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Epidemiology

Multimorbidity patterns in a primary care population aged 55 years and over

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Abstract

Background. To support the management of multimorbid patients in primary care, evidence is needed on prevalent multimorbidity patterns.
Objective. To identify the common and distinctive multimorbidity patterns.
Methods. Clinical data of 120 480 patients (≥55 years) were extracted from 158 general practices in 2002–11. Prevalence rates of multimorbidity were analyzed (overall, and for 24 chronic diseases), adjusted for practice, number of diseases and patients' registration period; differentiated between patients 55–69 and ≥70 years. To investigate multimorbidity patterns, prevalence ratios (prevalence rate index-disease group divided by that in the non-index-disease group) were calculated for patients with heart failure, diabetes mellitus, migraine or dementia.
Results. Multiple membership multilevel models showed that the overall adjusted multimorbidity rate was 86% in patients with ≥1 chronic condition, varying from 70% (migraine) to 98% (heart failure), 38% had ≥4 chronic diseases. In patients 55–69 years, 83% had multimorbidity. Numerous significant prevalence ratios were found for disease patterns in heart failure patients, ranging from 1.2 to 7.7, highest ratio for chronic obstructive pulmonary disease-cardiac dysrhythmia. For diabetes mellitus, dementia or migraine patients highest ratios were for heart failure-visual disorder (2.1), heart failure-depression (3.9) and depression-back/neck disorder (2.1), respectively (all *P*-values <0.001).
Conclusions. Multimorbidity management in general practice can be reinforced by knowledge on the clinical implications of the presence of the comprehensive disease patterns among the elderly patients, and those between 55 and 69 years. Guideline developers should be aware of the complexity of multimorbidity. As a consequence of this complexity, it is even more important to focus on what matters to a patient with multimorbidity in general practice.

Key words: Chronic disease, general practice, multimorbidity, prevalence, primary health care.

Introduction

Due to the aging of the population and improvements in medical care, a growing number of people are confronted with having one, and often multiple chronic conditions (i.e. multimorbidity) (1). Prevalence estimates of multimorbidity ranged from 20–30% in persons of all ages, to 55–98% in persons 60 years and older, although these estimates are highly dependent on the measurement methods (2,3). Multimorbidity is related to negative health consequences, such as a poorer quality of life and functional status,

higher rates of hospital admission and avoidable readmissions (4,5).

Next to the negative effects on the patient, multimorbidity provides challenges to health care professionals, such as the GP, since traditional clinical practice guidelines focus on patients with a single disease. The question rises whether these guidelines support multimorbidity management (6–8). Although studies have shown that the majority of the (reviewed) guidelines addressed the issue of comorbidity (7,9), few guidelines gave management guidance in the presence of two or more conditions, and far less addressed the issue specific for older patients. As a result, experts in the field state that future guidelines should become more patient centered, integrate similar disease processes, and incorporate quality of life, risks, benefits and burden of recommended treatments for patients with multimorbidity (7,10).

More insight into commonly occurring disease combinations (i.e. disease patterns) in the elderly could serve as a starting point for the development and formulation of evidence-based management plans for multimorbidity. Currently, consistent evidence about prevalence rates of multimorbidity patterns is lacking as available studies on the prevalence of disease combinations in (older) people (11) often have limitations. Most studies focus solely on disease pairs (12,13) which might not reflect the true situation, as elderly patients often have more than two diseases. Another issue is the age group under study. Some studies underline that multimorbidity is also prevalent among patients of younger age (12), but little is known about the multimorbidity patterns. Finally, the classification of disease patterns is described by using statistical techniques [e.g. factor or cluster analysis (11)] that require specific assumptions of the data which cannot always be met.

The objective of this study is therefore to identify highly prevalent, or prominent multimorbidity patterns in the elderly population. More specifically, two research questions are formulated:

1. What is the multimorbidity level for common chronic diseases in a primary care population aged 55 years and older, and the multimorbidity level in two distinct age groups?
2. Are there disease patterns that are significantly more or less prevalent in patients with a specific chronic disease compared to the population without that disease?

Methods

Study population

We selected patients aged 55 years and older from general practices that participated in NIVEL Primary Care Database [formerly known as National Information Network of General practice (LINH)]. This nationally representative database holds longitudinal data derived from patients' electronic medical records (EMRs) on for instance consultations, and morbidity, from about 90 Dutch general practices. The database includes a dynamic pool of practices and annually changes in composition (14). In The Netherlands, all citizens are required to be registered with a general practice, and the GP has a gatekeeper role for access to specialized care. As records from the GP are likely to be most complete and reflect the total population, these are especially suitable for estimating prevalence rates of multimorbidity.

We selected practices that provided morbidity data for at least two complete consecutive years in the period 2002–11. Quality checks on the data are part of the database protocol. Patients were required to be registered at the same practice for at least two full uninterrupted years. Diagnostic data were more accurate by using this minimum follow-up period, as for some chronic diseases patients do not necessarily visit their GP annually. Age of the patients was determined at start of their follow-up period. We only included patients diagnosed with at least one chronic condition, as we were interested in the prevalence and patterns of multimorbidity.

This study was executed according to the precepts of the Dutch legislation on privacy and the regulations of the Dutch Data Protection Authority. According to Dutch legislation, studies using this type of observational data do not require medical ethical approval, or informed consent.

Selection of chronic diseases

In The Netherlands, diagnostic codes for diseases are recorded according to the International Classification of Primary Care (ICPC-1) (15), and GPs are expected to structure their EMR around disease episodes (16). All patient contacts related to one health problem were clustered into a disease episode, constructed by using an algorithm to group ICPC-coded contact records from EMRs into episodes of care (17). We used these disease episodes for the selection of chronic diseases. We chose 28 common chronic diseases (18), and added hypertension to the list due to its high prevalence rate in the elderly (although a risk factor rather than a disease). This resulted in 29 diseases listed with their ICPC codes in Supplementary Table S1. A condition was included or present if there was a ICPC code corresponding to one of the selected diseases recorded in the patient's EMR during their complete follow-up period.

Statistical analysis

Multimorbidity level

The focus of this study was to determine the impact of diseases on the outcome per patient (i.e. multimorbidity yes/no). As a consequence, patients with multiple diseases were counted more than once, i.e. as often as their number of diseases. This would introduce bias; the disease specific multimorbidity proportions were biased towards the mean. To adjust for this phenomenon, we applied multilevel logistic regression analyses with a multiple membership structure (19). With this technique, each patient is weighted by means of their diagnosed number of diseases. Further, patients (level 1) were nested within general practices, and practices and diseases were cross-classified at level 2. Based on the fact that not all patients had a full practice registration period, a correction factor was added to the models, accounting for the size of deviation from complete 10 years of registration. As a result, the intercept of the model was estimated as if all patients were considered to have a complete follow up of 10 years.

The overall mean multimorbidity level (dependent variable) was estimated, and that for each of the chronic diseases included. The disease specific proportion was calculated as the sum of the overall adjusted rate, and the disease specific residual estimated from the disease level random effect (19).

Multilevel linear regression analyses were conducted with a similar model structure to analyse the overall adjusted mean number of diseases, and that for each chronic disease. All analyses were conducted for the total population, and separately for patients between 55 and 69 years, and ≥70 years. Diseases with a prevalence rate below 0.5% were excluded from these analyses. This since the number of patients diagnosed with one of the diseases was too minimal to ensure reliable prevalence rates assessed in the analyses. See Supplementary Box S1 for more information about the multiple membership analysis technique.

Multimorbidity patterns

Four chronic diseases were selected to examine their most prevalent disease patterns, and the degree of association between these patterns. The selection of these index-diseases was based on two criteria, namely (i) to cover the full range of multimorbidity levels (low versus high level of multimorbidity), and (ii) diseases that especially affected the elderly, since this patient group is most likely to be the target group with problems regarding treatment of multimorbidity. For each of the index-diseases, the most frequently co-occurring diseases were assessed, and those with a minimum prevalence rate of 10% were presented. Subsequently, prevalence ratios were calculated (i.e. prevalence rate disease pair within patients with index-disease/prevalence rate disease pair in patients without index-disease). The ratios indicated whether the occurrence of a disease pair was higher or lower in patients with compared to patients without the index disease. The ratio's magnitude equals the strength of the relationship of that disease pair. Since the focus was on disease patterns within a specific patient group, crude data and descriptive statistics were used. Statistical significance of the ratios was assessed using chi-square tests.

Descriptive statistics were performed to define the main characteristics of the study population, by using STATA SE version 12.1, and the multilevel analyses were performed by using MLwiN version 2.30.

Results

Initially, 170 583 persons aged 55 years and older were included. Prevalence numbers of five chronic diseases (i.e. HIV/aids, congenital cardiovascular anomaly, intellectual disability, schizophrenia and personality disorder) were less than 0.5%, and these diseases were therefore not included in the analyses. Further, 50 103 persons were not diagnosed with any of the 24 (i.e. 29 minus the five excluded diseases) diseases, and were therefore excluded. This resulted in a list of 24 chronic diseases among 120 480 patients, registered at 158 general practices. Patients' mean age was 67 years (SD 9.8), 45% were men, and 62% had multimorbidity (Table 1). Of the patients 55–69 years, and 70 years and older, 61% and 75% had multimorbidity, respectively.

Multimorbidity level

The majority of the patients were diagnosed with more than one chronic disease (overall adjusted mean: 86%) (Table 2). The multimorbidity level ranged from 70% (migraine/hypertension) up to 98% (heart failure). In total, heart failure, heart valve disorder and a history of stroke were diseases that were significantly more often associated with multimorbidity (98%, 95% and 94%, respectively) compared to other diseases.

On average, 83% of the patients aged 55–69 years and 94% of the patients 70 years and older were diagnosed with multiple chronic diseases. The highest multimorbidity level was found for heart failure, and the lowest for hypertension. Notably, in the oldest patients (i.e. 70 years and older) migraine had a relative high multimorbidity rate (97%), though it had nearly the lowest rate in patients 55–69 years (71%). Furthermore, dementia, Parkinson's disease and alcohol abuse turned out to be diseases with a relatively lower multimorbidity rate in patients aged 70 years and older. Results of the mean number of co-occurring diseases can be found in Table 2.

Disease patterns

Heart failure (high multimorbidity level), migraine (low multimorbidity level), diabetes mellitus (highly prevalent in the elderly) and dementia (specifically related to older age) were examined in more depth. Cluster diagrams (Figs. 1–4) illustrate the associations between the most frequently co-occurring disease triplets.

Heart failure

Thirteen chronic diseases were highly common within heart failure patients, with prevalence rates varying from 10% (asthma) to 49% (hypertension) (Fig. 1). Focusing on disease triplets, all prevalence ratios were statistically significant above 1.0, and 75% even above 2.0 (see Supplementary Table S2). Prevalence ratios of the triplets including cardiac dysrhythmia were high; they were at least 6.0 for the combination with coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD) and osteoporosis. The same holds for the prevalence ratio of CAD-COPD (ratio 5.4), which was much higher in heart failure patients in comparison to patients without it. Focusing on some remarkable quartets (data not shown), almost 3% of the patients were diagnosed with both cardiac dysrhythmia, COPD and CAD. This prevalence rate was 14.2 times higher than that in the population without heart failure. The combination cardiac dysrhythmia-COPD-osteoporosis within heart failure had a ratio of 13.6.

Migraine

Prevalence ratios of many of the disease triplets were around 1.0 (Fig. 2), indicating that the combinations for migraine were equally

Table 1. Demographic characteristics of the study population (patients aged ≥55 years diagnosed with at least one chronic disease in 2002–11[a])

	Total	Men	Women	*P* value[b]	Patients 55–69 years	Patients ≥70 years	*P* value[b]
Number of patients, (%)							
Total	120 480 (100.0)	54 375 (100.0)	66 105 (100.0)		75 310 (100.0)	45 170 (100.0)	
Multimorbidity (≥2 diseases)	74 733 (62.0)	32 420 (59.6)	42 313 (64.0)	<0.001	41 866 (55.6)	32 867 (72.8)	<0.001
Mean age in years, (SD)[c]							
Total	66.9 (9.8)	65.7 (9.1)	67.9 (10.2)	<0.001	60.4 (4.6)	77.6 (5.8)	<0.001
Multimorbidity	68.3 (9.8)	67.1 (9.3)	69.3 (10.2)	<0.001	60.9 (4.7)	77.8 (5.7)	<0.001
Mean number of years follow up, (SD)							
Total	4.6 (2.3)	4.6 (2.3)	4.5 (2.3)	0.05	4.7 (2.4)	4.2 (2.2)	<0.001
Multimorbidity	4.9 (2.4)	4.9 (2.4)	4.9 (2.4)	0.01	5.2 (2.5)	4.5 (2.2)	<0.001

In this table, crude frequencies, percentages and standard deviations (SD) are reported.

[a]Minimum follow-up period 2 years, maximum follow up 10 years.

[b]Statistical significance between men and women, and between patients 55–69 years and ≥70 years. Number of patients tested with chi-square tests, mean age and mean follow up with *t*-tests.

[c]Patient's age at the year of inclusion.

Table 2. Multimorbidity level and number of co-occurring diseases in patients diagnosed with at least one out of 24 chronic diseases, 2002–11

	Total		Patients aged 55–69 years			Patients aged ≥70 years[b]		
	% multimorbidity (95% CI)[a]	Mean no. of diseases (95% CI)[a,c]	N	% multimorbidity (95% CI)[a]	Mean no. of diseases (95% CI)[a,c]	N	% multimorbidity (95% CI)[a]	Mean no. of diseases (95% CI)[a,c]
Overall mean	85.6 (82.9–88.0)	3.25 (3.11–3.40)	75310	83.4 (80.2–86.1)	3.04 (2.89–3.18)	45170	93.5 (92.2–94.6)	3.96 (3.83–4.10)
Heart failure	98.4 (96.0–99.4)*	4.97 (4.31–5.63)*	2323	98.5 (96.2–99.4)*	5.06 (4.39–5.73)*	7197	97.4 (94.6–98.8)*	4.71 (4.14–5.28)*
Heart valve disease	94.5 (87.1–97.8)*	3.99 (3.34–4.65)*	1031	93.7 (85.3–97.4)*	3.60 (2.94–4.27)	1266	95.4 (90.9–97.7)	4.43 (3.87–4.98)
Stroke	94.0 (86.0–97.6)*	3.74 (3.08–4.40)	3008	92.7 (83.0–97.1)	3.48 (2.81–4.15)	4076	94.8 (89.5–97.5)	3.96 (3.39–4.53)
Cardiac dysrhythmia	91.0 (79.8–96.3)	3.66 (3.00–4.32)	4983	85.8 (69.8–94.0)	3.17 (2.50–3.85)	5797	96.7 (93.2–98.4)	4.41 (3.85–4.98)
Coronary artery disease	88.8 (75.5–95.3)	3.39 (2.73–4.05)	10108	85.9 (69.9–94.1)	3.09 (2.41–3.76)	9037	94.1 (88.1–97.2)	4.01 (3.44–4.58)
Diabetes Mellitus	88.5 (75.0–95.2)	3.23 (2.57–3.89)	15781	87.4 (72.7–94.8)	3.06 (2.38–3.73)	11226	93.1 (86.1–96.7)	3.77 (3.20–4.34)
COPD	88.1 (74.1–95.0)	3.40 (2.74–4.06)	8073	86.1 (70.4–94.2)	3.17 (2.49–3.84)	6623	93.1 (86.2–96.7)	3.97 (3.40–4.54)
Visual disorder	88.0 (74.1–95.0)	3.38 (2.72–4.04)	5964	82.6 (64.5–92.5)	2.98 (2.31–3.66)	7420	92.7 (85.5–96.5)	3.79 (3.22–4.35)
Dementia	85.4 (69.5–93.8)	3.26 (2.60–3.92)	422	85.0 (69.3–93.5)	3.13 (2.47–3.79)	3127	84.1 (71.0–91.9)*	3.25 (2.68–3.82)*
Rheumatoid arthritis	85.4 (69.5–93.7)	3.28 (2.62–3.94)	2138	81.6 (62.9–92.0)	2.95 (2.28–3.62)	1540	95.1 (90.1–97.6)	4.26 (3.70–4.82)
Parkinson's disease	84.5 (68.1–93.3)	3.23 (2.57–3.88)	450	81.6 (63.5–91.8)	2.94 (2.28–3.60)	963	86.6 (75.3–93.2)*	3.45 (2.89–4.01)
Asthma	84.4 (67.8–93.3)	3.24 (2.57–3.90)	6303	83.4 (65.7–92.9)	3.05 (2.38–3.72)	2471	96.7 (93.3–98.4)	4.70 (4.13–5.26)*
Anxiety disorder	83.9 (67.0–93.0)	3.21 (2.55–3.87)	2462	81.9 (63.5–92.2)	3.03 (2.36–3.70)	1084	96.2 (92.4–98.1)	4.40 (3.85–4.96)
Osteoporosis	83.3 (66.0–92.8)	3.22 (2.56–3.88)	4017	77.5 (56.9–90.0)	2.86 (2.18–3.53)	3964	92.6 (85.4–96.4)	3.91 (3.35–4.48)
Hearing disorder	83.3 (66.0–92.8)	3.15 (2.49–3.81)	3750	76.3 (55.2–89.3)	2.74 (2.07–3.41)	4326	92.3 (84.7–96.2)	3.78 (3.21–4.35)
Osteoarthritis	82.3 (64.3–92.3)	3.03 (2.37–3.69)	11275	77.3 (56.5–89.9)	2.75 (2.08–3.43)	9212	92.3 (84.8–96.3)	3.72 (3.15–4.29)
Depression	82.0 (63.9–92.2)	3.10 (2.44–3.76)	6289	79.3 (59.4–90.9)	2.88 (2.20–3.55)	3469	94.4 (88.8–97.3)	4.18 (3.62–4.75)
Chr. back or neck disorder	79.0 (59.3–90.6)	2.95 (2.29–3.61)	12166	76.4 (55.3–89.5)	2.75 (2.08–3.43)	5439	94.7 (89.3–97.5)	4.17 (3.60–4.74)
Alcohol abuse	78.5 (58.8–90.3)	2.89 (2.23–3.55)	1294	81.2 (62.5–91.8)	2.93 (2.26–3.60)	234	87.8 (78.5–93.4)*	3.65 (3.13–4.17)
Cancer	77.3 (57.0–89.8)	2.85 (2.19–3.51)	10222	72.7 (50.5–87.5)	2.62 (1.95–3.30)	8257	88.8 (78.5–94.5)	3.48 (2.91–4.05)
Epilepsy	76.8 (56.6–89.4)	2.98 (2.33–3.64)	874	73.5 (51.8–87.8)	2.77 (2.10–3.44)	490	93.2 (87.1–96.5)	4.03 (3.50–4.57)
Burnout	75.9 (55.1–89.0)	2.74 (2.08–3.40)	1938	77.5 (57.0–90.0)	2.73 (2.06–3.40)	350	93.6 (88.1–96.6)	4.05 (3.53–4.58)
Hypertension	69.9 (47.4–85.7)	2.57 (1.91–3.23)*	35726	68.1 (44.9–84.8)	2.46 (1.79–3.14)	22932	81.0 (66.3–90.2)*	3.04 (2.46–3.61)*
Migraine	69.9 (47.5–85.6)	2.62 (1.96–3.28)	2316	71.2 (48.6–86.6)	2.62 (1.95–3.30)	348	96.7 (93.9–98.2)*	4.02 (3.50–4.55)

N = number of patients; CI = confidence interval; Sign = significance; chr = chronic. Percentages (95% CI), and mean number of diseases are adjusted for the practice level, disease level (number of diseases), and the registration period at the practice (i.e. years of follow up with a minimum period of 2 years and a maximum period of 10 years).

[a]Disease outcome (i.e. multimorbidity level, mean no. of diseases) was statistically significant higher or lower (*$P < 0.05$) than the overall mean outcome.

[b]Between patients 55–69 years and patients ≥70 years, there was a statistically significant difference ($P < 0.05$) in the proportion of patients with multimorbidity (except for heart valve disorder and visual disorder).

[c]Mean number of co-occurring diseases including the concerning disease.

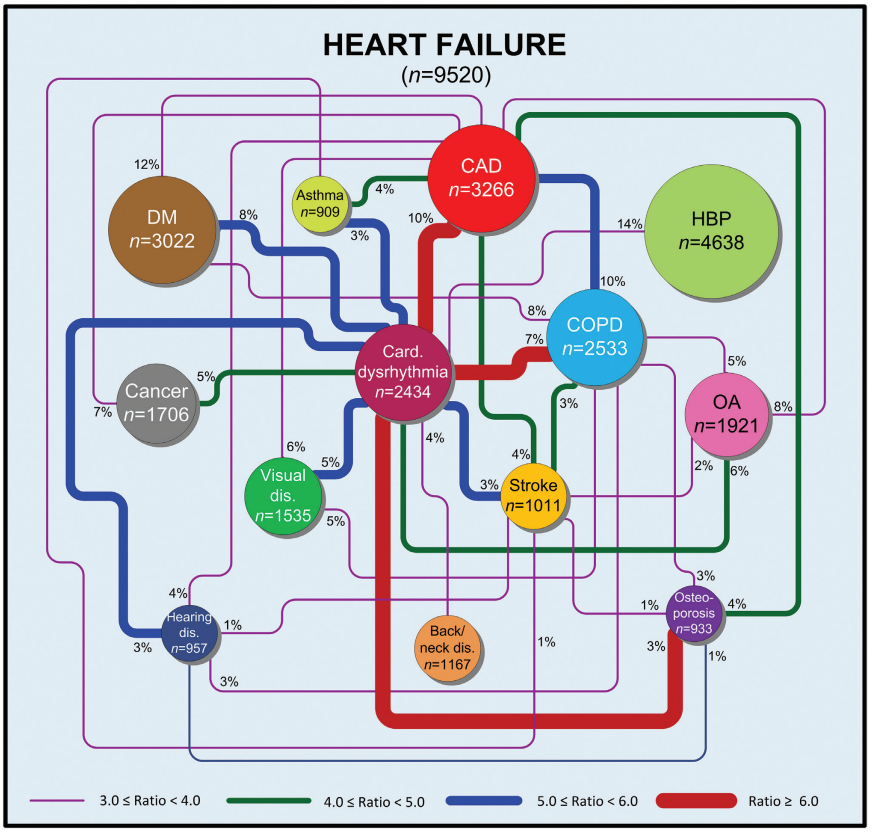

Figure 1. Cluster diagram of the most common disease patterns in patients with heart failure. CAD = coronary artery disease; Card. = cardiac; dis. = disorder; DM = diabetes mellitus; HBP = high blood pressure; HF = heart failure; OA = osteoarthritis. Cluster diagrams of the most common chronic diseases (with a prevalence of ≥10%) and disease patterns in patients with the index diseases heart failure (i), migraine (ii), diabetes mellitus (iii) or dementia (iv). Size of the circles is proportional to the number of patients diagnosed with that disease; the *n* in the circle refers to the number of patients with both the index-disease and a co-occurring disease (e.g. in this figure, 3022 patients were diagnosed with both heart failure and diabetes mellitus). Lines display statistically significant prevalence ratios of the observed prevalence rate of that combination within patients with the index-disease divided by the prevalence rate of that combination in the population without the index-disease (i.e. the non-index-disease population). Width of the lines reflects the magnitude of the ratio. For all ratios, see Supplementary Table S2. Percentages refer to the percentage of that combination within the index-disease population (e.g. in this figure, of the heart failure patients 5% were also diagnosed with COPD and osteoarthritis). In this figure, crude prevalence rates were presented. In this figure, to increase the visibility of this diagram, ratios with a minimum of 3.00 were presented (see Supplementary Table S2 for all ratios).

prevalent in patients with other chronic diseases [with the exception of chronic back or neck disorder with depression (ratio 2.1)]. Seven combinations were less frequent in patients with migraine in comparison to those without migraine (ratio < 0.8). In line with the frequently occurring triplet chronic back or neck disorder-depression-migraine, the quartet that also included osteoarthritis had a ratio of 2.4 (prevalence rate 0.9%).

Diabetes mellitus

Regarding the disease triplets, heart failure was highly associated with visual disorder and with hypertension in patients with diabetes mellitus (ratios 2.1 and 2.0, respectively) (Fig. 3). Other prevalence ratios of triplets that included diabetes mellitus and heart failure ranged between 1.5 and 2.0. More particularly common disease triplets were diabetes mellitus-CAD and COPD, or visual disorder, or hypertension, and diabetes mellitus-hypertension-visual disorder (see Supplementary Table S2). Some distinct disease quartets were found (data not shown), especially the combination heart failure-visual disorder-hypertension (prevalence ratio 2.6). Further, the quartet chronic back or neck disorder-heart failure-visual disorder had a ratio of 2.4 within diabetes mellitus patients.

Dementia

Patients with dementia were more often diagnosed with heart failure and depression, heart failure and stroke and depression and stroke (ratios 3.9, 3.5 and 3.3, respectively) (Fig. 4). There were four disease triplets with ratios between 2.5 and 3.0. Most quartets including stroke and depression plus one additional disease had prevalence ratios around 3.5. The quartet depression-stroke-diabetes-dementia, had a ratio of 6.2 (prevalence rate 0.9%).

When focusing on the patients aged 55–69 years, all ratios were higher for the patterns including heart failure, or diabetes mellitus, indicating that the identified disease combinations were even more specific for the index-disease patients (data not shown). For migraine, similar ratios were found since nearly all patients with migraine were less than 70 years old. For dementia, ratios were not calculated as almost all patients were older than 70 years.

Discussion

This study showed that multimorbidity is the rule rather than the exception in primary care; not only for patients of 70 years and older, but also for patients of 55–69 years, as 83% (of those diagnosed

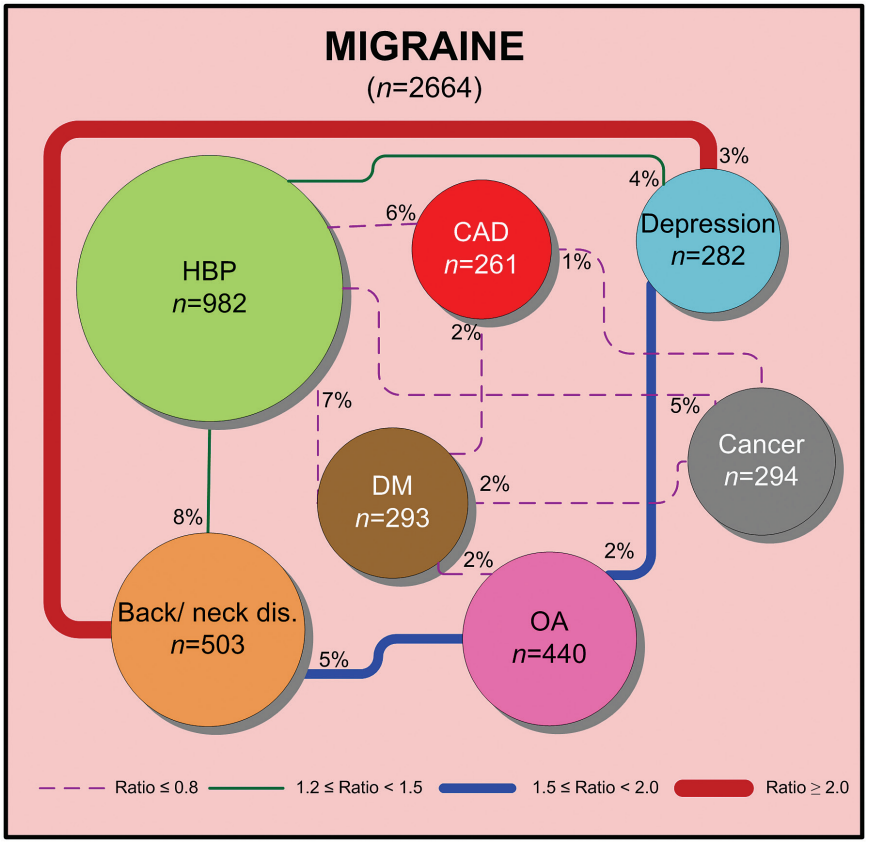

Figure 2. Cluster diagram of the most common disease patterns in patients with migraine (see Figure 1 legend for more details).

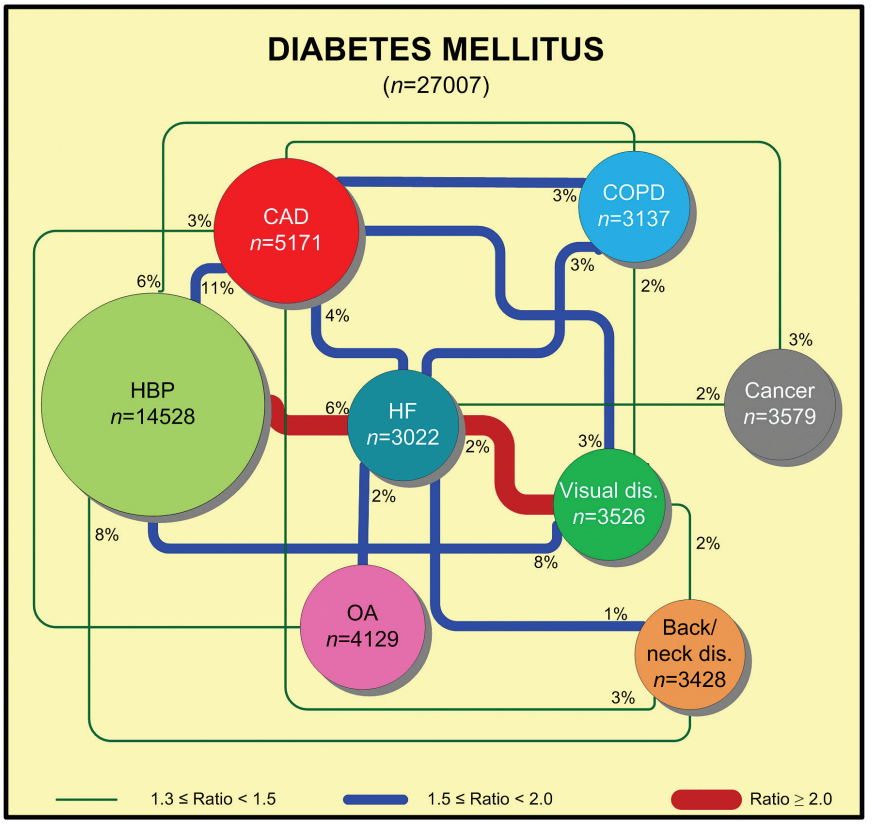

Figure 3. Cluster diagram of the most common disease patterns in patients with diabetes mellitus.In this figure, to increase the visibility of this diagram, ratios with a minimum of 1.30 were presented (see Supplementary Table S2 for all ratios) (see Figure 1 legend for more details).

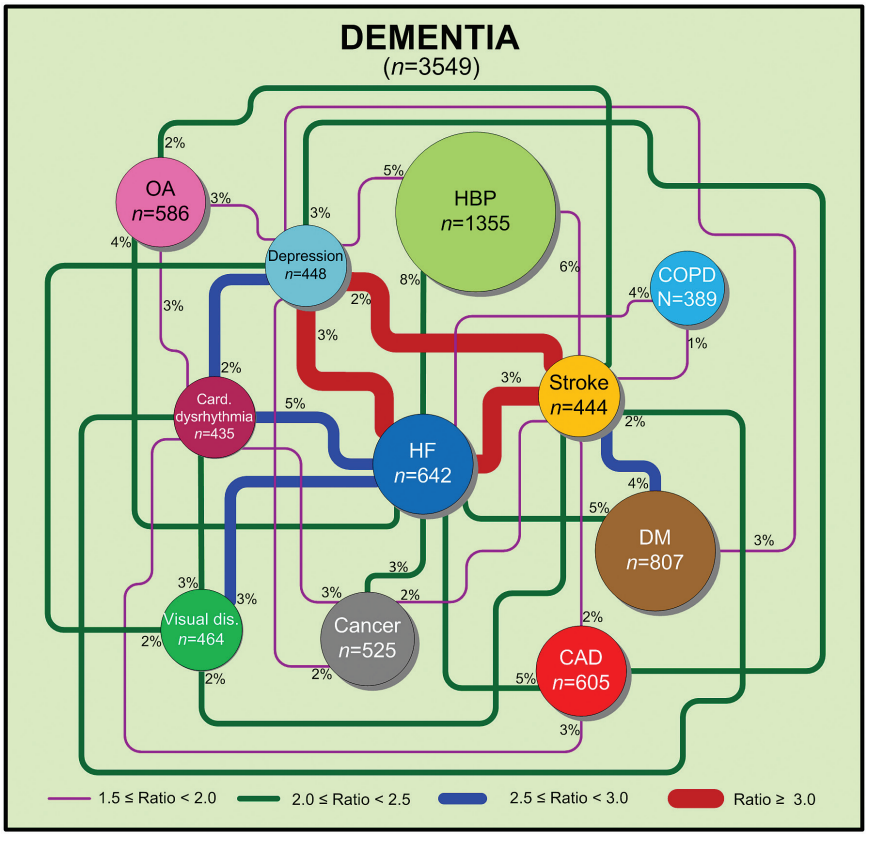

Figure 4. Cluster diagram of the most common disease patterns in patients with dementia.In this figure, to increase the visibility of this diagram, ratios with a minimum of 1.50 were presented (see Supplementary Table S2 for all ratios) (see Figure 1 legend for more details).

with a chronic disease) presented multimorbid problems in the general practice. Multimorbidity is not restricted to disease pairs, but often consists of more extensive patterns (i.e. triplets, quartets) of chronic diseases. These patterns relate to complicated care needs that require change in general practice management.

Other studies confirm the high multimorbidity rate for many chronic diseases, for instance for heart failure or diabetes mellitus (11,13), or confirm the finding that multimorbidity is not just a problem of the elderly (12). Yet, these studies did not focus on the complexity of multimorbidity (i.e. extensive disease patterns), especially not for patients younger than 70 years.

For four index-diseases, we identified the most common disease patterns of which some were specifically related to the index-disease and others were more common among the total population. Besides age as an explanation for the identified patterns, additional explanations for the co-occurrence of diseases are possible, as stated by van Weel and Schellevis (8). They divided the co-occurrence of diseases into four categories namely, (i) diseases with a common pathophysiology, (ii) diseases that have developed due to complications of another disease, (iii) intercurrent multimorbidity which considers acute diseases in patients diagnosed with a chronic disease and (iv) concurrent diseases without any known causal relation between the diseases. Most of the diseases presented in our cluster diagrams have a common pathophysiology. For instance, cardiac dysrhythmia and CAD are both common causes of heart failure, and diabetes and hypertension are risk factors for heart failure (20). Furthermore, the identified disease pattern diabetes mellitus-cardiac disease-COPD could be explained by shared cardiovascular and metabolic risk factors, such as hypertension and smoking. Visual disorder (e.g. retinopathy) as a common disease in diabetes mellitus patients can be considered as a complication of the presence of diabetes, and the same applies for dementia after stroke (21). Some identified disease combinations have similar symptoms, leading to intensive diagnostic tests that could result in both diagnoses (e.g. COPD and heart failure) (20). We found that COPD strongly clustered with CAD and cardiac dysrhythmia in heart failure patients. The intercurrence of multiple diseases could not be confirmed since our study did not focus on acute diseases. For some combinations, it is unclear how they are related, and if there is a causal relationship, these combinations could indicate concurrent co-occurring diseases, for instance cardiac dysrhythmia and osteoporosis in heart failure patients. Remarkably, disease patterns that included diabetes mellitus were less prevalent in migraine patients than in patients with other chronic diseases. A few studies do confirm the "protective" effect of diabetes on migraine (22). Considering the variation within the disease patterns, it may be useful to explore the patterns of disease for other common index-diseases.

The cluster diagrams showed that hypertension was highly prevalent in all four chosen index-diseases. This is also confirmed in other studies exploring disease pairs and triplets (11,13). The current study, moreover, showed that the ratios for hypertension and other diseases were not quite prominent, underlining that hypertension is not specifically related to one certain type of disease. Only in the cluster diagram for diabetes mellitus some distinct combinations were found that included hypertension. In a study by Islam *et al.* (11), it was found that diabetes and hypertension were always classified in the same cluster or group, using several analytic techniques. In a study by Marengoni *et al.* (13), cluster analysis revealed a cluster consisting of heart failure-hypertension-atrial fibrillation-CAD.

These diseases are also highly prevalent, and strongly clustered (i.e. high prevalence ratios), in our cluster diagram of heart failure. A second cluster found by Marengoni *et al*. was dementia, depression and hip fracture (13). Our study showed that depression was highly prevalent in dementia patients, and it clustered strongly with most cardiac diseases, and with osteoarthritis.

With the applied study design, we were able to provide reliable prevalence rates of common disease patterns in an elderly population. Data of a large sample of patients were available and minimal selection bias exists as the practices included are representative for The Netherlands. Furthermore, information related to chronic diseases is most likely complete in general practice registries since the GP acts as gatekeeper for secondary care. Recording in EMRs is most likely accurate as practices also used their files for reimbursements. Possible bias due to patients' perception of the presence of a chronic illness, or other factors that are related to the accuracy of self-reported disease diagnosis (3), is excluded when using EMR data. Another major strength of this study is the use of the multiple membership technique. Most studies do not account for the fact that elderly patients often are diagnosed with multiple diseases and thus are counted several times in multimorbidity prevalence estimations. With the multiple membership technique, this bias is eliminated by weighting each patient by means of their number of diseases.

This study also has some limitations. Although quality requirements regarding data recordings exist, possible mistakes in ICPC recording could have been made, for instance due to typing errors or incorrect coding. Though, it is not likely that errors occurred systematic differently for the index-disease and non-index-disease group. Further, it may be possible that GPs differ in their decision of reporting a chronic disease diagnosis, for instance for diagnoses that rely on more subjective criteria (e.g. depression). However, we have taken this into account by the correction for practice in the statistical model. In addition, one can argue whether the disease depression reflects a chronic depression. Although no information about the diagnostic method was available, the ICPC-1 codes for depression were classified in the 'diagnosis section' of the ICPC-1 classification system. This considers a more definitive diagnosis than a registration in the 'symptoms/and complaints section'. Another limitation relates to the data sample. We consider the large data sample of patients as a strength of this study, but to account for the variance in follow-up period of the patients we adjusted for the years of registration. As a result, the overall adjusted mean is somewhat overestimated since it considers the mean multimorbidity level as if all patients were registered for the complete follow-up period of 10 years. Further, although the data were collected within a 10-year period, we could not determine the direction of the identified associations. This since we determined whether a disease was present (yes/no) after the follow-up period, but did not determine which disease was diagnosed first, or second, or last. Another issue for consideration is that we have determined patients' age at moment of inclusion. This means that some patients, that were classified to the 55–69 years group, turned 70 years during their follow-up period. If other age categories were chosen, some of the patients moved from the 'younger' category to the 'older' category, which could have altered the results. Yet, the overall findings, including the cluster diagrams, would have been unchanged and still demonstrate that multimorbidity is most often characterized by the presence of complex disease patterns.

As older people frequently visit their GP, findings from this study seem particularly relevant to GPs. The multimorbidity patterns displayed in this study illustrate the heterogeneous nature of this patient group (10). Patients with multimorbidity differ widely as regards the possible diagnosed diseases. Since they are also heterogeneous in terms of their disease severity, functional status, or prognosis this may lead to a great variety in different treatments considered by the GP. GPs should be aware of the fact that not only patients of 70 years and older, but also those between 55 and 70 years have complex health care needs and require complex management. Further, they should keep in mind that the proportion of patients, for which recommendations reported in current practice guidelines are limited applicable, might be even larger than one expects, and that this is already true for younger elderly. As a consequence, the workload for the GP might be higher than expected due to more time consuming consultations. Due to the large extent of all possible disease combinations, it seems unrealistic to develop new guidelines for all possible combinations. Therefore, GPs may need other information, skills and tools to provide optimal care for this patient group. For instance, to inquire about patient preferences during a consultation, and to integrate these preferences into medical decision making. This requires patient's ability to prioritize their preferences for care, and to weigh risks and benefits of the treatment and the various decision options given by the GP. In turn, it requires skills and time from the GP to discuss all options with the patient.

Conclusions

This study stresses the complexity of multimorbidity, and the challenges to provide (high quality) care for patients with multimorbidity by GPs. Guideline developers should be aware of this complexity, and GPs should focus on what matters to the patient, rather than on what is the matter in this patient group.

Supplementary material

Supplementary material is available at Family Practice online.

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Declaration

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