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RESEARCH ARTICLE

The role of diseases, risk factors and symptoms in the definition of multimorbidity – a systematic review

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ABSTRACT

Objective is to explore how multimorbidity is defined in the scientific literature, with a focus on the roles of diseases, risk factors, and symptoms in the definitions. Design: Systematic review. Methods: MEDLINE (PubMed), Embase, and The Cochrane Library were searched for relevant publications up until October 2013. One author extracted the information. Ambiguities were resolved, and consensus reached with one co-author. Outcome measures were: cut-off point for the number of conditions included in the definitions of multimorbidity; setting; data sources; number, kind, duration, and severity of diagnoses, risk factors, and symptoms. We reviewed 163 articles. In 61 articles (37%), the cut-off point for multimorbidity was two or more conditions (diseases, risk factors, or symptoms). The most frequently used setting was the general population (68 articles, 42%), and primary care (41 articles, 25%). Sources of data were primarily self-reports (56 articles, 42%). Out of the 163 articles selected, 115 had individually constructed multimorbidity definitions, and in these articles diseases occurred in all definitions, with diabetes as the most frequent. Risk factors occurred in 98 (85%) and symptoms in 71 (62%) of the definitions. The severity of conditions was used in 26 (23%) of the definitions, but in different ways. The definition of multimorbidity is heterogeneous and risk factors are more often included than symptoms. The severity of conditions is seldom included. Since the number of people living with multimorbidity is increasing there is a need to develop a concept of multimorbidity that is more useful in daily clinical work.

KEY POINTS

- The increasing number of multimorbidity patients challenges the healthcare system. The concept of multimorbidity needs further discussion in order to be implemented in daily clinical practice.
- Many definitions of multimorbidity exist and most often a cut-off point of two or more is applied to a range of 4–147 different conditions.
- Diseases are included in all definitions of multimorbidity.
- Risk factors are often included in existing definitions, whereas symptoms and the severity of the conditions are less frequently included.

Introduction

The occurrence of multimorbidity (MM), which can be defined as the co-existence in one patient of two or more concurrent chronic conditions (e.g., diseases, risk factors, or symptoms) is increasing.[1,2]. Even though the prevalence increases with age, the majority of patients suffering from MM are of working age.[3] For society, MM results in increased costs and more frequent hospital admissions.[4] For the individual, mortality increases [5] and quality of life decreases with the number of conditions.[6]

Definitions of MM are wide-ranging with conditions varying in number, kind, and severity. Sources of data and settings around the definitions are diverse, and sometimes social aspects or mental health are included in the definition.[7–9] The definition of MM is mainly

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based on diseases.[9] In general, a disease is an entity based on either symptoms and/or objective measures. A disease is often labelled with a diagnosis, and the diagnosis serves as a tool for health professionals to communicate and find optimal treatments and solutions for medical problems.[10,11] Risk factors for developing disease, however, are also often treated as diseases, as the purpose of paying attention to a risk factor is to create the basis for actions from the patient and the doctor to prevent disease.[12,13] Symptoms may be defined as "any expression of disturbed function or structure of the body and mind by a patient",[14] and the patient's interpretation of the intensity and the presumed danger of symptoms is central to decisions about if and when a doctor is consulted.[15,16] Diseases and risk factors can sometimes be less meaningful to patients since they do not always explain co-occurring symptoms.[17] Furthermore, a diagnosis, whether it comes from a disease or a risk factor, can lower self-rated health [18] and the relevance of becoming labelled with MM when only suffering from risk factors is questionable. On the other hand, symptoms cannot always be explained and can contain more dimensions of the human mind than strictly medical.[19] This means that substantially different aspects of health are included in definitions of MM. Existing MM definitions may seem more suitable for epidemiological research than for clinical work. In the light of the increasing prevalence and burden of MM, definitions which are more useful in daily practical work could be more helpful for both clinicians and patients.

The aim of this study was to review the literature on MM in order to examine how it is defined: What diseases, risk factors, and symptoms are included in the definition? Are the duration and severity of conditions considered? Are complications to a disease included together with this disease in the definition of MM or are they included as separate disease categories, e.g., retinopathies in the course of diabetes? Is clustering considered, e.g., the likelihood of conditions to appear together?

Methods

The review process was conducted according to PRISMA guidelines.[20]

Search strategy

A literature review was conducted in MEDLINE (PubMed) and Embase. The databases were searched up until 4 October 2013 (protocol can be forwarded on request). We applied the search string with different linguistic variations of the terms multimorbidity and comorbidity, and also with related synonyms, in order to increase sensitivity, i.e., the chance of finding articles considering MM without using the term itself. Since the word "multimorbidity" does not exist as a MeSH-term (Medical Subject Heading) in MEDLINE, we searched for it as a keyword. We searched for comorbidity both as a MeSH-term and as a keyword. The search was restricted to research on humans, in the English language, and articles with available abstracts. In addition, the same search was performed in The Cochrane Library up until 10 October 2013, but without restrictions. After exclusion of irrelevant references and removal of duplicates, no references remained from The Cochrane Library. One author (TGW) performed and conducted the search. For the search in MEDLINE (Box 1).

Selection of studies

After removal of duplicates, one author (TGW) screened all titles and abstracts for relevance. The eligibility of potentially relevant articles was assessed in full text (by TGW). For inclusion in the final synthesis, the articles had to be empirical and contain a definition of MM. Systematic reviews and theoretical articles were excluded because they mainly summarized the work of others without creating their own definitions (Figure 1). Since the aim of this study was to describe how MM is defined, we did not assess the quality of the articles included. Reference lists for all eligible articles and the systematic reviews that were excluded were searched by title for further articles. The first author (TGW) extracted data items into a pre-specified table. The following items were extracted: cut-off point in the number of conditions in the definition of MM, population size, setting, sources of data, the number and kind of conditions included, risk factors, symptoms, complications, duration of the conditions, considerations of clustering between conditions, and finally considerations

Box 1. Results of search strategy in MEDLINE.

#1,"Search (comorbidity AND ""multiple chronic disorders"")", 0
#2,"Search (comorbidity AND ""multiple chronic diseases"")", 30
#3,"Search (comorbidity AND ""multiple chronic conditions"")", 70
#4,"Search (co-morbidity AND ""multiple chronic disorders"")", 0
#5,"Search (co-morbidity AND ""multiple chronic diseases"")", 31
#6,"Search (co-morbidity AND ""multiple chronic conditions"")", 74
#7,"Search multi-morb*", 174
#8,"Search multimorb*", 1076
#9, "#1OR#2OR#3OR#4OR#5OR#6OR7#OR#8", 1313
#10, "#9, with Filters: Abstract available", 1204
#11, "#9, with Filters: Abstract available, Humans", 984
#12, "#9, with Filters: Abstract available, Humans, English", 588

| Matches identified through database searching in Embase (n=982) and PubMed (n=588) on the 4th Oct 2013. | → | Duplicates removed (n=627) |

Abstracts and titles screened (n=943)

Excluded articles (n=695):
Not addressing multimorbidity or comorbidity (n=390)
Exclusively considering comorbidity indices or comorbidity (n =8)
Exclusively addressing psychiatric comorbidities (n = 12)
Considering a specific disease/particular combinations of diseases (n = 161)
Population aged under 18 years (n = 5)
Conference abstracts (n=80)
Qualitative studies (n = 35)
Other language than English (n=4)

Articles assessed for full text reading (n=248)

Excluded articles (n= 98):
Not stating a definition of multimorbidity (n =32)
Systematic reviews or reviews (n=26)
Theoretical/methodological articles (n=26)
Dealing with co-morbidity only (n=9)
Editorial or commentary (n=4)
Already included in another article (n=1)

Articles meeting inclusion criteria (n=150)

Additional articles from searching cross-references (n=13)

Articles included in the review (n=163)
Articles presenting specific types and numbers of conditions (n=115)
Articles using multimorbidity indices (n=30)
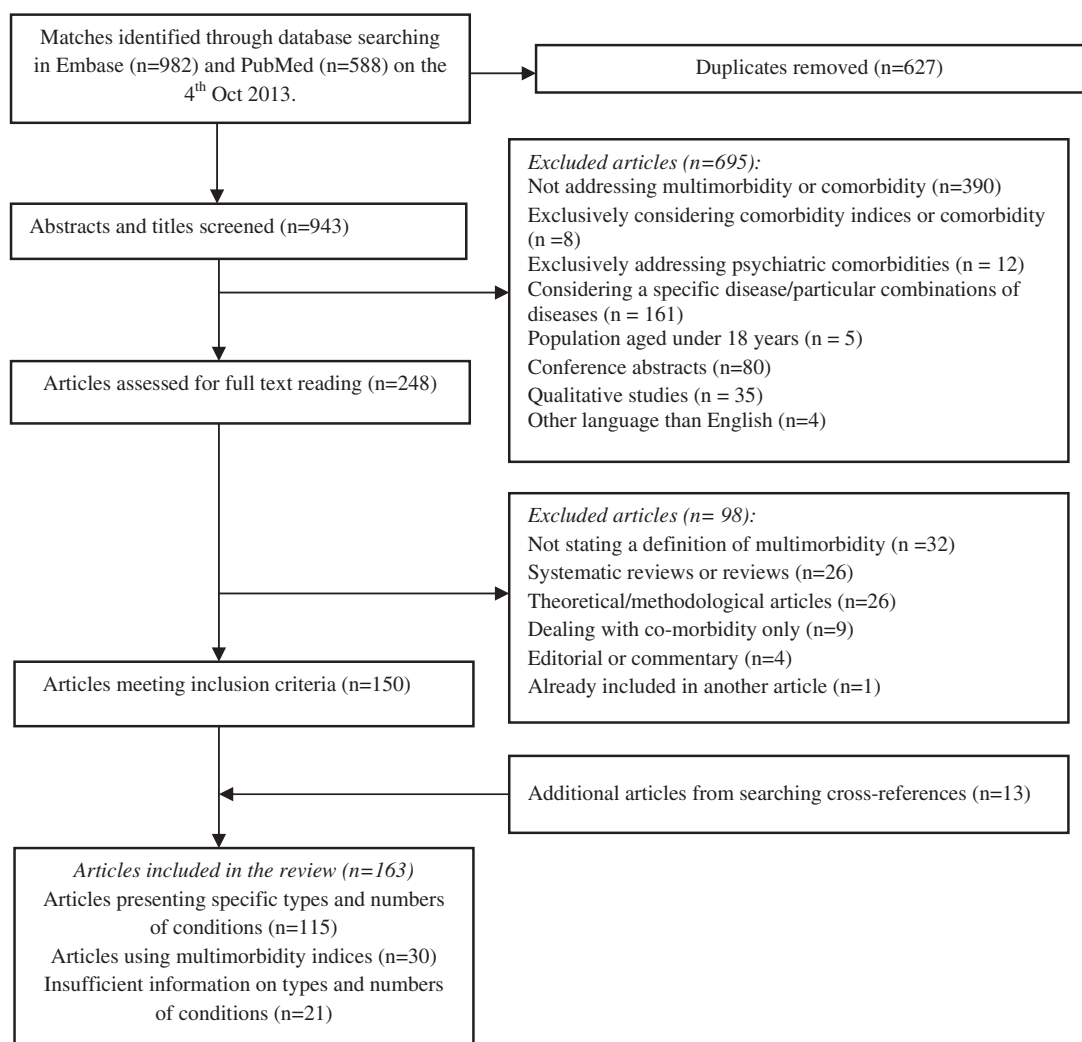Insufficient information on types and numbers of conditions (n=21)

Figure 1. Flow-chart describing the selection of studies.

about and measurement of the severity of conditions included. (The full document and the references of all 163 articles included in our study are available as an electronic appendix 1 and 2 at http://almenpraksis.ku.dk/english/research/appendix_1.pdf/ and at http://almenpraksis.ku.dk/english/research/appendix_2.pdf/ Ambiguous findings that emerged after titles and abstracts were screened, and then read in full text, were discussed and resolved with one of the co-authors (NdFO).

Definition of diseases, risk factors and symptoms

Diseases were defined based on the assumption that they were health conditions diagnosed by objective measures, symptoms or both, and that a distinct diagnostic code exists to describe them. Risk factors were defined as conditions or measurements associated with the probability of disease or death [21,22] not necessarily recognised by the patient. Symptoms were defined by using ICPC's definition of symptoms.[23]

Results

Of 248 articles screened, we included 163 in our study (Figure 1). The majority of these articles were observational and only three were randomized controlled trials.

Definition of MM, population size, setting, and data sources

Of the 163 articles we selected, 61 (37%) used a cut-off point of two or more conditions in their definition of MM (i.e., diseases, risk factors, and symptoms); four (2%) used a cut-off point of one condition, and 11 (7%) used a cut-off point of three conditions. Thirteen articles (8%) had several cut-off points, 19 (12%) used different MM-indices without a specific cut-off, while 55 (34%) did not specify cut-offs at all.

The population size varied considerably in the selected articles. Twenty-four articles (15%) had

Table 1. Most prevalent diseases, risk factors and symptoms in the definition of multimorbidity in the 115 articles.

Most prevalent conditions	Number of articles	Frequency (%)
Diseases		
Diabetes	112	97
Stroke	92	80
Cancer	91	79
Ischemic heart disease (incl. MI and angina)	81	70
COPD	73	63
Heart failure	70	61
Asthma	66	57
Depression	58	50
Kidney disease	52	45
Osteoarthritis	50	43
Risk factors*	98	85
Hypertension	91	79
Osteoporosis	43	37
Hypercholesterolemia	34	30
Obesity	28	24
Overweight	7	6
Symptoms	71	62
Back pain	32	28
Visual impairment	25	22
Urinary incontinence	16	14
Alcohol disorder/abuse	16	14
Hearing impairment	14	12
GI-problems	11	10
Headache	14	12
Dizziness	13	11
Tobacco abuse	9	8
Sleeping disorders (incl. insomnia)	8	7

*Only five risk factors are included in the MM-definitions.

>100.000 participants and 48 (29%) had <1000 participants, with a range from 38 patients in the smallest to approximately 31 million in the largest. Participants were mainly recruited from the general population (68 articles, 42%), while many came from primary care (41 articles, 25%), and some from secondary care (16 articles, 10%). In one article, participants were recruited from a nursing home,[24] and in 26 articles (16%) they came from specific databases, for example veterans,[25] twins,[26] or employees.[27] Eleven articles (7%) included people from several settings simultaneously. Data were from self-reports (56 articles, 34%), registries (36 articles, 22%), medical records (22 articles, 13%), clinical examinations (3 articles, 2%), and medication data (2 articles, 1%). Finally, 44 articles (27%) had data from several sources concurrently.

Of the 163 articles included in our study, 115 (71%) used individually constructed definitions of MM and only a handful of the articles used an existing definition. The results of the 115 articles are presented below. Thirty articles (18%) defined MM using either existing morbidity indices, which were not originally designed to rate MM, or a clinical database of ICPC codes (see below). Three articles were included in two categories: as an individually developed definition and as an index. These articles used an index but explicitly selected some of the conditions from the index in question, indicating a process of reflection when defining MM (see electronic appendix 1). Finally, 21 articles (13%) presented insufficient information about types of conditions, or did not select the conditions in advance, and they are not reported upon here.

In the 115 articles that used individually constructed definitions of MM, the pool of conditions to choose from varied from 4 [28] to 147.[29] The conditions included were primarily chronic as defined by WHO: "health problems that require on-going management over a period of years or decades".[30] Other definitions were also used, e.g., if the condition was presumed permanent or caused by pathological alterations without chance of reversibility.[31]

Diseases

All 115 articles reported information on diseases. Some included clear diagnostic entities such as myocardial infarction,[32] while others included broader diagnostic groups like heart disease.[33] Diabetes, stroke, and cancer were the most frequently occurring diseases (Table 1). Fibromyalgia, sexually transmitted diseases, parasites, and infections were the least frequently occurring diseases.

Risk factors

Ninety eight articles (85%) included one or more of the following risk factors: hypertension, osteoporosis, hypercholesterolemia, obesity, and overweight (Table 1). Risk factors were included in the definitions in the same way as diseases with one risk factor representing one condition.

Symptoms

Seventy one articles (62%) reported information on symptoms. As for diseases and risk factors, one symptom represented one condition. The most frequently occurring symptom was back pain, followed by visual impairment, and urinary incontinence (Table 1). Several symptoms occurred in only one definition, e.g., itching, nausea, dysphagia, diarrhea and abdominal pain.

The role of duration, severity, clustering of conditions, and occurrence of complications

The duration of a condition was explicitly mentioned and specified as an inclusion criterion for the definition of MM in 32 of the 115 articles (28%). However, when used, duration was operationalized in many different

Table 2. Every aspect of duration mentioned in the 115 articles.

Author, publication year	Disease	Duration
Agborsangaya, 2013	All	Health status the past 12 months.
Alonso, 2004	Ischemic heart disease	Last year
Andrade, 2010	Psychiatric disorders	"…felt for a period longer than two weeks…" and "have you had feelings of anxiety and tension for more than one month".
Ataguba, 2013	Illness	1 month
	Disabilities	6 months
Barnett, 2012	Any kind	For prescriptions >12 months
Bayliss, 2004	Myocardial infarction	Within the past 6 months and more than 1 year ago
	Angina	History
Bayliss, 2005	Cancer	Past 5 years
	All (except cancer)	Two years before
Bernabeu-Wittel, 2009	Chronic renal disease	Creatinemia or proteinuria for at least 3 months
Bernabeu-Wittel, 2011	Chronic renal disease	Creatinemia or proteinuria for at least 3 months
Bernabeu-Wittel, 2011	Chronic renal disease	Creatinemia or proteinuria for at least 3 months
Cheung, 2013	Malignancy	Within 5 years
Diederichs, 2012	All	Occurrence the last 5 years
Drewes, 2011	Depressive symptoms	Previous year
	Cancer and myocardial infarction	History
Fried 2012	All	"Have you ever been told by a doctor?"
	Asthma	During the past 12 months have you had an episode of asthma?
Fuchs, 2012	All	Ever told by a physician and present the last 12 months
	Cancer	Life time medical history
	Chronic back pain	At least 3 months the last 12 months
Grimby, 1997	Knee joint disorders, hip joint disorders and upper extremity disorders	More than 6 months
	All	Experienced the disease in the last 12 months
Gunn, 2012		
Haggerty, 2010	Cancer	Past 5 years
Hunger, 2011	All	Ever had
	Sputum for chronic bronchitis	3 months
Härter, 2007	All	Present within the previous 12 months.
Marengoni, 2008	Malignancy	Anamnestic and current
Marengoni, 2008	Malignancy	Anamnestic and current
Marin-Ruiz, 2011	Cancer	Diagnosed within past 5 years.
McDaid, 2013	All	Present the previous year.
McRae, 2013	All	More than 6 months.
Menotti, 2001	COPD	Productive cough for at least three months
Neeleman, 2001	All	Experienced the previous 1 year
Neeleman, 2002	Psychiatric symptoms	Present during the preceding year
Payne, 2013	Based on prescription	12 months
	Cancer	Last 5 years
Rincon-Gomez, 2011	Chronic renal disease	Creatinemia or proteinuria for at least 3 months
Salive, 2013	All	1, 2, or 3 years, depending on condition
Schneider, 2009	Cancer, COPD, depression	1-year look back period
	Chronic kidney disease, diabetes, heart failure	2-years look back period
van Oostrom, 2012	All	Registered with the condition in 3 consecutive years.

ways by, for instance, including only conditions present during the last year, or using more specific time limits for certain conditions, such as excluding cancer diagnosed more than 5 years before the study (Table 2). Severity was included to some extent in 26 of the articles (23%). It varied from patients' self-reported severity of a condition, to only including diseases with defined severity stages, e.g., heart failure with at least NYHA II (New York Heart Association functional classification, stage 2). Considerations on how conditions are clustered in the individually constructed MM definitions were only apparent in a few articles. These mainly described conditions within different organ groups, or they grouped conditions with the same pathophysiological mechanisms. However, considerations of clustering did not influence the results since most of the conditions were not reported upon as a

group but as separate diagnoses. Complications were in general not stated as such even though, for example, renal failure that could be considered a complication of diabetes was included in some definitions of MM. Therefore, information on clustering and complications could not be summarised.

Multimorbidity indices

Almost all indices include diseases. The Adjusted Clinical Groups (ACG) Case Mix System and its subgroups, Aggregated Diagnosis Groups (ADG), Medication-based Rx-MG, Expanded Diagnosis Clusters (EDC), and Resource Utilization Bands (RUB) almost all contain information on both risk factors and symptoms. Severity is also included in most ACG subgroups (Table 3). For Clinical Classifications Software (CCS), risk

Table 3. Multimorbidity indices and databases used in 30 articles out of the total of 163 articles.

Index	Classification codes	Outcomes of interest	Number of diseases	Risk factors included	Symptoms included	Severity included
The Charlson Comorbidity Index (CCI)	ICD, ICPC or self-reports	Mortality	19 (17 in modified version)	No	Yes	Yes
Clinical Classification Software (CCS)	ICD-9-CM (5-digit codes)	Cluster diagnoses and procedures in clinically meaningful categories	14,000 codes grouped in 285 diagnose categories and 231 procedure categories	Yes	Yes	No
Cumulative Illness Rating Scale (CIRS) and geriatric version (CIRS-G)	ICD, ICPC and self-reports	Physical impairment	13 body systems (14 in CIRS-G)	Not specified	Not specified	Yes
Adjusted Clinical Groups (ACG-Case Mix System)	ICD-9 and -10	Health care utilization and costs	25,000 diagnoses and 3900 procedures	Yes	Yes	Yes
Aggregated diagnosis groups (ADG)*	ICD-9, 9-CM and -10	Health care use	The 25,000 diagnoses divided in to 32 diagnostic clusters	Yes	Yes	Yes
Medication-based Rx-MG*	US NDC codes and Anatomical Therapeutic Chemical (ATC) system codes	Medical and total health care costs	19 major Rx-MG categories	Not stated	Yes	Not stated
Expanded Diagnosis Clusters (EDC)*	ICD-9, -9-CM and -10	Identifying people with specific symptoms and diagnoses	264 EDC further divided in 27 Major Expanded Diagnosis Clusters (MEDCs)	Yes	Yes	No
Resource Utilization Bands (RUBs)*	IC-9 and -10	Predict resource use	Four categories RUB 0 (No resource use)-RUB 3 (High expected costs)	Yes	Yes	Yes
The Functional Comorbidity Index (FCI)	Self-reports	Physical function	18 conditions	Yes	Yes	No
The Index of Coexistent Disease (ICED)	Self-reports and laboratory tests	Comorbidity severity	13 disease categories with 17 conditions and 11 domains of physical impairment	Yes	No	Yes
Quality and Outcomes Framework (QoF)	Read codes	For payment and performance of GPs	17 conditions	Yes	Yes	No
The Registration Network Family Practices (RNH)	ICPC	To identify health problems and combinations of health problems	335 chronic diagnostic categories (database includes 700)	Yes	No	No

*Based on ACG-Case Mix System

factors and symptoms are included in the index, but not severity. The Cumulative Illness Rating Scale (CIRS), which includes diseases from 13 different organ systems, does not specify whether risk factors or symptoms are included but it places severity at the centre of the index (with rating of every condition on a four grade scale). Charlson Comorbidity Index (CCI) includes some symptoms and rates severity to some extent, but contains no risk factors. Systems such as the Quality and Outcomes Framework (QoF) and The Functional Comorbidity Index (FCI) include risk factors and symptoms but do not consider their severity. The Index of Coexistent Disease (ICED), on the other hand, contains both risk factors and severity, but has no symptoms. Finally a Dutch database, The Registration Network Family Practices (RNH) includes risk factors, but neither symptoms nor severity. Some articles that used an index did not explicitly mention if they used all conditions included in the index or just a selection.

Discussion

We found great heterogeneity in the definition of MM and the pool of conditions to choose from varied from 4 to 147. Most often a cut-off point of two or more conditions was used to define MM. Diseases were used in all definitions, and the most common were diabetes, stroke, cancer, ischaemic heart disease, and COPD (Table 1). Risk factors were included in 85% of the individually developed definitions of MM and in all indices except CCI. Two further indices gave inadequate information (Table 3). Hypertension was the most frequent risk factor and was included to the same degree as a cancer diagnosis in MM definitions. Other risk factor-based conditions were osteoporosis, hypercholesterolemia, obesity, and overweight (Table 1). Symptoms were included in 62% of the articles with great diversity regarding the types of symptoms. The most frequent symptoms were back pain, visual impairment, urinary incontinence, alcohol disorder, and hearing impairment (Table 1). Duration was mentioned in 28% of the articles (Table 2) and, to some extent, the severity of conditions was included in 23% of the articles.

The role of diseases

Diseases are included in all definitions of MM. However, they do not always explain the patient's experience of symptoms, and patient needs and symptom experience are not necessarily an indication of an underlying disease. Relying only on diseases when

defining MM may lead to a concept that does not reflect patients' perspectives. Previously, diabetes has been found to be the most frequent disease in the definition of MM, followed by stroke, cardiovascular disease, hypertension, and cancer.[9] We identified a similar pattern, even though we found that cancer was used more often than cardiovascular disease. This could be due to different ways of defining cardiovascular disease.

The role of risk factors

Risk factors, based on objective rather than subjective measures, are easy to quantify [34] and therefore easy to use in epidemiological research. Hypertension and hyperlipidaemia were observed as the most prevalent conditions in a population study that included almost 31 million Americans.[35] Similarly, in other studies in different settings and countries, hypertension is reported as the most prevalent chronic condition.[36,37] We found this mirrored in the definitions of MM as well. One systematic review found that prevalence was the main reason for including conditions in MM.[9] Nevertheless, conditions that are common in the population, like allergies and hypertension, are not necessarily those with the largest impact on patients' functional status or quality of life.[38] Furthermore, the burden of illness reported by patients is lower among those having hypertension compared to patients with other conditions.[37] If relying too much on risk factors when defining MM, the MM measure will probably become too coloured by aspects concerning awareness of future illness, rather than the actual disease burden or functional status.

The role of symptoms

Symptoms are generally the focus of patients' concerns and are dependent on the experiences and history of the patient and often the reason for contacting a doctor. For the doctor, the symptom and what the patient presents are central for the diagnostic process and the doctor grades according to importance and frames what the patient says.[39] Headache and back pain seem to be the most debilitating symptoms among people who report poor self-rated health,[40] and back pain is reported as among the most prevalent conditions in all age groups.[41] Furthermore, symptoms are an important factor for mortality in line with diseases.[42] In this review, we found that symptoms occur less frequently in the definition of MM than risk factors.

Relation to other studies

Since useful clinical guidelines for patients with MM are scarce it was expected [43] that only a minority of the articles found in the literature search were randomized controlled trials. Furthermore, randomized controlled trials involving primary care patients rarely report whether patients with coexisting conditions are excluded or not, and if they are included only few conditions are considered.[44] Pharmaceutical trials often have many exclusion criteria for chronic conditions compared to observational studies.

The considerable variability in the prevalence of MM between studies may have several explanations. First, the setting is important. MM is obviously very common in nursing homes, and patients recruited in family practice are more likely to have more conditions compared to those recruited in the general population.[45] Second, MM increases with the range of conditions included in the definition.[8] Third, the longer the observation period, the more conditions and clusters of diagnoses are captured.[46] Fourth, sources of data can affect prevalence. Prevalence is higher when more conditions are considered or when the cut-off of two or more conditions is used instead of a higher cut-off. Furthermore, the prevalence of MM rises when conditions are counted as single diseases with a unique diagnosis code instead of being included in the group of codes (often organ system) the condition belongs to.[47] On the other hand, complexity of the conditions and also health care use are dependent on if conditions are concordant or discordant, i.e. have the same pathophysiology with equal management or not [48] and conditions that cluster tend to be more concordant.

Within the last 5 years, there have been several systematic reviews on MM. Their focus has varied from occurrence, patterns, and consequences of MM,[8,49,50] to interventions,[51] functional status,[52] self-management,[53] and implementation of care programs.[54] One review focused on measures of disease burden and found indices like CCI, CIRS, and ACG System useful depending on the outcome of interest.[55] We found 30 articles that used indices for measuring MM. Indices of MM may be better than simple counts of conditions to detect certain circumstances that are important for the patient, such as psychological distress.[56] This is because some indices allow important information from the text of the medical record to be included with diseases. However, prevalence estimates using either chapters in ICPC, ICD-10, or CIRS have shown to be comparable.[47]

To the best of our knowledge, only two reviews have studied the definition of MM until now. In 2009,

Diederichs et al. collected information on the number and type of conditions from 39 selected articles.[9] As in the present review, they found great heterogeneity between studies in the type of conditions that could account for MM and they highlighted the need for a uniform way to estimate MM. In 2013, Le Reste et al. suggested a comprehensive definition of MM specifically suited to primary care. Based on a selection of 54 qualitative articles, they concluded: "MM is defined as any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor". In accordance with our findings, all definitions of MM contained several chronic diseases. Thus, while it seems meaningful to include at least one chronic condition as Le Reste et al. suggest, we found that acute conditions are very rarely included. In some specialties one chronic condition could be meaningful in the co-occurrence of an extra acute condition, e.g., diabetes in a surgical patient. However, for general practice where the acute complaints can be less severe the importance of this way of defining MM can be less clear, especially if we will use MM prevalence to plan healthcare.[47] Including biopsychosocial factors opens up the possibility of including symptoms, which is one way of integrating patient perspectives in MM-definitions, as long as a symptom is not classified as a chronic condition and already included. Thus, Le Reste et al. consider disease burden, risk factors, social network etc. to be modifiers of the effects of MM [7] and their definition may better reflect daily clinical work in general practice in comparison with counting diseases. By including the disease burden, they also consider the severity of the conditions, which we found included in only a quarter of the articles we selected. While we found risk factors to be one of the most important features of the MM definition to date, Le Reste et al. maintain that risk factors only contribute to the definition of MM when they occur in combination with other chronic conditions, implying that risk factors alone cannot lead to MM. Further, Le Reste et al. include social networks as modifiers which seems meaningful since the contextual factors surrounding a patient are sometimes as important as a disease.[57] However, operationalization of social factors is difficult. While patients can have a large social network, support from it can be of low quality, and religious beliefs or cultural traditions can give patients obligations that are difficult to capture in a definition. Furthermore, the point in time to concentrate on a problem can be more important than the diagnosis itself. For example, a diagnosis made 5 years ago is often not the focus of concern any more.[58]

Limitations and strengths

The objective of this study was to shed light on the diversity of definitions of MM. It is possible, however, that our search strategy has overlooked important articles having a unique definition, and in this context the lack of a MeSH-term for MM was a limitation. We compensated for this by choosing a broad search strategy with several linguistic variations of MM to increase sensitivity. Furthermore, there was only one reader making the selection of articles, but even minor inconsistencies were settled in consensus between two authors. We could have included languages other than English in our study, but a substantial number of the selected articles came from authors whose mother tongue is not English. Therefore, we believe our findings are not restricted to English-speaking countries. A major strength of the current review is the thorough systematic work in accordance with PRISMA-guidelines. We therefore expect that most of the existing definitions of MM were detected and included.

Clinical implications

The increase in MM is consistent between countries and one study examining the development of MM over the last 20 years found the largest increase in MM prevalence for those with four or more conditions.[2] MM accounts for many consultations in primary care. The number of conditions is associated with the number of consultations [4] and is inversely associated with continuity of care.[59] Furthermore, when defining MM as two or more conditions almost half of the patients in primary care are multimorbid [47] and this will become even more pronounced in the future. However, counting diseases and mapping patterns are maybe of less relevance compared to the disability connected with and the severity of the conditions,[52] also because interventions for MM have shown to be most effective when focusing on functional difficulties rather than the individual diseases.[51] There is a need to discuss definitions of MM that are more relevant for daily clinical work with patients, and that have a better capability of capturing the patient's perspective. These definitions can help us identify MM where it is imperative to treat, and MM where the best solution may be not to treat. Based on qualitative data, Le Reste et al. [7] have given the most inspiring and comprehensive definition of MM so far, one that is particularly suited to primary care. Since this review has explored the role of symptoms and risk factors in the definition of MM, it can make a valid contribution to the discussion of future definitions of MM.

Conclusion

In line with earlier research, this review of 163 articles shows a large variation in the number and types of conditions that are included in the definition of MM, which consist mainly of diseases. The fundamental role of risk factors in the definition of MM is one reason for the high prevalence of MM. Symptoms and severity are included less often and this contributes to making the existing definitions more usable for epidemiologists than for clinicians and patients. This review adds to the discussion about more comprehensive and clinically relevant MM definitions.

Disclosure statement

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