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Title: Defining and measuring multimorbidity: a systematic review of systematic reviews

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Abstract

Background

Multimorbidity, the coexistence of multiple health conditions, is a growing public health challenge. Research and intervention development are hampered by the lack of consensus regarding defining and measuring multimorbidity. The aim of this systematic review was to pool the findings of systematic reviews examining definitions and measures of multimorbidity.

Methods

Medline, Embase, PubMed and Cochrane were searched from database inception to February 2017. Two authors independently screened titles, abstracts and full texts and extracted data from the included papers. Disagreements were resolved with a third author. Reviews were quality assessed.

Results

Of six reviews, two focussed on definitions and four on measures. Multimorbidity was commonly defined as the presence of multiple diseases or conditions, often with a cut-off of two or more. One review developed a holistic definition including biopsychosocial and somatic factors as well as disease. Reviews recommended using measures validated for the outcome of interest. Disease counts are an alternative if no validated measure exists.

Conclusions

To enable comparison between studies and settings, researchers and practitioners should be explicit about their choice of definition and measure. Using a cut-off of two or more conditions as part of the definition is widely adopted. Measure selection should be based on tools validated for the outcome being considered. Where there is no validated measure, or where multiple outcomes or populations are being considered, disease counts are appropriate.

Keywords

- Multimorbidity
- Comorbidity
- Systematic Review

Introduction

Multimorbidity is commonly understood to be the coexistence of multiple health conditions in an individual.^{1,2} A related term, comorbidity, describes the burden of illness co-existing with a particular disease of interest.³ Multimorbidity is a growing global public health challenge as populations age and the prevalence of long term conditions rises.^{1,2}

Multimorbidity is associated with poorer outcomes and the increased use of health and social care services with associated costs.^{4,5} There is increasing awareness that healthcare services are not adequately designed to meet the challenges of multimorbidity. Secondary care services are generally single disease focussed.^{6,7} Practitioners, particularly in primary care, face challenges in using clinical guidelines which are generally developed for single conditions or groups of similar conditions.⁸ These issues bring associated risks, for example polypharmacy,^{8,9} and challenges associated with managing patients with complex needs in resource limited environments.⁶ Multimorbidity also places a burden on individuals who face poorer quality of life and increased disability.¹⁰ It is highly correlated with frailty (an age related decline leading to reduced reserves of physical and mental health capacity, resulting in vulnerability to stressors and an increased risk of poor health outcomes).^{11,12}

Despite these challenges, there is no international consensus regarding the best way to define and measure multimorbidity.¹³ This makes carrying out and interpreting research, comparing findings across populations and developing guidelines and interventions difficult. A review of prevalence studies of multimorbidity, found estimates ranging between less than 5% to more than 95%, often due to differences in the operational definition of multimorbidity.² The National Institute for Health and Care Excellence (NICE) recently developed a multimorbidity guideline and commented that measuring the prevalence of multimorbidity is complex due to the varying measures being used.¹⁴

A number of reviews have summarised the multimorbidity definitions or measures used in primary studies. Our aim was to build consensus on the most appropriate ways to define and measure multimorbidity by pooling the findings of these systematic reviews.

Methods

The PRISMA 2009 checklist guided method development and reporting of findings.¹⁵ Medline, Embase, PubMed and the Cochrane database of systematic reviews were searched from database inception to 13th February 2017. The search strategy was comparable across all databases. At the time of searching, there was no MeSH term for multimorbidity. The search terms relating to “multimorbidity” and its measures were drawn from a previous systematic review of the multimorbidity literature.¹⁶ These were combined by the Boolean operator “AND” with “review” as a title word. The terms were searched in the title only, as an initial trial search found that widening this to the abstract or full text significantly reduced the ability to detect relevant reviews. The search strategy is in Supplementary Table 1.

Systematic reviews of the multimorbidity literature which examined multimorbidity definitions and/or measures as a central focus of the review were included. Whilst comorbidity is now commonly accepted to be distinct from multimorbidity, it is known that the terms have been used synonymously in the past. Reviews of comorbidity where no specific index disease was considered were therefore eligible. Systematic reviews which did not have the primary aim to summarise multimorbidity definitions and measures were excluded. Reviews which were “narrative” or “semi-structured” or which otherwise were not systematic reviews were excluded.

Title, abstract and full-text screening were carried out independently by two authors (MCJ and SWM). Disagreement was resolved by CB. Primary data extraction was carried out by MCJ with four others acting as independent second reviewers (CB, MC, GJP and SWM). The data extraction form was prepared and piloted by MCJ and finalised by discussion with the other reviewers. Data extraction included: the review characteristics, the definition and measures of multimorbidity presented in the review and the rationale behind any recommended measures of multimorbidity (if given). Scottish Intercollegiate Guidelines Network critical appraisal checklists¹⁷ were used to assess the quality of

included reviews (“low quality”, “acceptable” or “high quality”). The results were combined narratively.

Results

Figure 1 summarises the results of the search. Out of 1,051 articles sourced during the search, there were 432 duplicates. Following screening of titles, abstracts and full texts, six reviews were included.^{16,18-22} The characteristics of these reviews, including their stated aims, are presented in Table 1. The Le Reste and Willadsen reviews focused on the definition of multimorbidity, whilst the remaining four focussed on measures. The number of studies included by the reviews ranged from 39 to 194. Five reviews were of “acceptable quality”.^{16,19-22} De Groot was “low quality” as they did not report the literature search strategy, the results of the literature search and the identification of papers clearly.¹⁸

Definitions

The multimorbidity definitions used in the included reviews are in Table 2. As described above, Le Reste and Willadsen were the only papers focused on reviewing definitions^{20,22} and so the definitions provided by the other four were the authors own.

Le Reste produced a new multimorbidity definition as a result of their review:

*“...any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor”.*²⁰

Willadsen found that more than a third of studies used a cut-off of two or more conditions to define multimorbidity, another third did not specify any cut-off and the remainder had varying cut-off points. The authors found that less than a third of their included studies used an existing definition of multimorbidity. Additionally, definitions varied according to whether or not they specified a duration of condition (e.g. “occurrence in the last 5 years” or having lasted “for at least 3 months”) and whether

or not they specified the severity of the condition (e.g. staging of the disease). The authors state that consideration of whether included diseases clustered together was considered in only “a few” articles and there was little consideration of complications of diseases. The authors concluded that the majority of existing definitions are “*more usable for epidemiologists than for clinicians and patients*” and recommended the Le Reste definition due to its comprehensive nature for including more than just disease.²²

In the remaining reviews, De Groot and Yurkovich primarily used the term “comorbidity”.^{18,21} The consensus amongst all four was that multimorbidity is the occurrence of multiple diseases or conditions. Diederichs specified that multimorbidity is *two or more* chronic conditions.¹⁹

Measures

Commonly used measures

Le Reste did not focus on multimorbidity measures.²⁰ The measures covered by the remaining five reviews are in Table 3. Whilst the stated aim of Willadsen was to “*explore how multimorbidity is defined in the scientific literature*”, there was overlap between definitions and measures.²²

The measures included by reviews encompassed disease counts and weighted indices such as the Charlson Index, the Cumulative Illness Rating Scale (CIRS), the Index of Coexistent Disease (ICED), the Adjusted Clinical Groups (ACG) System and the Duke Severity of Illness.

Yurkovich and Huntley examined the frequency of measures. Yurkovich categorised measures as “administrative data” (the most common being Charlson) and “medication-based” (the most common being the Chronic Disease Score).²¹ Huntley categorised the most common measures as: disease counts, the Charlson index and variations, the ACG system, the CIRS and the Duke Severity Illness

Check-list System.¹⁶ Despite the name, disease counts included more than just diseases (e.g. they included categories of conditions). The authors found disease counts being used in 98 studies and the number of disease “items” included within counts ranged from 9 to 35.¹⁶ Willadsen found that measures included by their papers contained conditions ranging in number from 4 to 147.²²

Recommended measures

Yurkovich found that diagnosis based measures such as the Elixhauser index and the Romano adaptation of the Charlson index were best able to predict mortality outcomes whilst the medication based Chronic Disease Score, was best able to predict health care use.²¹ Huntley recommended that researchers select a measure for a study based upon the measure validated for use in that scenario, for example, the Charlson index for predicting mortality. The authors also state that simple counts of diseases or medications perform almost as well as complex measures in predicting most outcomes.¹⁶

De Groot assessed the content, criterion and construct validity of measures. They concluded that the Charlson, CIRS, ICED and Kaplan indices are valid and reliable methods for use in clinical research but that other measures (such as disease counts) were more difficult to assess due to limited data.¹⁸

Willadsen did not recommend a single measure and instead, as described previously, stated the importance of including risk factors, symptoms and severity of diseases.²² Diederichs also did not recommend a single measure. They found studies of disease counts often did not specify the criteria for the selection of diseases, but if criteria were given these were: high prevalence of the disease, using other indices as a reference point for the selection of disease, or high impact conditions in terms of increased mortality risk, an impact on function and health and the need for management. They recommended 11 conditions selected on the basis of being the most common causes of inpatient and

outpatient attendance as well as death in people aged over 64 in Germany. The conditions included cancer, depression, myocardial infarction and hypertension.¹⁹

Data sources

All five reviews found patient self-report, physician reports, clinical examinations, medical record reviews and administrative data ('coded databases' or 'routine data') were common sources of multimorbidity data amongst their included studies.^{16,18,19,21,22} No review studied whether any source was superior, although Yurkovich found evidence that the Charlson index derived from self-report and that derived from administrative data had similar abilities to "*predict various outcomes*".²¹ De Groot stated that medical chart reviews are preferable for use in smaller studies as they likely yield the most complete data but that this is likely impractical in larger studies and so administrative databases can be used.¹⁸ Similarly, Huntley noted that administrative data have the advantage of ease of use but may be limited by data quality issues.¹⁶

Discussion

Summary of findings

Our review pooled the findings of six systematic reviews. We found heterogeneity of multimorbidity definitions and measures but there were a number of commonalities.

Most reviews defined multimorbidity as the occurrence of multiple diseases or conditions, the most common cut-off being two or more. Le Reste produced a new definition which encompassed biopsychosocial factors and somatic risk factors along with disease.²⁰ This was recommended by Willadsen as being the most clinically relevant definition of multimorbidity available.²²

Common measures included the Charlson, CIRS, ICED, Kaplan, the ACG system and disease counts, with advice that measures be selected based upon the purpose of a particular study.^{16,18} No reviews made recommendations about the most appropriate data sources to use when measuring multimorbidity.

Strengths and limitations

Our systematic review provides a high-level summary of both the definition and measurement of multimorbidity in relevant systematic reviews. Ours is the first to focus upon those reviews which primarily aimed to examine multimorbidity definitions or measures. This is important given the heterogeneity in definitions and measures available and the associated complexity in developing consensus. We acknowledge that reviews such as that by Fortin et al (of prevalence studies of multimorbidity)² and Marengoni et al (of ageing and multimorbidity)⁵ discuss recommended definitions and measures at the end of their reviews but we have not included these as their primary aim did not meet our inclusion criteria.

A limitation is that search terms were limited to the title only for practical reasons which means some relevant reviews could be missed. We conducted a test search including these terms in the abstract or full text which revealed no additional reviews in the first 100 titles screened. Additionally, as recommended by PRISMA, systematic reviews should be identified as such in the title.¹⁵

One of the included reviews (examining measures of multimorbidity) was classed as low quality. However, as there were three other reviews examining multimorbidity measures this should reduce the likelihood that this affected our findings.

Comparison with literature

Our findings are consistent with other systematic reviewers who have encountered challenges due to the lack of common approach towards measuring and defining multimorbidity.^{2,23-25}

Definitions

Willadsen highlighted that many definitions and measures seem to be tailored towards use in research rather than being clinically relevant.²² It is true that traditional approaches, for example measuring multimorbidity using the Charlson or disease counts, do not capture the holistic experience of multimorbidity. For example, we know that an individuals' ability to cope with disease is influenced by both person factors and wider socio-environmental factors and that at a population level, multimorbidity is associated with higher levels of deprivation.^{4,26-30} The definition by Le Reste is more likely to capture this complexity but the multi-faceted nature of the definition makes it difficult to operationalise in practice. Instead of adding further elements to the definition and measurement of multimorbidity, it is perhaps more appropriate to ensure there is consideration of its holistic nature

when studying its determinants and outcomes and when managing it clinically. This would include understanding its relationship with health inequalities in areas of high deprivation, as well as to frailty and the ageing process.^{11,12}

The cut-off point regarding the minimum number of conditions to equate to being multimorbid needs further consideration. The most common cut-off point found by our reviews was *two or more* conditions and this was consistent with the findings of Fortin in their review of prevalence studies of multimorbidity.² The prevalence of multimorbidity is inevitably affected by the cut-off selected and additionally it is likely that a higher cut-off would select a patient group with a higher burden of multimorbidity.² This needs further research, for example by testing the number of conditions which best identify patients at higher risk of outcomes such as hospital stay, disability, frailty or mortality.

Measures

When multimorbidity is defined and measured on the basis of a count of conditions the measurement of multimorbidity is closely linked to the definition. We have used the term “disease counts” as this is the common phrase used in the literature, but acknowledge these measures can include a wider spectrum of health conditions (for example risk factors for disease). Disease counts are likely more appropriate for scenarios where multiple outcomes are being considered or in which no single weighted measure has been validated.¹⁶ They may also be a more intuitive summary of multimorbidity burden in patients, for example when showing the link between multimorbidity and socioeconomic status.⁴ Additionally, reviews have found that multimorbidity may be more appropriately considered as different common clusters of conditions and this is easier to measure using counts.^{24,31} If researchers are selecting conditions to include in a count the purpose of the work being conducted must be considered. Some conditions, for example depression, may have greater impact upon patients

in terms of quality of life or function.³² Other conditions such as heart disease may impact more upon health services in terms of number of admissions or treatment costs.^{2,19}

In studies using weighted measures the definition and measurement of multimorbidity are more distinct. Many weighted measures were originally developed as comorbidity measures but are increasingly being used as multimorbidity measures.¹⁸ Weighted measures, if used for appropriate outcomes, can assist in predicting patient outcome and future healthcare usage and can also provide an assessment of the burden of multimorbidity experienced by the patient, their carers or health and social care services.³³ Therefore, where the aim is to examine outcomes in patients and to account for the presence of multiple conditions, a validated weighted measure may be more appropriate or informative than a disease count.

Data sources

No review recommended a particular data source to measure multimorbidity. In the wider literature, a number of studies and reviews have compared data sources for comorbidity and multimorbidity measures, often with conflicting findings.^{3,34} The availability of data and the resource implications will additionally affect the choice of data used. For example, whilst case-note review is viewed as being more complete than administrative data it is more resource intensive.^{3,34} Another important data source is patient self-report, which may be more likely to capture conditions which may not be seen as important clinically but impact on function or quality of life.³² Regardless of measure, different data sources will affect the prevalence of multimorbidity.^{2,35}

Implications for research and practice

Our key recommendation is that researchers be explicit about the definitions and measure(s) they are using and give a rationale for their choice. This will enable comparison of findings across different

settings and outcomes as well as progress the evidence base regarding the most appropriate definitions and measures for particular scenarios.

Multimorbidity is an important public health challenge, which is influenced strongly by wider social and environmental factors. In this review, the paper by Le Reste highlighted the holistic nature of multimorbidity.²⁰ In clinical and public health practice, holistic approaches which take into account more than just the medical management of disease could assist with reducing its impact. However, there is a need for more evidence on the effectiveness of primary care and community based interventions, including those tackling the challenges experienced by individuals with socio-economic deprivation.³⁶ Despite this, recent research in primary care in deprived areas has shown that a co-development model of intervention development for multimorbidity (CARE Plus) was feasible and may be cost-effective, thus pointing to future directions in reducing the burden of multimorbidity.^{37,38}

Overall, a definition of multiple co-existing conditions is reasonable and a cut-off should be explicitly defined. Researchers would be consistent with others by using a cut-off of two or more. Using a weighted measure validated for the outcome being considered is advised, but where evidence is weak or where multiple outcomes or populations are being considered, the use of disease counts is appropriate. There is precedence for the inclusion of conditions other than solely chronic disease in a multimorbidity measure but a rationale for included and excluded conditions should be given.

Conflicts of interest

The authors report no conflicts of interest.

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Key points

- To improve consensus in defining and measuring multimorbidity we recommend researchers and practitioners be explicit about the definitions and measure(s) they are using and give a rationale for their choice.
- We conclude that multimorbidity is the coexistence of multiple conditions (most commonly defined as two or more conditions).
- Validated multimorbidity measures for particular scenarios should be chosen if these exist. Where there is no validated measure or where multiple outcomes or populations are being considered, disease counts are appropriate.

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Tables and Figures

Table 1: Characteristics of included reviews

Review reference	Stated Aim of the review	Databases and dates of search undertaken by the review	Total titles / abstracts screened	Total texts included	Quality assessment*
De Groot et al, 2003 ¹⁸	'Which methods are available for measuring comorbidity that can be used in RCTs and prognostic studies'	Medline: January 1966 to September 2000. Embase: January 1988 to September 2000.	Not reported	Not reported	Low quality
Diederichs et al, 2011 ¹⁹	'Multimorbidity, defined as the coexistence of 2 or more chronic diseases, is a common phenomenon especially in older people. Numerous efforts to establish a standardized instrument to assess the level of multimorbidity have failed until now, and indices are primarily characterized by their high heterogeneity. Thus, the objective is to provide a comprehensive overview on existing instruments on the basis of a systematic literature review.'	Medline: January 1, 1960 to August 31, 2009	1120	39	Acceptable
Huntley et al, 2012 ¹⁶	'The aims of this review were (1) to identify and describe measures of multimorbidity that are most suitable for use in research in primary care and community populations, taking into account the data and resources they require, and (2) to investigate the validity of these measures in terms of whether they have demonstrated anticipated associations with patient characteristics, process measures, and health outcomes.'	Medline and Embase: database inception to December 2009	11191	194	Acceptable

Le Reste et al, 2013 ²⁰	'What are the criteria for multimorbidity found in the scientific medical literature and what definition could be produced with these criteria?'	PubMed, Embase and Cochrane: January 1, 1990 to December 31, 2010.	416	54	Acceptable
Yurkovich et al, 2015 ²¹	'To conduct a systematic review of studies reporting on the development or validation of comorbidity indices using administrative health data and compare their ability to predict outcomes related to comorbidity (i.e., construct validity).'	Medline and Embase: 1946 to September 2012	955	76	Acceptable
Willadsen et al, 2016 ²²	'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.'	PubMed, Medline and Embase: inception to October, 4, 2013. Cochrane database: inception to October,10, 2013	943	163	Acceptable

Abbreviations: SIGN, Scottish Intercollegiate Guidelines Network; RCT, randomised controlled trial

* Based upon SIGN categories

Table 2: Multimorbidity definitions from included reviews

Review reference	Definition given <i>a priori</i> * or as a result of evidence review	Definition
De Groot et al, 2003 ¹⁸	<i>a priori</i>	'the co-occurrence of multiple chronic or acute diseases and medical conditions in one person'
Diederichs et al, 2011 ¹⁹	<i>a priori</i>	'Multimorbidity describes "the coexistence of two or more chronic diseases" in the same individual.'
Huntley et al, 2012 ¹⁴	<i>a priori</i>	'the co-occurrence of multiple diseases or medical conditions within 1 person.'
Le Reste et al, 2013 ²⁰	Review of evidence	'Multimorbidity 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. Any biopsychosocial factor, any somatic risk factor, the social network, the burden of diseases, the health care consumption, and the patient's coping strategies may function as modifiers (of the effects of multimorbidity). Multimorbidity may modify the health outcomes and lead to an increased disability or a decreased quality of life or frailty.'
Yurkovich et al, 2015 ²¹	<i>a priori</i>	This review used the definition of comorbidity: 'Comorbidity may be defined as the total burden of illnesses unrelated to the principal diagnosis'
Willadsen et al, 2016 ²²	Review of evidence	Provides no single definition. Conclusion: -Existing definitions (consisting mainly of diseases) are 'more usable for epidemiologists than for clinicians and patients'. -Recommends definition by Le Reste et al (above)

* *a priori* indicates this is the reviewers own definition

Table 3: Multimorbidity measures, conditions and data sources recommended by included review

Review reference	Measures included	MM measure recommended?	Rationale for MM measure recommended	Specific MM conditions recommended?	MM data sources recommended?
De Groot et al, 2003 ¹⁸	Disease counts and 12 weighted measures (Burden of disease index, Charlson index, CIRS, Cornoni-Huntley index, Duke Severity of Illness index, Hallstrom index, Hurwitz index, ICED, Incalzi index, Kaplan index, Lui index, Schwartz index)	Concludes Charlson, CIRS, ICED and Kaplan are valid and reliable methods to measure comorbidity in clinical research.	Validity and reliability	No	No specific recommendation. - Commonly used methods to obtain data in included studies: 'interviews, questionnaires, physical examinations, medical chart reviews and coded databases'.
Diederichs et al, 2011 ¹⁹	Weighted indices: Charlson Index, Comorbidity Symptom Scale, Seattle Index of Comorbidity, Medication-Based Disease Burden Index, KoMo Score, Index of Coexisting Diseases, Functional Comorbidity Index, Incalzi Index, Kaplan-Feinstein Index, Physiologic Index of Comorbidity, Geriatric Index of Comorbidity, Self-Administered	Recommends a disease count of 11 conditions. Found most studies did not specify criteria for selection of diseases. If criteria given: high prevalence of the disease, using other indices as a reference point for the selection of disease, conditions which are associated with an	Disease count based on conditions which are the 20 most frequently listed diagnoses for people aged greater than or equal to 65 years in three data sources in Germany (the inpatient sector, the outpatient sector and	Cancer, diabetes, depression, hypertension, MI, chronic ischaemic heart disease, heart arrhythmias, heart insufficiency, stroke, COPD, arthritis.	No specific recommendation. - Included studies used: patient self-report, physician reports, clinical examinations, medical records, and administrative data. - Gives advice on self-report: 'use disease specifications that can be distinguishable by lay persons [in order to increase validity of self-report]'.

	Comorbidity Questionnaire, Shwartz Index and Chronic Disease Score.	increased mortality risk, conditions associated with impact on function and health and the need for management.	mortality statistics).		
Huntley et al, 2012 ¹⁶	Disease counts and weighted measures. Most common measures (n studies): disease count (98), Charlson (38), ACG System (25), CIRS (10), Duke Severity of Illness (6).	1. Care utilisation: the ACG System, Charlson index, or disease counts 2. Costs: The ACG System 3. Mortality: Charlson index 4. Quality of life: Disease counts or Charlson index 5. Other outcomes: Simple counts of diseases or medications	Recommendations based upon purpose of study and evidence base behind measures used for that purpose.	No	No specific recommendation. - Commonly used measures: interviews, questionnaires, physical examinations, medical chart reviews, and coded databases.
Yurkovich et al, 2015 ²¹	Administrative data measures (n studies): Charlson and its adaptations (35); Elixhauser (2); Fleming et al. index (1); Abildstrom et al. index (1) Medication- based indices:	Diagnosis-based measures, (particularly Elixhauser and the Romano adaptation of the Charlson) resulted in higher ability to predict mortality outcomes.	Recommends selection of measure to be based on 'type of data available, the study population, and the specific outcome of interest in the study.'	No	No specific recommendation. Review was limited to administrative data indices only but the authors commented on included studies which compared data sources (all were Charlson studies): - two studies found self-report and administrative data had similar ability to 'predict various outcomes'

	Chronic Disease Score (9), Rx-Risk (3) and Medication Based Disease Burden Index (2)	Medication-based indices, (such as the Chronic Disease Score) demonstrated better performance for predicting health care utilization.			-One review and two studies found poor agreement between case note review and administrative data
Willadsen et al, 2016 ²²	Charlson, Clinical Classification Software, CIRS, ACG, Aggregated Diagnosis Groups, Medication based, Expanded Diagnosis Clusters, Resource Utilization Bands, The Functional Comorbidity Index, ICED, QoF, The Registration Network Family Practices	Does not recommend a single measure. As documented in Table 2, the authors state the importance of including risk factors and symptoms and severity as well as diseases if want a clinically relevant definition (and thus measure)	N/A	No	No specific recommendation. The included studies used data from administrative data and self-report

Abbreviations: MM, multimorbidity; CIRS, Cumulative illness rating scale; ICED, Index of Coexistent disease; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; ACG, Adjusted Clinical Groups; QoF, Quality Outcomes Framework; N/A, not applicable

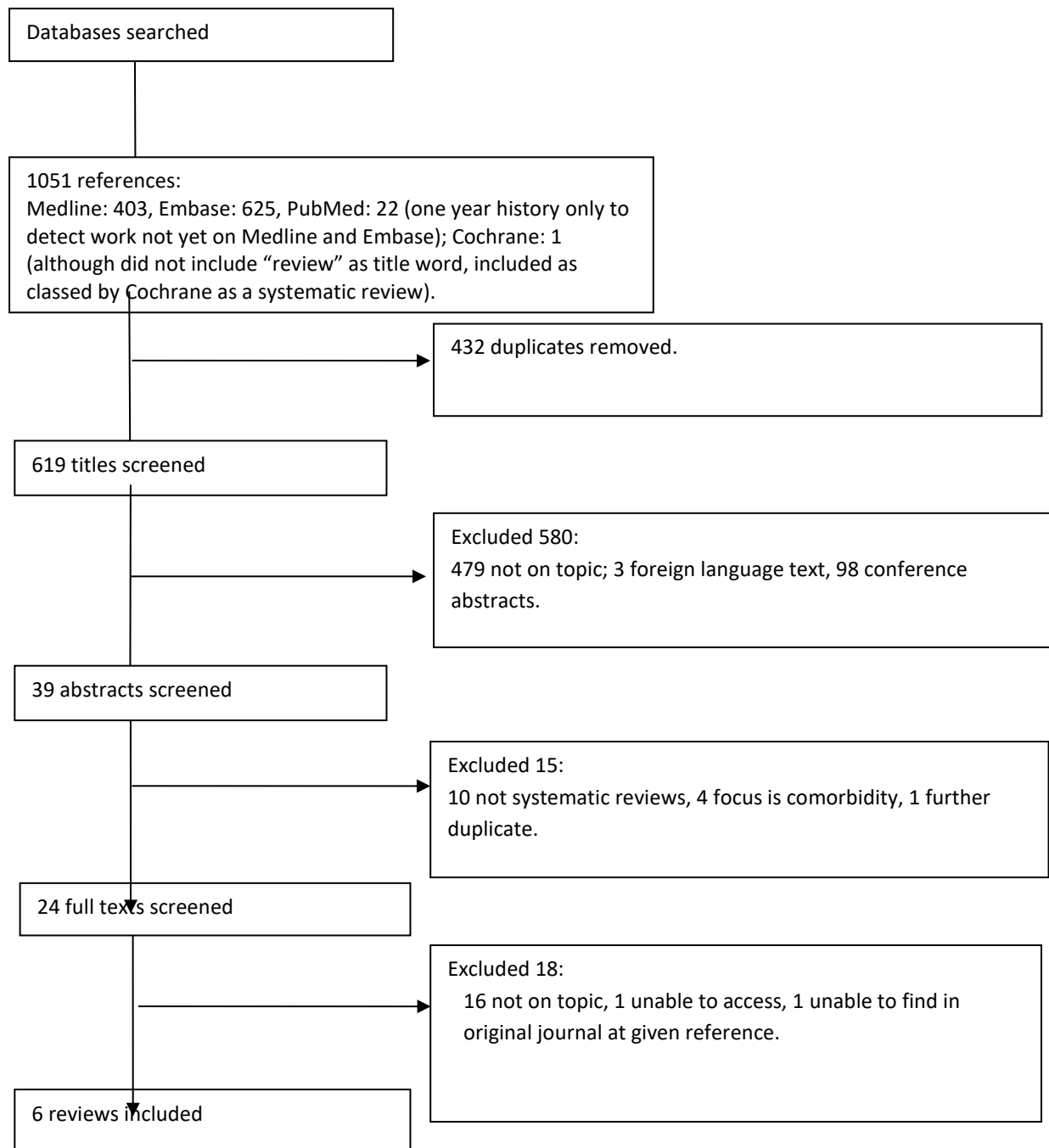


Figure 1: Flow-chart of search strategy