

Comorbidity of chronic gastro-intestinal disorders

A cross-sectional analysis in a large general practice population in the Netherlands

by

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Abstract

Objectives: *Comorbidity is an issue of increasing interest. In addition, chronic gastrointestinal disorders show high prevalences in general practice.*

Comorbidity of chronic gastrointestinal disorders was assessed by means of a descriptive, cross-sectional analysis of a large general practice population.

Methods: *Data were obtained from the central database of the Registration Network of Family Practices (RNH) in the Netherlands. This*

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database consisted of 62,684 individuals at the time of our analysis and resembled the general Dutch population.

Six groups of chronic gastrointestinal disorders were selected: peptic ulcer, non-ulcer dyspepsia, esophageal disease, inflammatory bowel disease, irritable bowel syndrome, and diverticular disease. By means of logistic regression analysis with adjustment for age and sex, comorbidity for each of these six groups was studied by comparing each group with 37 other groups of chronic diseases involving all body systems.

Results: Especially esophageal and diverticular disease showed a high amount of comorbidity. In general, chronic gastrointestinal diseases were especially associated with chronic diseases affecting the locomotor tract, depressive disorders, psychosocial disorders and different types of headaches.

Key-words

Comorbidity, gastro-intestinal, chronic disease.

Introduction

Comorbidity, defined as the occurrence of medical conditions additional to an index disease (1), is an issue of increasing interest. The phenomenon comorbidity is of special importance to general practice, where personal and continuous care is provided.

In the Netherlands, the general practitioner, who is the gatekeeper to other health care facilities, is increasingly confronted with the co-occurrence of chronic medical conditions in patients (2). This is partly due to a relative shift from acute to more chronic conditions and partly the result of ageing of the population.

Co-occurrence of more than one chronic disorder mainly affects the elderly and both the number and percentage of old people in society are increasing (3, 4). For example, in 1990 12% of the Dutch population was 65 years or older and this is expected to rise to 21% by the year 2025. Furthermore, within the age group of 65 and over the mean age is still rising (5). About 50% of the elderly are thought to have more than one active medical problem at any time (6). Co-occurrence of diseases presents more serious consequences than a single disease and may be

reflected in pain and suffering, loss of independence, disability and decline in quality of life (4, 7). In all age groups the burden of illness, as expressed by associated physical and social disability, rises with the number of chronic conditions, which is even more pronounced in the elderly (3, 4, 8, 9).

Comorbidity not only affects the patient, but also people close to him, and society. Knottnerus and colleagues introduced the concept of "social prevalence", meaning that not only the patients themselves but also their family and friends are involved with the disease (10). Taking care of a patient with multiple medical conditions may substantially influence the lives of the patients' families or other care providers by forcing job changes, changing life styles and demanding a lot of time and energy (7). As a result of the co-occurrence of chronic diseases the consumption of health care facilities is likely to increase, resulting in a rise in the costs of medical and health care expenses. Moreover, in younger subjects, absence due to illness and loss of productivity will make the costs to society rise (4, 7).

Gastrointestinal (GI) disorders are a disease category with a high prevalence in general practice, especially in the elderly. In geriatric clinics about 18% of all patients have significant gastrointestinal problems and 20% of all geriatric deaths are caused by GI problems (6).

As essential human needs as feeding and defecation may be impaired in chronic gastrointestinal diseases, the influence of these disorders on life style and quality of life may be substantial. For example, in inflammatory bowel disease, that usually affects young people, impaired bowel function, pharmacological or surgical treatment and possible dietary restrictions may seriously affect the patients' way of living and quality of life (11). The co-existence of another chronic condition additional to gastrointestinal disorder aggravates this burden of illness.

The aim of the present study was to assess the point prevalence and comorbidity of chronic gastrointestinal disorders in a large general practice population. This can supply relevant information for both GPs and other medical specialists, and policy makers.

Methods

Patients and Setting

For this study we used data from the Registration Network of Family Practices (RNH), available on 1 September 1996. At that moment the

RNH consisted of forty-two general practitioners (GPs) in fifteen practices, mainly situated in the southern part of the province of Limburg, the Netherlands. The RNH was described extensively elsewhere (12). The population consisted of 62,684 individuals of which 30,637 (48.9%) were males and 32,047 (51.1%) females. The age distribution is presented in table 1.

All essential health problems, as well as personal characteristics of the patients (including birth date, sex, level of education, health insurance status, and type of household) are registered (12). Health problems that are recorded on the problem list are either serious, permanent, chronic (duration longer than six months) or recurrent (more than three recurrences within a 6-month period) and are coded using the International Classification of Primary Care (ICPC) (13) and the diagnostic criteria of the International Classification of Health Problems in Primary Care (ICH-PPC-2-defined) (14).

Definitions

In order to study the comorbidity of chronic gastrointestinal diseases a selection was made out of the wide range of gastrointestinal disorders. Firstly, conditions under study had to be coded as a disease entity in the International Classification of Primary Care (ICPC) (13). Our focus being on chronic conditions, only diseases with a chronic character and affecting the esophagus, stomach or intestine were selected which ruled out all infectious diseases as well as disorders affecting mouth, teeth, liver, bile ducts, or pancreas. All GI tumours, either benign or malignant were excluded, because of the possible bias that might occur due to the nature or spread of (malignant) tumours. The selected chronic gastrointestinal disorders were grouped in 6 categories as presented in appendix 1.

TABLE 1
Distribution of RNH patients among age and sex categories (N = 62,684)

Age group	male	female	Total
0-25	9334 (30.5%)	9074 (28.3%)	18408 (29.4%)
26-65	17718 (57.8%)	17644 (55.1%)	35362 (56.4%)
> 65	3585 (11.7%)	5329 (6.6%)	8914 (14.2%)

To study the comorbidity for these selected GI disorders, thirty-seven groups (see appendix 2) that consisted of chronic diseases with common symptomatology or pathophysiologic mechanism were identified. This selection was based on a previous study of chronic illness in the community (10).

Statistical analysis

The RNH database was analysed cross-sectionally to assess the point prevalences of both the selected gastrointestinal disorders and the other chronic disorders according to age and sex. To study the comorbidity of gastrointestinal disease the relation between all 37 groups of chronic diseases and each GI disease category was tested by means of logistic regression analysis, adjusting for age and sex. The presence of one of the 37 chronic conditions, age, and sex served as independent variables, whereas the presence of each GI disease category studied served as the dependent variable. The results of the analyses were expressed as odds ratios (OR) with 95% confidence intervals (95% CI).

Additional analyses were performed to study the relation between a GI disease category and combinations of some of the thirty-seven chronic disorders groups if indicated. In such cases a number of the 37 groups with a logical coherence were merged and then compared to a GI disease category using logistic regression again.

Results

The point prevalence of the chronic gastrointestinal diseases in relation to sex and age categories is shown in appendix 1. Peptic ulcer clearly affected men twice as often as women, and was rare in persons younger than 25 years of age. In the elderly (over 65 years of age) it was more frequent. Both non-ulcer dyspepsia and esophageal disease were about equally distributed over the sexes and mostly affected the elderly. As for inflammatory bowel disease, there was no preference for either one of the sexes and the prevalence was highest among patients older than 25 years of age. A slight preference for the female sex was seen for diverticular disease as well as an apparent predominance in the age group 65 and over. A diagnosis of irritable bowel syndrome was made 2.5 times as often in women than in men and hardly ever in young people. The prevalences of the 37 groups of chronic diseases are shown in appendix 2 in relation to sex and age groups.

Logistic regression analyses

An overview of the results of the logistic regression analysis is shown in table 2. Only relationships between gastrointestinal categories and other chronic diseases that yielded statistical significance ($P < 0.05$) are presented in the table with the odds ratios, and their 95% confidence intervals.

Peptic Ulcer

Significantly positive associations were found for osteoporosis, depressive disorder, ischaemic heart disease and a "headache" group (migraine, cluster headache and trigeminal neuralgia).

The combination of depressive disorders, the group of psychosocial disorders (neurosis, personality disorders, mental retardation, and suicide attempt), and the "headache" group also showed a relation (OR = 1.5, 95% CI 1.1-2.0). Combining osteoarthritis, acquired deformities of limbs, rheumatoid arthritis and allied conditions, and osteoporosis yielded no statistical significance.

Non-ulcer dyspepsia

Both the group of psychosocial disorders and the "headache" group proved to be positively related with non-ulcer dyspepsia. Other findings were the significantly positive associations with parkinsonism, osteoporosis, and congenital anomalies of the urinary tract.

Esophageal disease, including diaphragmatic hernia

Esophageal disease was positively and significantly associated with a number of chronic disorders. A significant association was found with conditions of the locomotor tract. Osteoporosis and acquired deformities of spine or limbs showed a very strong relation with esophageal disease as did the group of rheumatoid arthritis and allied conditions. Combining these three groups to one cluster also showed a strong relation (OR = 2.0, 95% CI 1.6-2.4). Adding osteoarthritis in the analysis had the same effect (OR = 2.0, 95% CI 1.7-2.4). Secondly, metabolism disorders turned out to be associated with esophageal disease, with lipid disorders presenting the strongest relation. A striking result was the negative relation that was found for diabetes mellitus indicating a less frequent occurrence of diabetes mellitus in esophageal disease. Another negative relation was found for the group of dementia and other organic psychoses.

Both the group of psychosocial disorders and the "headache" group were significantly related with esophageal disease. Combining these two

TABLE 2

Relations between GI disorders and other chronic disorders, adjusted for age and sex. Significant odds ratios, 95% CI and significant power are presented

	Peptic ulcer	Non-ulcer dyspepsia	Esophageal disease incl. diaphr. hernia	Inflammatory bowel disease	Diverticular disease	Irritable bowel syndrome
Osteo-arthritis				1.47 (1.20-1.82)		
Acquired deformities of limbs			1.67 (1.26-2.22)			1.97 (1.45-2.67)
Rheumatoid arthritis, allied conditions			1.74 (1.16-2.59)	3.66 (1.89-7.09)	1.99 (1.31-3.03)	
Osteoporosis	1.81 (1.08-3.04)	2.17 (1.07-4.39)	2.53 (1.82-3.53)		1.52 (1.03-2.26)	
Chronic lung disease					1.67 (1.27-2.20)	
Asthma			1.77 (1.29-2.42)			
Ischaemic heart disease	1.46 (1.13-1.88)		1.38 (1.11-1.72)		1.36 (1.08-1.72)	
Peripheral arterial disease			1.36 (1.00-1.86)		1.41 (1.02-1.97)	
Phlebitis and thrombophlebitis				4.42 (1.36-14.4)		
Hypothyroidism/myxedema					1.67 (1.27-2.20)	
Diabetes mellitus			0.71 (0.52-0.97)			
Gout			1.75 (1.13-2.73)		1.83 (1.12-2.99)	
Lipid metabolism disorders			1.74 (1.33-2.27)		1.41 (1.00-1.98)	
Dementia, other organic psychosis			0.27*** (0.08-0.87)			

TABLE 2 (continued)

	Peptic ulcer	Non-ulcer dyspepsia	Esophageal disease incl. diaphr. hernia	Inflammatory bowel disease	Diverticular disease	Irritable bowel syndrome
Neurotic or personality disorder; mental retardation, suicide attempt		2.12* (1.24-3.62)	1.67* (1.18-2.37)		2.15*** (1.46-3.18)	4.29*** (3.29-5.60)
Depressive disorder	1.77 (1.08-2.89)				2.16*** (1.43-3.26)	2.82*** (1.96-4.06)
Atopic dermatitis, eczema				2.01 (1.01-4.00)		
Otosclerosis, deafness (partial or complete)				1.43	(1.03-1.98)	
Congenital anomalies urinary tract		4.31 (1.32-14.0)				
Benign prostatic hypertrophy					1.98 (1.19-3.30)	
Migraine/ cluster headache/ trigeminus neuralgia	2.00 (1.19-3.36)	2.39 (1.24-4.58)	1.80 (1.18-2.76)			
Parkinsonism		3.67* (1.44-9.35)				

* POWER \geq 0.80;

** POWER > 0.90;

*** POWER > 0.95

with depressive disorders in additional analysis again showed a relation (OR = 1.7, 95% CI 1.4-2.2). Other associations with esophageal disease were found for asthma, ischaemic heart disease, and peripheral arterial disease.

Combining ischaemic heart disease, hypertension, cerebrovascular accident/stroke, and peripheral arterial disease showed no significant association.

Inflammatory bowel disease

Inflammatory bowel disease was strongly associated with the group of rheumatoid arthritis and allied conditions. Furthermore, both atopic dermatitis and (thrombo)phlebitis coincided significantly with inflammatory bowel disease.

Diverticular disease

Chronic disorders of the locomotor tract turned out to be associated with diverticular disease. Both osteoarthritis and the group of rheumatoid arthritis and allied conditions showed strong relations. Less strong but statistically significant was the association with osteoporosis.

Apparent associations were found with hypothyroidism/myxedema, gout and lipid metabolism disorders. Depressive disorders and the group of psychosocial disorders both related strongly with diverticular disease. Combining these two with the "headache" group also resulted in a strong association (OR = 1.9, 95% CI 1.4-2.5). Cardiovascular disorders and ischaemic heart disease showed a stronger relation than peripheral arterial disease.

Furthermore, chronic lung disease, benign prostatic hypertrophy, and hearing loss showed apparent associations, although the latter was less strong related than the other two groups.

Irritable bowel syndrome

A significant association was found for acquired deformities of limbs or spine. Other findings were the strong relations with depressive disorder, the group of psychosocial disorders and the headache group. Combining these three again showed a strong relation with irritable bowel syndrome (OR = 3.2, 95% CI 2.6-4.0).

The combination of osteoarthritis, acquired deformities of spine or limbs, rheumatoid arthritis and allied conditions, and osteoporosis also showed a significant association (OR = 1.5, 95% CI 1.2-1.9).

Discussion

Esophageal and diverticular disease in particular proved to be disease categories with a high amount of comorbidity. Surprisingly, cancer of the gastrointestinal tract was not associated with the GI disorders analysed in the present study. Especially inflammatory bowel disease

and peptic ulcer showed no relation with malignancy. This might be explained by the cross-sectional nature of this study, which makes it impossible to detect a possible transition from a non-malignant disease into a malignant one in the course of time. Therefore, it is still possible to find such a relation in a longitudinal analysis.

Diabetes mellitus, known for its high occurrence of comorbidity, showed no association with the GI disease categories, except for esophageal disease that proved to be negatively associated with diabetes mellitus. It could be hypothesised that diabetes is a condition protecting against the development of esophageal disease because of alterations in life style in diabetics as refraining from alcohol intake and smoking. Additional research is needed, however, to test this hypothesis.

A remarkable finding was the fact that all categories of GI disorders were related to conditions affecting the locomotor tract. This was most distinct for diverticular and esophageal disease. As correction for age and sex was provided in the analysis these factors are not likely to offer an explanation for the association with locomotor disorders. Significant associations between the occurrence of GI syndromes such as dyspepsia or irritable bowel syndrome and a reduction of mobility, lower limb function or functional ability have been mentioned by others in the literature. They suggested a diffuse disorder affecting both smooth and striated muscles as a possible explanation (15).

An additional striking result was the association of most of the GI disease categories with depressive disorders, the group of psychosocial disorders, and the "headache" group. Inflammatory bowel disease was the only category that showed no association with these disorders. It has been suggested that a depression may result from having any chronic disease rather than from a typical gastrointestinal disorder (16). Emotional symptoms and psychiatric disorders, however, have been reported to be associated with gastrointestinal illness in general and irritable bowel syndrome, non-ulcer dyspepsia, peptic ulcer and inflammatory bowel disease in particular (2, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30).

A finding for which we have no good explanation was the lack of an association between peptic ulcer and the group of psychosocial disorders. For many years peptic ulcers have been considered a true example of a psychosomatic disease.

A more frequent occurrence of peptic ulcer in ischaemic heart disease, rheumatoid arthritis, and liver cirrhosis, and association between peptic ulcer and chronic disease of the joints, lungs, pancreas, and liver

have been mentioned by Sonnenberg et al (31, 32). However, the nature of these studies is incomparable to the nature of our study.

Inflammatory bowel disease showed remarkable little comorbidity. The most important finding was the association with rheumatoid arthritis and allied conditions. A possible explanation is provided by the concept of a common determining factor of genetic or biologic nature (4), perhaps suggesting a role for HLA subtypes.

We used data from the Registration Network of Family Practices. Previous research has shown that patients included in this registry are comparable to the Dutch population with regard to socio-demographic characteristics (33). For comparison of the health status some reports about self-reported health and life style are available. People living in the province of Limburg report a somewhat lower health status, and higher number of chronic conditions and disabilities than the average Dutch citizen (34). The life expectancy of Dutch citizens is comparable to the average of the European Community (35).

We are aware of the considerable number of analyses performed in this study. Many statisticians are concerned about the interpretation of significant results when multiple comparisons are made. In this study more than 250 logistic regression analyses have been performed. This means that, testing significance at 5 percent, about 12 analyses will randomly show significance (type I error). Traditionally, using more stringent values has solved this problem. Bonferroni e.g. suggests dividing the α (percentage of accepted false positive results) by the number of tests. However, using this procedure one might rule out random associations, but at the same time the number of type II errors (rejecting a true association) will increase (36). It is however a warning to be cautious when interpreting multiple comparisons.

Our results support the hypothesis of a relation between gastrointestinal disease and conditions affecting the locomotor tract as well as psycho social and depressive disorders and different types of headaches. The direction of this relationship remains unclear as no incidence rates have been studied.

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Appendix 1

*Point prevalence of gastrointestinal disorders stratified for age and sex categories:
total number of patients and percentage*

Category	male		female		0-25 yrs		26-65 yrs		65 and over		Total	
Peptic ulcer disease	392	(1.3%)	194	(0.6%)	3	(0.0%)	358	(1.0%)	225	(2.5%)	586	(0.9%)
Non ulcer dyspepsia	153	(0.5%)	114	(0.4%)	7	(0.0%)	173	(0.5%)	87	(1.0%)	267	(0.4%)
Esophagusdisease + diaphragmatic hernia	390	(1.3%)	444	(1.4%)	17	(0.1%)	417	(1.2%)	400	(4.5%)	834	(1.3%)
Inflammatory bowel disease	113	(0.4%)	121	(0.4%)	12	(0.1%)	189	(0.5%)	33	(0.4%)	234	(0.4%)
Diverticular disease	237	(0.8%)	349	(1.1%)	0	(0.0%)	166	(0.5%)	420	(4.7%)	586	(0.9%)
Irritable Bowel Syndrome	186	(0.6%)	480	(1.5%)	41	(0.2%)	480	(1.4%)	145	(1.6%)	666	(1.1%)

Appendix 2

Point prevalence of chronic disease stratified for sex and age categories

Chronic disease	male	female	0-25	26-65	65+	Total
Osteoarthritis	4.0	6.0	0.1	3.7	20.6	5.0
Acquired deformities of limbs	2.9	3.4	1.9	3.3	5.3	3.2
Rheumatoid arthritis, allied conditions	0.8	1.2	0.1	1.0	2.8	1.0
Osteoporosis	0.2	1.2	0.0	0.2	4.1	0.7
Chronic lung disease	3.3	2.0	0.9	1.8	9.6	2.7
Asthma	4.8	3.9	1.5	3.4	3.0	4.4
Ischaemic heart disease	4.3	2.8	0.0	2.1	16.3	3.5
Heart failure	0.5	0.6	0.0	0.1	3.3	0.5
Hypertension with organ involvement	0.7	0.8	0.0	0.5	3.2	0.7
Cerebrovascular accident/stroke	0.8	0.7	0.0	0.4	3.6	0.7
Peripheral arterial disease	1.8	1.3	0.0	0.9	6.9	1.5
Pulmonary embolism	0.0	0.1	0.0	0.0	0.3	0.1
Phlebitis and thrombophlebitis	0.2	0.3	0.0	0.2	0.8	0.2
Hyperthyroidism/thyrototoxicosis	0.2	0.9	0.0	0.5	1.6	0.5
Hypothyroidism/myxedema	3.3	2.0	0.9	1.8	9.6	2.7
Diabetes mellitus	2.5	3.2	0.1	2.2	11.3	2.9
Gout	1.2	0.3	0.0	0.8	2.1	0.7
Lipid metabolism disorders	2.7	2.2	0.0	2.7	6.2	2.4
Dementia, other organic psychosis	0.2	0.4	0.0	0.1	1.8	0.3
Psychosis (including schizophrenia)	0.5	0.4	0.1	0.6	0.5	0.4
Neurotic disorder, personality disorder, mental retardation, suicide attempt	2.4	2.4	1.0	3.1	2.5	2.4
Depressive disorder	0.8	1.7	0.1	1.6	2.5	1.3
Atopic dermatitis, eczema	2.3	2.6	5.2	1.4	0.8	2.5
Retinopathy	0.4	0.6	0.0	0.4	2.0	0.5
Macular degeneration, blindness (all types)	0.8	0.9	0.4	0.7	2.9	0.9
Otosclerosis, deafness (partial or complete)	2.5	2.1	0.9	2.0	6.1	2.3
Malignant neoplasms gastrointestinal tract	1.6	2.0	0.1	1.4	6.8	1.8
Malignant neoplasms other tracts	0.4	0.4	0.0	0.2	1.6	0.4
Congenital anomalies urinary tract	0.2	0.3	0.2	0.3	0.3	0.2
Glomerulonephritis/nephrosis	0.1	0.1	0.0	0.2	0.3	0.1
Benign prostatic hypertrophy	0.9	0.0	0.0	0.2	2.2	0.4
Migraine/cluster headache/ trigeminal neuralgia	1.0	2.4	0.7	2.3	1.2	1.7
Poliomyelitis/enterovirus	0.0	0.0	0.0	0.0	0.1	0.0
Congenital anomalies CNS	0.2	0.1	0.2	0.1	0.1	0.1
Multiple sclerosis	0.0	0.1	0.0	0.1	0.1	0.1
Parkinsonism	0.2	0.2	0.0	0.0	1.2	0.2
Epilepsy (all types)	0.7	0.6	0.5	0.7	0.8	0.7