.28–1.29)	1.02 (1.01–1.04)	0.77 (0.70–0.84)
Age					
0–9	0.94 (0.93–0.94)	1.00 (1.00–1.01)	0.62 (0.60–0.65)	1.59 (0.66–3.83)	N/A
10–19	0.93 (0.93–0.94)	0.96 (0.95–0.97)	1.11 (1.08–1.14)	3.31 (2.39–4.58)	N/A
20–29	0.99 (0.98–1.00)	0.99 (0.98–0.99)	1.35 (1.32–1.38)	3.36 (2.89–3.91)	N/A
30–39	0.96 (0.95–0.96)	0.94 (0.94–0.95)	1.39 (1.36–1.42)	2.64 (2.36–2.96)	4.55 (0.95–21.8)
40–49	0.97 (0.96–0.97)	0.94 (0.94–0.95)	1.21 (1.19–1.23)	1.95 (1.80–2.11)	4.23 (1.38–12.9)
50–59	0.98 (0.97–0.99)	0.98 (0.97–0.99)	0.89 (0.88–0.91)	1.19 (1.13–1.24)	1.30 (0.81–2.09)
60–69	1.03 (1.02–1.04)	1.15 (1.14–1.16)	0.77 (0.77–0.78)	0.79 (0.77–0.82)	0.96 (0.75–1.24)
70–79	1.13 (1.12–1.14)	1.46 (1.44–1.49)	0.86 (0.85–0.87)	0.72 (0.71–0.74)	0.87 (0.76–1.01)
80–89	1.48 (1.46–1.50)	2.15 (2.07–2.23)	1.27 (1.25–1.30)	1.05 (1.03–1.08)	0.96 (0.85–1.07)
90–99	2.46 (2.38–2.54)	3.54 (3.20–3.93)	2.34 (2.23–2.45)	1.80 (1.72–1.89)	1.32 (1.03–1.70)
100+	5.95 (4.59–7.70)	6.99 (3.59–13.6)	5.52 (3.77–8.09)	4.31 (2.84–6.54)	N/A
Number of medications					
0–4	0.88 (0.87–0.88)	0.92 (0.92-0.92)	0.78 (0.78–0.79)	0.67 (0.63–0.72)	0.54 (0.19–1.53)
5–9	1.43 (1.42–1.44)	1.84 (1.82–1.85)	0.98 (0.97–0.99)	0.71 (0.69–0.72)	0.28 (0.15–0.52)
10–14	1.64 (1.62–1.66)	2.66 (2.60–2.73)	1.34 (1.32–1.36)	0.93 (0.91–0.95)	0.58 (0.45–0.73)
15+	1.93 (1.90–1.96)	3.05 (2.89–3.21)	1.92 (1.87–1.96)	1.40 (1.37–1.42)	1.17 (1.12–1.22)
Common multimorbid diseases					
Heart failure	0.87 (0.85–0.89)	0.80 (0.68–0.94)	0.69 (0.67–0.72)	0.85 (0.83–0.87)	0.98 (0.93–1.04)
Chronic renal disease	0.70 (0.68–0.72)	0.69 (0.62–0.78)	0.57 (0.55–0.60)	0.68 (0.65–0.70)	0.72 (0.65–0.79)
Coronary heart disease	0.63 (0.62–0.64)	0.43 (0.40–0.46)	0.47 (0.46–0.48)	0.68 (0.67–0.70)	0.93 (0.87–0.99)
Atrial fibrillation	0.73 (0.72–0.74)	0.42 (0.39–0.45)	0.58 (0.56–0.59)	0.77 (0.75–0.78)	0.84 (0.78–0.90)
COPD	1.34 (1.31–1.36)	1.30 (1.23–1.37)	1.18 (1.15–1.21)	1.14 (1.11–1.17)	1.13 (1.03–1.23)
Stroke/TIA	0.91 (0.89–0.92)	0.99 (0.92–1.06)	0.74 (0.72–0.76)	0.84 (0.82–0.86)	0.94 (0.85–1.04)
Dementia	1.72 (1.67–1.77)	2.65 (2.35–2.98)	1.66 (1.59–1.73)	1.24 (1.19–1.30)	1.11 (0.91–1.35)
Peripheral vascular disease	1.33 (1.28–1.37)	2.39 (2.16–2.63)	1.26 (1.20–1.32)	0.89 (0.85–0.94)	0.96 (0.80–1.16)
Bronchiectasis	2.16 (1.98–2.36)	2.34 (1.82–3.00)	1.87 (1.66–2.11)	1.85 (1.60–2.14)	1.77 (1.06–2.94)
Hypertension	1.07 (1.06–1.07)	1.18 (1.16–1.20)	0.85 (0.84–0.86)	0.93 (0.92–0.93)	0.98 (0.96–1.00)
Diabetes	0.75 (0.74–0.76)	0.59 (0.57–0.61)	0.60 (0.60–0.61)	0.77 (0.75–0.78)	0.91 (0.84–0.98)
Cancer	1.00 (0.99–1.02)	1.29 (1.26–1.33)	0.82 (0.81–0.84)	0.74 (0.72–0.75)	0.75 (0.68–0.83)
Physical–mental health co-morbidity	1.56 (1.54–1.57)	N/A	1.28 (1.26–1.29)	1.31 (1.29–1.33)	1.16 (1.07–1.25)
1-Year mortality	1.07 (1.03–1.10)	0.97 (0.89–1.05)	0.97 (0.92–1.01)	0.95 (0.91–1.00)	0.90 (0.75–1.10)

Table 3. The 12 most common conditions with prevalence of the top 25 claimed medication groups (*N* = 469 778)

		Heart failure	Chronic renal disease	Coronary heart disease	Atrial fibrillation	COPD	Stroke/TIA	Dementia	Peripheral vascular disease	Bronchiectasis	Hypertension	Diabetes	Cancer
	N (%)	36444 (1.6%)	25443 (1.1%)	63778 (2.7%)	58841 (2.5%)	48620 (2.1%)	42027 (1.8%)	18202 (0.8%)	14220 (0.6%)	2411 (0.1%)	334935 (14.4%)	105534 (4.5%)	98369 (4.2%)
	Number of drugs (median)	12	11	10	9	10	9	9	8	9	7	8	7
B01A	ANTITHROMBOTIC AGENTS	80%	54%	83%	83%	38%	75%	51%	56%	26%	36%	39%	33%
C07A	BETA BLOCKING AGENTS	77%	53%	70%	74%	33%	42%	34%	36%	23%	39%	37%	27%
C10A	LIPID MODIFYING AGENTS, PLAIN	47%	44%	69%	38%	30%	55%	27%	46%	19%	37%	53%	25%
N02B	ANALGESICS AND ANTIPYRETICS	46%	41%	39%	38%	38%	39%	47%	35%	35%	30%	32%	31%
C08C	CALCIUM CHANNEL BLOCKERS	25%	39%	29%	24%	22%	30%	21%	30%	15%	37%	30%	20%
C09A	ACE INHIBITORS, PLAIN	42%	29%	33%	27%	18%	26%	20%	22%	10%	29%	27%	15%
A02B	DRUGS FOR PEPTIC ULCER, REFLUX	35%	34%	35%	27%	30%	29%	26%	28%	31%	23%	25%	24%
C09C	ANGIOTENSIN II RECEPTOR BLOCKERS	29%	30%	24%	23%	18%	20%	13%	18%	16%	28%	21%	15%
N05C	HYPNOTICS AND SEDATIVES	32%	28%	26%	27%	29%	29%	34%	26%	25%	21%	20%	23%
J01C	PENICILLINS	26%	25%	21%	23%	27%	20%	15%	23%	38%	19%	20%	22%
M01A	NSAIDS	9%	9%	14%	8%	18%	11%	6%	15%	18%	17%	17%	16%
A06A	DRUGS FOR CONSTIPATION	29%	26%	23%	24%	22%	27%	41%	21%	23%	17%	17%	23%
B03B	VITAMIN B12 AND FOLIC ACID	30%	30%	24%	24%	21%	26%	44%	22%	18%	18%	22%	17%
N02A	OPIOIDS	26%	23%	21%	21%	23%	21%	23%	22%	19%	16%	17%	19%
N06A	ANTIDEPRESSANTS	20%	18%	17%	16%	21%	25%	41%	17%	17%	15%	16%	15%
D02A	EMOLLIENTS AND PROTECTIVES	25%	23%	18%	20%	18%	20%	34%	18%	19%	14%	17%	15%
A10B	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	14%	12%	17%	11%	10%	11%	8%	11%	5%	14%	56%	7%
R03A	ADRENERGICS, INHALANTS	20%	14%	15%	14%	53%	12%	9%	15%	48%	13%	12%	11%
D07A	CORTICOSTEROIDS, PLAIN	14%	14%	13%	14%	15%	13%	12%	14%	14%	12%	13%	13%
R06A	ANTIHISTAMINES FOR SYSTEMIC USE	10%	11%	10%	9%	16%	11%	8%	11%	17%	11%	11%	11%
H03A	THYROID PREPARATIONS	13%	13%	11%	11%	12%	11%	15%	11%	12%	11%	12%	11%
N05B	ANXIOLYTICS	16%	13%	13%	13%	17%	15%	27%	12%	13%	11%	10%	11%
R05C	EXPECTORANTS EXCL. COMBINATIONS	17%	13%	13%	13%	28%	12%	10%	13%	38%	10%	10%	11%
H02A	CORTICOSTEROIDS FOR SYSTEMIC USE	15%	19%	11%	12%	20%	10%	6%	11%	24%	9%	9%	13%
A12A	CALCIUM	15%	15%	11%	12%	14%	12%	15%	12%	19%	10%	9%	11%

top 12. Our list overlaps with the common conditions identified in multimorbid populations by several other large population-based studies (3,22,24).

Three general patterns of non-random associations between conditions have been identified by systematic review: cardiovascular and metabolic diseases, mental health problems and musculoskeletal

Table 4. Clusters of co-morbidities in 501 611 individuals in the Stockholm Region in 2017

Clusters of multimobidity n=501611	Anxiety Depression Alcohol problems	Hypertension	Diabetes Hypertension	Cancer	Thyroid disorders	Hearing loss	Hypertension Cardiovascular disease
Proportion	27%	19%	13%	12%	12%	11%	7%
Age (median)	40	68	67	72	59	63	79
No. of morbidities (median)	2	2	3	3	3	3	6
No. of drugs (median)	5	7	9	8	7	6	12
One-year mortality	1%	2%	2%	5%	1%	2%	12%
Hypertension	0%	100%	86%	70%	38%	35%	85%
Heart failure	1%	2%	2%	3%	1%	2%	82%
Atrial fibrillation	3%	10%	7%	10%	4%	6%	74%
Coronary heart disease	3%	14%	14%	11%	5%	7%	64%
Diabetes	2%	0%	100%	17%	6%	4%	30%
Gout/rheumatoid arthritis	9%	15%	12%	12%	10%	9%	24%
Cancer	2%	0%	0%	100%	7%	7%	22%
Stroke/TIA	3%	11%	9%	9%	4%	6%	22%
Chronic renal disease	1%	6%	6%	6%	2%	2%	21%
COPD	6%	11%	8%	9%	6%	7%	19%
Prostate disorders	7%	13%	10%	18%	3%	9%	17%
Hearing loss	0%	0%	8%	10%	0%	100%	16%
Thyroid disorders	0%	0%	11%	9%	100%	15%	15%
Glaucoma	6%	14%	11%	14%	9%	10%	13%
Dementia	2%	4%	3%	4%	3%	3%	9%
Periph. vascular disease	2%	3%	3%	3%	2%	2%	6%
Psoriasis or eczema	15%	7%	5%	7%	7%	8%	5%
Alcohol problems	17%	8%	6%	4%	4%	4%	5%
Painful condition	8%	6%	5%	5%	6%	5%	5%
Asthma	13%	6%	4%	4%	6%	7%	5%
Blindness	3%	3%	3%	3%	2%	4%	5%
Anxiety disorders	40%	11%	5%	4%	18%	13%	5%
Depression	26%	7%	5%	4%	10%	7%	4%
Constipation	5%	2%	2%	3%	2%	4%	4%
Diverticular disease	9%	3%	3%	4%	4%	5%	4%
Irritable bowel syndrome	14%	5%	3%	4%	9%	7%	3%
Chronic liver disease	2%	2%	3%	3%	2%	1%	2%
Dyspepsia	5%	2%	2%	2%	3%	3%	2%
Inflam. bowel disease	5%	2%	2%	2%	2%	2%	1%
Substance misuse	12%	2%	2%	1%	2%	2%	1%
Epilepsy	2%	1%	1%	1%	1%	1%	1%
Chronic sinusitis	3%	2%	1%	2%	2%	2%	1%
Viral hepatitis	3%	1%	1%	1%	1%	1%	1%
Schizophrenia	4%	1%	2%	1%	3%	1%	1%
Bronchiectasis	0%	0%	0%	1%	0%	0%	1%
Migraine	4%	1%	1%	1%	2%	2%	0%
Multiple sclerosis	1%	1%	0%	0%	1%	0%	0%
Anorexia or bulimia	5%	0%	0%	0%	2%	1%	0%
Learning disability	5%	0%	0%	0%	1%	3%	0%

disorders (25). In our study, the mental health cluster and the thyroid disease cluster are both younger than the other clusters and have a very low 1-year mortality rate. We identified three cardiovascular/metabolic disease clusters that seemed to represent different phases and/or possibly different health trajectories. Individuals in the hypertension cluster had a low level of associated cardiovascular conditions, no diabetes, and few drugs while individuals in the hypertension-metabolic cluster had diabetes, more co-morbidities and more medication. Individuals in the cardiovascular cluster were older, had many concurrent conditions and drugs, and had a high one-year mortality rate. Hypertension was highly prevalent in the multimorbid population, not specific to any one cluster. Hypertension may be best understood as a disease marker or a predictive factor for multimorbidity, and it would be interesting to further evaluate differences between individuals in the hypertension cluster compared to other clusters.

A cohort study of a population aged 77 years or older in Region Stockholm identified similar clusters: two clusters of cardiovascular conditions, one mental illness and musculoskeletal cluster, a diabetes mellitus and malignancy cluster, and a visual impairment and anaemia cluster (16). The clusters in the current study included all age groups, explaining some of the differences between studies. The mental health and thyroid clusters as well as the three cardiovascular/metabolic clusters may represent causal associative multimorbidity, or common pathophysiological pathways within these clusters (26).

Our study aligns with other cross-sectional analyses showing an increase in prescribing with increased age, for example in Scotland (27), Italy (28) and Sweden (27). However, this is the first study of its size to identify the frequencies of claimed prescription for the most common multimorbid conditions. A recent Swedish study of polypharmacy in the elderly found similar trends for potentially

inappropriate prescribing, including high frequencies of anxiolytics and hypnotics (29). Our study may indicate deficiencies in appropriate prescribing for atrial fibrillation (30) and heart failure (31), similar to a recent Irish study (32).

Strengths and weaknesses

This study used the total population of Stockholm County, >2 million individuals and is one of the largest population-based studies of multimorbidity to date. This is a complete data set comprising all health care visits, diagnoses and claimed prescription medications for this population. This data set is representative for Sweden but may have limited generalizability in other settings.

Registry data relies on reporting and therefore risks misclassification of diagnoses. Previous studies have shown much higher prevalence of anxiety (33) and depression (34) than in the VAL database, and have identified underreporting of these diagnoses (35). In our data, individuals with multimorbidity more often had a prescription for anti-depressants than a diagnosis of mental disorder, indicating underdiagnosing in this group. Mental disorders are often underdiagnosed in the elderly population. Our 'mental health' cluster is younger than the other clusters. Using medication data in our clustering model as proxy for mental health diagnoses might yield different clusters. Our data likely reflects underdiagnosing of chronic kidney disease. A study of the total population of Stockholm, reported only 12 % of individuals with a glomerular filtration rate below 60 ml/min/1.73 m^2 ICD-coded for chronic kidney disease (36). Accurate prevalence figures could result in these conditions being much higher. In the VAL database, inpatient and outpatient data are reported to the Swedish National Inpatient Register, which has been validated (37). However, data from primary care have not been validated. An individual's age and sex are identifiable from the national identification number, and registered visits are directly relayed to VAL, so these variables are unlikely to be misclassified. Residual confounding by variables not recorded in VAL could not be evaluated. Data includes only claimed prescription drugs, not written prescriptions, adherence to treatment, nor over the counter drugs.

Implications for practice

Patient-centred primary care should take account of patient complexity and multimorbidity (38). The Ariadne principles of multimorbidity management in primary care advise patients and providers to set realistic treatment goals based on assessment of interactions between conditions and treatment, patient priorities, and individualized plans and follow-up (39). This requires the physician to identify serious or debilitating dominant conditions for prioritization and to distinguish between concordant conditions (with shared pathophysiology profile and similar management strategies), and discordant conditions (that may require separate or competing management strategies) (40). In this study, the identified clusters include concordant conditions, but also discordance, potentially complicating individual management (25). For example, while clustering of cancer and hypertension cluster may not change cancer management *per se*, it points out that even management of cancer patients needs to take account of multimorbidity. Better understanding of disease clustering and development of clinical management guidelines for common clusters could help clinicians with the difficulties of managing the complexity of multimorbidity.

Future research should explore understanding why many patients with multimorbidity are prescribed potentially inappropriate drugs such as sedatives, opioids and anxiolytics, and if there are potential omissions in prescribing. Finally, the findings from this study should inform development and testing of interventions for improving the health care of the steadily growing multimorbid population.

Conclusions

Individuals with chronic conditions often show clinical complexity with both concordant and discordant conditions and polypharmacy. This study indicates that clinical guidelines addressing clustering of conditions may be one strategy for managing complexity.

Supplementary material

Supplementary data are available at *Family Practice* online.

Declaration

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