BMJ Open

Systematic review on the instruments used for measuring the association of the level of multimorbidity and clinically important outcomes

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ABSTRACT

Objectives There are multiple instruments for measuring multimorbidity. The main objective of this systematic review was to provide a list of instruments that are suitable for use in studies aiming to measure the association of a specific outcome with different levels of multimorbidity as the main independent variable in community-dwelling individuals. The secondary objective was to provide details of the requirements, strengths and limitations of these instruments, and the chosen outcomes.

Methods We conducted the review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PROSPERO registration number: CRD42018105297). We searched MEDLINE, Embase and CINAHL electronic databases published in English and manually searched the Journal of Comorbidity between 1 January 2010 and 23 October 2020 inclusive. Studies also had to select adult patients from primary care or general population and had at least one specified outcome variable. Two authors screened the titles, abstracts and full texts independently. Disagreements were resolved with a third author. The modified Newcastle-Ottawa Scale was used for quality assessment.

Results Ninety-six studies were identified, with 69 of them rated to have a low risk of bias. In total, 33 unique instruments were described. Disease Count and weighted indices like Charlson Comorbidity Index were commonly used. Other approaches included pharmaceutical-based instruments. Disease Count was the common instrument used for measuring all three essential core outcomes of multimorbidity research: mortality, mental health and quality of life. There was a rise in the development of novel weighted indices by using prognostic models. The data obtained for measuring multimorbidity were from sources including medical records, patient self-reports and large administrative databases.

Conclusions We listed the details of 33 instruments for measuring the level of multimorbidity as a resource for investigators interested in the measurement of multimorbidity for its association with or prediction of a specific outcome.

BACKGROUND

Multimorbidity is defined as the co-occurrence of two or more chronic medical conditions in an individual.1 It is a growing public health challenge and accounts for most of the expenditures in the healthcare system.2 The complex interactions of several coexisting diseases have profound implications on individuals3 4 and their healthcare providers.5 6

There are multiple instruments for measuring multimorbidity and many of them do not usually specify the severity of individual conditions.7 No gold standard multimorbidity measurement instrument exists and there is also no agreed categorisation of the available instruments. Safati8 9 classified the various measurement instruments into four broad approaches. They are as follows: (1) by simple counts of individual conditions (ie, Disease Count), (2) by organ or system-based approaches, (3) by weighting conditions and combining them into indices and (4) by other miscellaneous approaches. Most of these measurements are used to measure the prevalence or patterns of multimorbidity. However, they can also be used to predict an outcome or to evaluate an intervention for a desired outcome. A set of core outcomes of multimorbidity (COSmm) was proposed

Strengths and limitations of this study

• This review builds on Huntley et al’s 2012 review article and provides an updated, comprehensive list of instruments that measure levels of multimorbidity in community-dwelling individuals.
• A thorough literature search of three major electronic databases was conducted with the involvement of a health science librarian.
• The review is reported based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
• This review excluded non-English language articles and grey literature.
after consulting a panel of international experts in multimorbidity intervention studies using a Delphi process. Core outcome sets represent the minimum that should be measured and reported in all clinical trials of multimorbidity.

Huntley et al. published a systematic review in 2012 describing the instruments used to measure the morbidity burden in primary care and the general population. They found 17 different instruments from 194 articles. The most widely used instruments and those with the most significant evidence of validity were the Charlson Comorbidity Index (CCI), Disease Count and the Adjusted Clinical Groups (ACG) system. However, this review was conducted in 2009 and multimorbidity research has increased exponentially since then.

The present review was to build on the review article by Huntley et al. in order to provide a current and comprehensive list of instruments that measure levels of multimorbidity for community-dwelling individuals. We used the term ‘level of multimorbidity’ to refer to the combined effects of multiple conditions on an individual. The main objective of this review was to list instruments for measuring the levels of multimorbidity. We specifically look for studies that measure the association of a clinically important outcome with different levels of multimorbidity as the main independent variable in community-dwelling individuals. Our second objective was to provide details of the requirements, strengths and limitations of these instruments, and the chosen outcomes in the studies so that clinicians and researchers can select or develop instruments that match their needs for predicting a specific outcome.

One reviewer (ESL) conducted a preliminary screen of titles and abstracts to exclude articles that were irrelevant. Abstracts of the remaining articles were screened independently by two reviewers (ESL and EQ-YH) according to the eligibility criteria. Disagreements were resolved through discussion until a consensus was reached. The full-text articles were then retrieved for the agreed list and independently assessed according to the eligibility criteria by the same reviewers. Disagreements were resolved through discussion with a third reviewer (TSH) until a consensus was reached. After agreement on the list of articles, the reference lists of included articles were hand-searched for additional eligible articles. We reported multimorbidity instruments that were described in all selected articles.

The risk of bias of the study design of selected articles was next appraised independently by three reviewers (ESL, EH and TSH) using the modified Newcastle-Ottawa Scale (NOS). Each article was assessed under the three broad categories: (1) selection, (2) comparability and (3) outcome (online supplemental appendices 2 and 3).

We contacted the authors, as needed, for additional information or clarification up to three times spaced 1 week apart. We contacted 25 authors and 19 of them replied. Any disagreements on the risk of bias were resolved among the three reviewers through regular meetings. HLK and FYW were responsible for tracking and updating the final outcome of the risk of bias assessment.

**Patient and public involvement**

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or to interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

**METHODS**

A protocol for this systematic review (CRD42018105297) was published online on PROSPERO. We searched MEDLINE, EMBASE, CINAHL and also manually searched the Journal of Comorbidity for potential studies. The medical subject headings and keywords used for the search are shown in online supplemental appendix 1.

We selected studies that included (1) adult patients from primary care or the general population as the majority of patients with multimorbidity are managed by primary care physicians; (2) at least one specified outcome variable; and (3) published full-text articles from 1 January 2010 to 23 October 2020. Studies were excluded if they (1) selected patients from the hospital or nursing home only or patient data were drawn solely from the hospital or the nursing home; or (2) selected patients with an index condition; or (3) used level of multimorbidity as a covariate and not the main independent variable; or (4) were not written in English. We did not include a specific definition of multimorbidity instrument because, given a lack of consensus in the literature on the use of this term, we wanted to include a diverse range of studies on the above topic.

The instruments were categorised according to Sarfaty into (1) simple counts of individual conditions; (2) organ or system-based approaches; (3) conditions that have been weighted and combined into indices; and (4) other approaches. A total of 150 outcomes were reported from all the studies. No studies were excluded for an outcome that was not deemed to be clinically important. Online
supplemental appendices 4 and 5 summarise the risk of bias assessment of each study. Table 1 provides a summary of the study design, population source, age group, multimorbidity measurements, outcome measures and risk of bias assessment of all the studies.

Table 2 summarises the 33 instruments that were identified from all the studies. Table 3 provides a summary of multimorbidity instruments and their associations with the outcomes measured from all the included studies.

Simple counts of individual conditions
Disease Count was based on the total number of all the conditions an individual had, usually from a prespecified list of chronic conditions. It was used in 59 out of the 96 studies (61.5%). Disease Count was reported to be associated with activity limitations, continuity of care, disability, healthcare cost, healthcare utilisation, medications, mental disorders, mortality, general health, physical function, quality of life and self-rated health (table 3).
| Author (Year)                          | Study design | Population source | Age | Multimorbidity measurement | Outcomes measured                                           | Risk of bias |
|---------------------------------------|--------------|-------------------|-----|-----------------------------|------------------------------------------------------------|--------------|
| Agborsangaya et al (2013)             | CS           | GP                | ≥18 | DC                          | HRQoL                                                      | Good         |
| Bähler et al (2015)                   | CS           | GP                | ≥65 | DC-ATC classification system| Total number of consultations                              | Good         |
| Barile et al (2013)                   | Cohort       | GP                | ≥65 | DC                          | ADL limitations, physically unhealthy days, mentally unhealthy days | Good         |
| Barile et al (2012)                   | CS           | GP                | ≥65 | DC                          | Physical HRQoL, mental HRQoL                               | Good         |
| Barnett et al (2012)                  | CS           | PC                | ≥0  | DC                          | Presence of mental health disorder                        | Good         |
| Biehl et al (2016)                    | Cohort       | PC                | ≥65 | ERA, CCI                    | Presence of critical illness                              | Good         |
| Boeckxstaens et al (2015a)            | CS           | PC                | ≥80 | DC, CCI, CIRS               | Disability (measured by ADL), frailty (five components)    | Poor         |
| Boeckxstaens et al (2015b)            | Cohort       | PC                | ≥80 | DC, mCCI, CIRS              | Mortality at 3 years, hospitalisation at 3 years, functional decline at 19 months (ADL, physical, mental decline) | Fair         |
| Brilleman et al (2014)                | Cohort       | PC                | ≥18 | QOF count, CCI, EDC count, ACG, RUB | Primary healthcare cost                                    | Good         |
| Brilleman and Salisbury (2013)        | Cohort       | PC                | ≥18 | QOF count, CCI, EDC count, ACG, RUB, prescribed drugs count | Mortality: The CCI was the best performing measure followed by the number of prescribed drugs. Number of primary care consultations (3-year period): The number of prescribed drugs had the greatest predictive validity followed by the ACG-based measures (ACG, EDC count and RUB). | Good         |
| Caballer-Tarazona et al (2019)        | CS           | GP                | ≥0  | CRG                         | Expenditure of integrated healthcare (hospital, primary healthcare (PHC) and pharmaceutical prescription) | Poor         |
| Author (Year)          | Study design | Population source | Age   | Multimorbidity measurement | Outcomes measured                                                                 | Risk of bias |
|-----------------------|--------------|-------------------|-------|-----------------------------|----------------------------------------------------------------------------------|--------------|
| Carey et al (2013)    | Cohort       | PC                | ≥60   | Standard QOF, extended QOF, CCI (Khan) | Mortality (1-year period) The standard QOF score outperformed the CCI (Khan). The extended QOF score produced only a modest improvement in overall model performance. | Good         |
| Chapman et al (2015)  | Cohort       | GP                | ≥18   | CCI, CCI-PSR                | Mortality (5, 10, 15, 20, 25-year period) The CCI-PSR showed substantially better discrimination than the CCI. | Good         |
| Charlson et al (2014) | Cohort       | GP                | ≥0    | CCI                         | Healthcare cost, utilisation of services                                           | Good         |
| Chen et al (2011)     | CS           | GP                | ≥18   | DC                          | General health, mental distress, physical distress, activity limitations            | Good         |
| Chen et al (2018)     | CS           | GP                | ≥45   | DC                          | Health service utilisation                                                          | Poor         |
| Chu et al (2018)      | CS           | PC                | ≥40   | DC, CIRS                    | Healthcare utilisation                                                             | Good         |
| Clynes et al (2020)   | CS           | GP                | (Born in 1931–1939) | DC                          | Physical functioning                                                              | Poor         |
| Crane et al (2010)    | Cohort       | PC                | ≥60   | ERA                         | Number of hospital visits, ED visits, hospital admissions, days hospitalised (1-year period) | Good         |
| Crooks et al (2016)   | Cohort       | PC                | 20–100 | Comorbidity linked score, CCI, EI | Mortality (1-year period) The linked score had significantly improved discrimination and fit compared with the CCI and the Elixhauser Index | Good         |
| Crooks et al (2015)   | Cohort       | PC                | ≥20   | CCI (Read), CCI (ICD-10), CCI (Read and ICD-10) | All-cause mortality (1–5 years) There was no large difference in the discrimination of the model for whichever codes that were used to derive the CCI. | Good         |
| DiNapoli et al (2017) | CS           | PC                | ≥50   | Organ systems with chronic disease | Presence of depressive or anxiety disorder                                           | Good         |
| Formiga et al (2013)  | Cohort       | PC                | 85    | CCI                         | Mortality (3-year period)                                                          | Good         |
| Formiga et al (2011a) | Cohort       | GP                | 90 to 99 | CCI                         | Mortality (5-year period)                                                          | Good         |
| Author (Year)       | Study design | Population source | Age | Multimorbidity measurement | Outcomes measured                                                                 | Risk of bias |
|---------------------|--------------|-------------------|-----|-----------------------------|----------------------------------------------------------------------------------|--------------|
| Formiga et al (2011b) | CS           | PC                | 85  | CCI                         | Successful ageing                                                                | Good         |
| Formiga et al (2016)  | Cohort       | PC                | 85  | CCI                         | Mortality (5-year period)                                                         | Good         |
| Fraccaro et al (2016)  | Cohort       | PC                | ≥18 | CCI (Khan)                  | Mortality (1, 5, 10-year period), mortality (3, 6, 12-month period)              | Good         |
| Galenkamp et al (2011) | CS           | GP                | 57–98 | DC                         | SRH                                                                             | Good         |
| Garin et al (2014)   | CS           | GP                | ≥50 | DC                          | QOL, disability                                                                  | Good         |
| Glynn et al (2011)   | CS           | PC                | >50 | DC                          | Primary care consultations, hospital outpatient visits, hospital admissions, healthcare cost (all 1-year period) | Good         |
| Gunn et al (2012)    | CS           | PC                | 18–76 | DC                         | Depressive symptoms (CES-D score)                                                | Fair         |
| Haas et al (2013)    | Cohort       | PC                | ≥18 | ACG, Minnesota Healthcare Home Tiering, HCC, ERA, CCC, CCI, hybrid model | Hospitalisation, ED visits, readmission within 30 days, healthcare expenditure (all 1-year period) The ACG model outperformed the other five models in all outcomes | Good         |
| Hanmer et al (2010)  | CS           | GP                | 22 to 106 | Additive model, minimum model, multiplicative model | Health utility (SF-6D)                                                           | Fair         |
| Hu et al (2017)      | CS           | PC                | ≥65 | Age-adjusted CCI            | Frequency of family physician visits                                              | Fair         |
| Hwang et al (2015)   | Cohort       | GP                | ≥0  | ACE-27, ACE-27 count        | Healthcare expenditure The model, using year 1 data to determine if an individual would be classified into the persistent high-user group for the following 3 years, indicates a very high level of accuracy in predicting membership in a high-user group | Good         |
| Isaacs et al (2014)  | CS           | PC                | 18–101 | DC                         | Prescription costs                                                               | Poor         |
| Jennings et al (2015) | Cohort       | PC                | ≥75 | DC                          | Count of fall-related injuries in the 24 months after the date of screening      | Fair         |
| Jia et al (2018)     | Cohort       | GP                | ≥65 | DC                          | Quality-adjusted life years (QALY)                                                | Poor         |
| Jia and Lebetkin (2017) | Cohort     | GP                | ≥65 | DC                          | Quality-adjusted life years (QALY)                                                | Poor         |
| Author (Year) | Study design | Population source | Age | Multimorbidity measurement | Outcomes measured | Risk of bias |
|---------------|--------------|-------------------|-----|---------------------------|-------------------|-------------|
| Jindai et al (2016) | CS | GP | ≥65 | DC | Functional limitations (ADL, IADL, leisure and social activities, lower-extremity mobility, general physical activities) | Good |
| Kim et al (2012) | CS | GP | ≥65 | DC | Quality of life (EQ5D) | Poor |
| Kojima et al (2011) | CS | PC | ≥65 | DC | Fall tendency | Poor |
| Kristensen et al (2014) | CS | PC | >0 | RUB | Fee-for-services expenditures | Good |
| Lapi et al (2015) | CS | PC | ≥15 | HSMI | Total mean healthcare cost per year The HSMI explained 50.17% of the variation in costs | Good |
| Lawson et al (2013) | CS | GP | ≥20 | DC | Preference-weighted HRQoL | Good |
| Lemke et al (2012) | Cohort | GP | ≥0 | CCI, ACG | Inpatient hospitalisations ACG-based predictive model was superior to CCI model. | Good |
| Li et al (2016) | CS | GP | 16–68 | DC | Health-related quality of life | Poor |
| Loprinzi et al (2016) | CS | GP | 60–85 | DC | Cognitive function | Good |
| Macinko et al (2019) | CS | GP | ≥18 | DC (categorical 2 and 3 or more) (self-reported) | Primary care experience (self-reported) | Good |
| Marengoni et al (2011) | CS | GP | ≥75 (baseline) ≥77 (follow-up) | DC | Disability | Good |
| McDaid et al (2013) | CS | GP | ≥50 | DC | Disability, QoL, SRH | Good |
| Md Yusof et al (2010) | Cohort | GP | 64–85 | CCI, | Mortality over 7 years | Fair |
| Milla-Perseguer et al (2019) | CS | PC | ≥18 | CRG | Health-related quality of life (HRQL)—EQ-5D-3L | Good |
| Monterde et al (2020) | Cohort | GP | ≥18 | Adjusted morbidity group (GMA), CCI, DC, CRG | Use of healthcare resources | Good |
| Muggah et al (2012) | CS | GP | ≥20 | DC | Primary healthcare use | Poor |
| Mujica-Mota et al (2015) | CS | PC | ≥18 | DC | Health-related quality of life (EQ5D) | Fair |
| Naessens et al (2011) | CS | GP | 18–64 | DC | Healthcare cost | Poor |
| Østergaard and Foldager (2011) | CS | PC | ≥18 | DC | Major depressive episode (measured by DSQ) | Poor |

Continued
Table 1  Continued

| Author (Year)              | Study design | Population source | Age   | Multimorbidity measurement | Outcomes measured                                                                 | Risk of bias |
|---------------------------|--------------|-------------------|-------|----------------------------|-----------------------------------------------------------------------------------|--------------|
| Palladino et al (2019)93  | CS           | GP                | ≥50   | DC                         | Primary care use, reduced functional capacity, self-perceived health, hospital admissions, quality of life | Good         |
| Pati et al (2019)94       | CS           | PC                | ≥18   | Severity burden score (21 conditions) | Health-related quality of life (SF-12)                                          | Good         |
| Payne et al (2013)95      | Cohort       | PC                | ≥20   | DC                         | Unplanned hospital admission, potentially preventable admission (all 1-year period) | Good         |
| Payne et al (2014)96      | Cohort       | PC                | ≥20   | DC                         | Unplanned hospital admissions (1-year period)                                     | Good         |
| Payne et al (2020)97      | Cohort       | PC                | ≥20   | CCI, DC (37 read codes), Cambridge Multimorbidity Score | Mortality, unplanned inpatient hospital admission, primary care consultations | Good         |
| Peters et al (2018)98     | CS           | PC                | 18–101| DC, DBIS                   | Quality of life                                                                   | Fair         |
| Quail et al (2011)99      | Cohort       | GP                | ≥20   | DC, CCI (Quan), Elixhauser (Quan), number of different dispensed drugs, CDS | Mortality (1-year period): Elixhauser (Quan) performed best followed by CCI. One or more hospitalisations; two or more hospitalisations: DC was the best performing measure | Good         |
| Ranstad et al (2014)100   | CS           | GP                | ≥0    | RUB                        | Registered active listing in primary care and all healthcare                        | Good         |
| Reinke et al (2019)101    | CS           | PC                | 30–94 | DC                         | Symptom burden (MSAS-SF), quality of life (Veterans RAND 12)                          | Good         |
| Renne and Gobbens (2018)102| CS           | PC                | ≥70   | DC                         | Quality of life                                                                   | Poor         |
| Reyes et al (2014)103     | Cohort       | PC (men)          | ≥65   | CCI                        | Hip fractures                                                                      | Good         |
| Ryu et al (2015)104       | CS           | PC                | ≥18   | DC                         | Deficits of perceived general health, depressive symptoms                          | Good         |
| Salisbury et al (2011)105 | Cohort       | PC                | ≥18   | QOF count, EDC count       | Primary care consultation rates, continuity of care (all 3-year period)             | Good         |
| Saver et al (2014)106     | Cohort       | GP                | ≥65   | CCI (Romano)+Hypertension  | Acute ACSH, chronic ACSH                                                            | Good         |

Continued
| Author (Year) | Study design | Population source | Age | Multimorbidity measurement | Outcomes measured | Risk of bias |
|--------------|--------------|-------------------|-----|----------------------------|-------------------|-------------|
| Shadmi et al (2011) | CS | GP | ≥18 | ADG, CCI | Number of primary care physician visits, specialist visits, hospitalisation ADG explained the largest percent of variance or in healthcare resource use | Good |
| Sibley et al (2014) | CS | GP | ≥65 | DC | Self-reported falls in the last 12 months | Poor |
| Stanley and Sarfati (2017) | Cohort | PC | ≥18 | M3 Index, CCI, Elixhauser (van Walraven) | Mortality, overnight hospitalisation (all 1-year period) M3 Index outperformed both CCI and Elixhauser (van Walraven) | Good |
| St John et al (2014) | Cohort | GP | ≥65 | DC (0–36 conditions) | Mortality in 5 years | Good |
| St John et al (2019) | Cohort | GP | ≥65 | DC | Functional impairment in 5 years | Good |
| Streit et al (2014) | Cohort | PC | 50–80 | CCI, DC | Quality of cardiovascular preventive care, quality of preventive care | Good |
| Sullivan et al (2012) | CS | GP | ≥18 | DC | Preference-based HRQoL | Good |
| Takahashi et al (2011) | Cohort | PC | >60 | ERA | Mortality, nursing home placement (all 2-year period) | Good |
| Takahashi et al (2016) | Cohort | PC | ≥18 | Minnesota Tiering (ACG), enhanced model | Hospitalisation/ED visits The enhanced model is better | Good |
| Tyack et al (2016) | Cohort | PC | ≥18 | DC | Health-related quality of life | Fair |
| Ubalde-Lopez et al (2016) | CS | GP | F (mean): 35.9, M (mean): 37.9 | MDMS | Sickness absence episodes taken in last 2 years | Good |
| van den Bussche et al (2011) | CS | PC | ≥65 | DC | Frequency of contacts with physicians, number of different ambulatory physicians contacted (all 1-year period) | Good |
| van Oostrom et al (2014) | CS | PC | ≥55 | DC | Number of contacts with general practice, medications prescribed, referrals | Good |
| Vos et al (2013) | CS | PC | 70–74 | DC | Self-rated health (SF-36) | Poor |

Table 1 Continued
| Author (Year) | Study design | Population source | Age | Multimorbidity measurement | Outcomes measured | Risk of bias |
|--------------|--------------|--------------------|-----|----------------------------|-------------------|-------------|
| Wallace et al (2016a) | Cohort | PC | ≥70 | Pra tool, modified Pra tool | Emergency hospital admission (1-year period) Both models demonstrated poor model discrimination | Good |
| Wallace et al (2016b) | Cohort | PC | ≥70 | DC, Barnett conditions DC, CCI, prescribed drugs count, RxRisk-V | Emergency admission, functional decline (all 2-year period) All measures demonstrated poor discrimination | Good |
| Wei et al (2018) | CS | GP | ≥51 | MWI | Subjective physical functioning, grip strength, gait speed, cognitive performance, ADL limitations, IADL limitations | Good |
| Wei et al (2019a) | Cohort | GP | ≥51 | MWI | Physical functioning—SF-36, mortality | Good |
| Wei and Mukamal (2019b) | Cohort | GP | ≥51 | MWI | Suicide mortality, health-related quality of life | Good |
| Wei et al (2020a) | Cohort | GP | ≥51 | MWI | Cognitive functioning | Good |
| Wei et al (2020b) | Cohort | GP | ≥51 | MWI, ICD, DC, CCI, Elixhauser, health-related quality of life comorbidity index | Mortality, future physical functioning | Poor |
| Wei and Mukamal (2018) | Cohort | GP | ≥36 | MWI, DC, CCI | Mortality (10-year period), future physical functioning MWI performed best in predicting mortality as compared with DC and CCI | Good |
| Wikman et al (2011) | CS | GP | ≥50 | DC | QoL, affective well-being | Good |
| Wister et al (2015) | CS | GP | ≥65 | MM additive scale, MM weighted by HUI3, MM weighted by ADL scale, MM weighted by HUI3 betas | Life satisfaction, perceived health status | Good |

ACE, Adult Comorbidity Evaluation; ACG, Adjusted Clinical Groups; ACSH, Ambulatory Care Sensitive Hospitalisation; ADG, Aggregated Diagnosis Groups; ADL, Activities of Daily Living; CCC, Chronic Condition Count; CCI, Charlson Comorbidity Index; CCI-PSR, Charlson Comorbidity Index-Psychosocial Risk; CDS, Chronic Disease Score; CIRS, Cumulative Illness Rating Scale; CRG, Clinical Risk Groups; CS, Cross-Sectional; DBIS, Disease Burden Impact Scale; DC, Disease Count (Unweighted); ED, Emergency Department; EDC, Expanded Diagnosis Clusters; EI, Elixhauser Index; ERA, Elder Risk Assessment; GP, General Population; HCC, Hierarchical Condition Categories; HRQoL, Health-Related Quality of Life; HSMI, Health Search Morbidity Index; HUI3, Health Utility Index; IADL, Instrumental Activities of Daily Living; ICD-10, International Classification of Diseases, Tenth Revision; mCCI, modified Charlson Comorbidity Index; MDMS, Multidimensional Multimorbidity Score; M3 Index, Multimorbidity Measure Index; MM, Multimorbidity; MWI, Multimorbidity-Weighted Index; PC, Primary Care; Pra tool, Probability of repeated admission risk prediction tool; QOF, Quality and Outcomes Framework; QoL, Quality of Life; RUB, Resource Utilisation Band; RxRisk-V, A Veterans Association adapted pharmacy-based case-mix instrument; SRH, Self-Rated Health.
Table 2. Description of instruments used for measurement of multimorbidity and the data sources and resources required

| Category               | Instrument | System/Condition based | Weightage; Scoring method                                      | Data sources and resources required                                                                 |
|------------------------|------------|------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| **A: Count of individual conditions** |            |                        |                                                                 |                                                                                                     |
| A-1                    | DC         | Condition (7–147)      | Unweighted; condition count                                      | ATC list of conditions, Elixhauser list of conditions, EMR, GP records, health service database, hospital discharge abstract, insurance claims or questionnaires—telephone, face-to-face, mailed surveys. Participant involvement required. |
| A-2                    | CCC        | Condition (6)          | Unweighted; based on AHRQ's clinical classification software and number of conditions for each category | EMR                                                                                                  |
| **B: Organ or system-based approaches** |            |                        |                                                                 |                                                                                                     |
| B-3                    | Organ systems with CDC | Organ system (17) | Unweighted sum of organ systems                                   | EMR                                                                                                  |
| B-4                    | CIRS       | Body systems (13)     | 1–5 (based on severity of the condition); different weightage for diseases | EMR                                                                                                  |
| **C: Weighted indices** |            |                        |                                                                 |                                                                                                     |
| C-5                    | ACE        | Condition (27)         | 1–3 (based on severity of most severe condition); highest score of single item | Insurance claims' database                                                                         |
| C-6                    | Cambridge MM Score | Condition (20) | Weighted based on three different outcomes—primary care consultation, unplanned admission and mortality | EMR linked to mortality, hospital admission and socioeconomic deprivation                           |
| C-7                    | CCI        | Condition (19)         | 1–6 (based on impact on 1-year mortality (RR)—original); sum of weighted conditions | Administrative database, EMR, medical chart review, or interviews or postal questionnaire where participant involvement is required |
| C-8                    | CLS        | Condition (98)         | Based on impact for mortality (HR); sum of beta coefficients of each category | Linked patients’ records of all primary care events, hospital admissions and causes of death.       |
| C-9                    | DBIS       | Conditions (25–28)     | Weighted according to the degree in which each condition interferes with daily activities | Patient involvement in the questionnaire is required                                               |
| C-10                   | EI (original and modified) | Condition (21–31) | Based on impact on in-hospital mortality; summing of beta coefficients | Insurance claims' or medical services database                                                       |
| C-11                   | ERA        | Condition (6–9)        | Weighted (based on impact on future hospitalisation); sum of weighted regression coefficients | EMR and administrative database                                                                   |

Continued
### Table 2  Continued

| Category | Instrument | System/Condition based | Weightage; Scoring method | Data sources and resources required |
|----------|------------|-------------------------|---------------------------|-----------------------------------|
| C-12     | HCC        | Condition (70)          | Based on Medicare capitation payments for health expenditure; more severe manifestations of a condition dominating (and zeroing out the effect of) less serious ones. Other diseases are summed additively. | EMR and HCC software licensing and fees |
| C-13     | M3 Index   | Condition (55)          | Weighted based on 1-year mortality; summing of beta coefficients | Linked patients' records |
| C-14     | MDMS       | Condition (7 chronic conditions, 2 health behaviours for first dimension and 5 symptoms for second dimension) | Weighted but not based on any specific outcome; sum of the value for the weighted absolute contributions of each of the dimensions. | Standardised medical evaluation (interviewer-administered); participant involvement is required |
| C-15     | MM weighted by ADL Scale | Condition (19) | Weighted based on OARS functional status scale measuring ADL; sum of weighted conditions | Face-to-face or telephone interviews where participant involvement is required |
| C-16     | MM weighted by HUI | Condition (19) | Weighted based on correlation with health utility index; sum of weighted conditions | Face-to-face or telephone interviews where participant involvement is required |
| C-17     | MM weighted by HUI betas | Condition (19) | Weighted based on correlation with health utility index and adjusted for age and sex; summing of beta coefficients | Face-to-face or telephone interviews where participant involvement is required |
| C-18     | MWI        | Condition (81)          | Weighted based on impact on SF-36 physical functioning scale; sum of weights | Interviewer-administered or mail questionnaire where participant involvement is required |
| C-19     | QOF standard (weighted) | Condition (14) | 0–6, based on impact on 1-year mortality (RR); sum of weighted conditions | EMR |
| C-20     | QOF extended (weighted) | Condition (9) | 1–3, based on impact on 1-year mortality (RR); sum of weighted conditions | EMR |
| C-21     | Severity Burden Score | Condition (21) | Sum of weights of diseases by the level of interference for each condition | Interviewer-administered structured questionnaire by nurses where participant involvement is required |

### D: Other approaches (D1=Case mix, D2=Pharmaceutical-based)

| D1-22 | ACG | Condition (93 mutually exclusive ACGs. Some are modified to 68 ACGs) | Incorporated into ACGs based on impact on resource use (proprietary); variable | EMR and ACG software licensing and fees |
| D1-23 | ADG | Condition (32 groups) | Based on duration, severity, diagnostic certainty, aetiology and need for specialty care; variable | EMR and ACG software licensing and fees |
| Category | Instrument | System/Condition based | Weightage; Scoring method | Data sources and resources required |
|----------|------------|------------------------|---------------------------|-----------------------------------|
| D1-24    | CRG<sup>35</sup> | NA; diagnostic categories derived from organ systems or clinical category (37) | Pre-formulated based on the 3M clinical risk groups and consists of 9 core health ranks | EMR—inpatient and outpatient and 3M Clinical Risk Grouping software V.1.6 and service fees |
| D1-25    | Adjusted Morbidity Groups (GMA)<sup>138</sup> | NA; mutually exclusive categories (31) | Based on multimorbidity and levels of patient complexity | Registry data |
| D1-26    | HM<sup>21</sup> | Condition (NS) | Only MN tier 4+MN tier 3 with ERA>10; variable | EMR, HCC software licensing, fees and administrative data |
| D1-27    | HSMI<sup>78</sup> | Condition (73 chronic and acute conditions) | Based on yearly healthcare costs directly derived from primary care setting; sum of regression coefficients (range from −0.06 to 1.04) | EMR |
| D1-28    | Minnesota Tiering<sup>138</sup> | Condition (NS) | Grouping patients into 'complexity tiers' based on the number of major condition categories; condition count | EMR or administrative data and MN Tiering software licensing and fees |
| D1-29    | Resource Utilisation Band<sup>137</sup> | Condition (six mutually exclusive bands) | Based on ACG algorithm on impact on resource use (proprietary); variable | EMR and ACG software licensing and fees |
| D2-30    | CDS<sup>13</sup> | Condition (17) | Weighted 1–5; sum of weights based on pharmacological database | Prescription drug database |
| D2-31    | Drug Count | NA; variable. Some may be based on pharmacologic-therapeutic classification system | Weighted; medication count | Self-reported questionnaire where participant involvement is required |
| D2-32    | Modified Pra tool using RxRisk-V<sup>34,119</sup> | NA; Pra tool+RxRiskV | Weighted due to RxRisk-V; 4 categories | GP medical record+linked pharmacy claims database |
| D2-33    | RxRisk-V<sup>24</sup> | NA; WHO-ATC classification system | Weighted according to the diagnostic group of drugs to predict future healthcare costs; sum of weights | GP medical record+linked pharmacy claims database |

ACE, Adult Comorbidity Evaluation; ACG, Adjusted Clinical Groups; ADG, Aggregated Diagnosis Groups; ADL, Activities of Daily Living; ATC, Anatomical Therapeutic Chemical; CCC, Chronic Condition Count; CCI, Charlson Comorbidity Index; CDC, Chronic Disease Count; CDS, Chronic Disease Score; CGI-S, Clinical Global Impression-Severity Scale; CIRS, Cumulative Illness Rating Scale; CLS, Comorbidity Linked Score; CRG, Clinical Risk Groups; DBIS, Disease Burden Impact Scale; DC, Disease Count; EDC, Expanded Diagnosis Clusters; Elixhauser Index; EMR, Electronic Medical Records; ERA, Elder Risk Assessment; GP, General Practitioner; HCC, Hierarchical Condition Categories; HM, hybrid model (MN Tier+ERA); HSMS, Health Search Morbidity Index; HUI, Health Utility Index; mCCI, modified Charlson Comorbidity Index; MDMS, Multidimensional Multimorbidity Score; M3 Index, Multimorbidity Measure Index; MM, Multimorbidity; MWI, Multimorbidity-Weighted Index; OARS, Older Americans Resources and Services; Pra tool, Probability of repeated admission risk prediction tool; QOF, Quality and Outcomes Framework; RxRisk-V, A Veterans Association adapted pharmacy-based case-mix instrument; SF-36, 36-item Short Form Survey.
## Table 3
Summary of multimorbidity instruments and their associations with outcomes measured from all the included studies

| Multimorbidity measures | Association between outcomes and multimorbidity |
|-------------------------|-------------------------------------------------|
| **A=Count of individual conditions** | Evidence of an association | No evidence of an association |
| DC (many different groupings ranging from 764 to 1476 conditions and some are further categorised) | ADL limitations, activity limitations, affective well-being, cognitive function, continuity of care (3 years), deficits of perceived general health, depression, depressive symptoms, disability, emergency hospital admission (2 years), fall-related injuries, fall risk, frequency of contacts with physicians (1 year), functional capacity, functional decline (2 years), functional impairments, general health, healthcare costs, health-related quality of life, hospitalisation (3 years), hospital admissions (1 year), hospital outpatient visits (1 year), hospitalisation/emergency department visits, life satisfaction, mental distress, mortality (1 year), (3 years), (5 years), (10 years), number of contacts with general practice (1 year), number of medications prescribed (1 year), number of mentally unhealthy days, number of different ambulatory physicians contacted (1 year), number of primary care consultations (1 year), (3 years), number of referrals (1 year), outpatient/Inpatient service use, physical distress, physical function, prescription costs, perceived health status, presence of mental health disorder, primary care consultations (1 year period), primary care experience—self-reported, primary healthcare cost, primary healthcare use, potentially preventable unplanned admission (1-year period), quality-adjusted life years, quality of life, self-rated health, self-reported falls (12 months), symptom burden, self-rated Health, self-perceived health, total number of consultation, total health care costs | Functional decline, quality of cardiovascular preventive care, quality of preventive care |

| **B=Organ or system-based approaches** | | |
| **Organ systems with CDC** | | |
| Presence of depressive or anxiety disorder | | |

| **CIRS** | | |
| Disability, frailty, healthcare utilisation, hospitalisation | Functional decline, mortality |

| **C=Weighted indices** | | |
| **ACE** | Healthcare expenditure |

| **Cambridge MM Score** | Mortality, primary care consultation, unplanned admission |
| **CCI** | Ambulatory care-sensitive hospitalisations (acute and chronic), disability, emergency department visits (1 year), emergency hospital admission (2 years), frailty, functional decline (2 years), future physical functioning, healthcare expenditure, hip fractures, hospitalisation (1 year), hospitalisation (3 years), mortality (1 year), (3 years), (5 years), (10 years), (15, 20, 25 years), number of primary care consultations (3 years), number of primary care physician visits (1 year), number of specialist visits (1 year), potentially preventable unplanned admission (1 year), presence of critical illness, primary healthcare cost, mortality (1 year), (3 years), (5 years), (7 years), (10 years), readmission within 30 days (1 year), successful ageing |

| **CLS** | Mortality (1 year) |
| **Continued** | | |
| Multimorbidity measures | Association between outcomes and multimorbidity | Evidence of an association | No evidence of an association |
|-------------------------|-----------------------------------------------|---------------------------|-----------------------------|
| DBIS                    | Quality of life\(^{98}\)                      |                           |                             |
| EI (original and modified) | Hospitalisation (1 year), \(^{99}\)\(^{109}\) mortality (1 year)\(^{57}\)\(^{99}\)\(^{109}\) |                           |                             |
| ERA                     | Healthcare expenditure, \(^{21}\) mortality (2 years), \(^{113}\) number of days hospitalised (1 year), \(^{107}\) number of emergency department visits (1 year), \(^{56}\) number of hospital admissions (1 year), \(^{56}\) number of hospital visits (1 year), \(^{11}\) nursing home placement (2 years), \(^{113}\) presence of critical illness, \(^{46}\) readmission within 30 days (1 year)\(^{11}\) |                           |                             |
| HCC                     | Hospitalisation (1 year), \(^{21}\) ED visits (1 year), \(^{21}\) readmission within 30 days (1 year), \(^{21}\) healthcare expenditure (1 year)\(^{21}\) |                           |                             |
| M3 Index                | Hospitalisation (1 year), \(^{109}\) mortality (1 year)\(^{109}\) |                           |                             |
| MDMS                    | Sickness absence episodes taken in 2 years (male)\(^{24}\) Sickness absence episodes taken in 2 years (female)\(^{22}\) |                           |                             |
| MM weighted by ADL scale | Life satisfaction, \(^{22}\) perceived health status\(^{22}\) |                           |                             |
| MM weighted by HUI      | Life satisfaction, \(^{22}\) perceived health status\(^{22}\) |                           |                             |
| MM weighted by HUI betas | Life satisfaction, \(^{22}\) perceived health status\(^{22}\) |                           |                             |
| MWI                     | ADL limitations, \(^{121}\) IADL limitations, \(^{121}\) mortality (10 years), \(^{38}\) cognitive performance, \(^{121}\) future physical functioning, \(^{121}\) grip strength, \(^{11}\) health-related quality of life, \(^{121}\) mortality, \(^{121}\) subjective physical functioning, \(^{121}\) suicide mortality\(^{123}\) Gait speed\(^{28}\) |                           |                             |
| QOF (standard)          | Mortality (1 year)\(^{50}\) |                           |                             |
| QOF (extended)          | Mortality (1 year)\(^{50}\) |                           |                             |
| Severity Burden Score   | Mental component score (SF-12)\(^{94}\) |                           |                             |
| D=Other approaches (D-1=CaseMix, D2=Pharmaceutical-based) |                               |                           |                             |
| ACG                     | Hospitalisation (1 year), \(^{80}\) mortality (3 years), \(^{48}\) number of primary care consultations (3 years), \(^{48}\) primary healthcare cost, \(^{47}\) readmission within 30 days (1 year)\(^{21}\) |                           |                             |
| ADG                     | Hospitalisation (1 year), \(^{107}\) number of primary care physician visits (1 year), \(^{107}\) number of specialist visits (1 year)\(^{107}\) |                           |                             |
| CRG                     | Healthcare expenditure, \(^{49}\) HRQoL using EQ-5D-3L\(^{87}\) |                           |                             |
| Adjusted Morbidity Groups (GMA) | Use of healthcare resources\(^{88}\) |                           |                             |
| HM                      | Emergency department visits (1 year), \(^{21}\) healthcare expenditure, \(^{21}\) hospitalisation (1 year), \(^{21}\) readmission within 30 days (1 year)\(^{21}\) |                           |                             |
| HSMI                    | Healthcare cost (primary care)\(^{78}\) |                           |                             |
| Minnesota Tiering       | Emergency department visits (1 year), \(^{21}\) healthcare expenditure, \(^{21}\) hospitalisation (1 year), \(^{21}\) readmission within 30 days (1 year)\(^{21}\) |                           |                             |
| Resource Utilisation Band | Fee-for-service expenditures, \(^{77}\) primary healthcare cost, \(^{47}\) mortality (3 years), \(^{38}\) number of primary care consultations (3 years), \(^{48}\) registered active listing in primary care, \(^{100}\) registered active listing in all healthcare\(^{100}\) |                           |                             |
| CDS                     | Hospitalisation (1 year), \(^{99}\) mortality (1 year)\(^{99}\) |                           |                             |
| Drug Count              | Emergency hospital admission (2 years), \(^{120}\) functional decline (2 years), \(^{120}\) hospitalisation (1 year), \(^{47}\) mortality (1 year), \(^{47}\) (3 years), \(^{47}\) number of primary care consultations (3 years)\(^{48}\) |                           |                             |
| Pra tool Modified using RxRisk-V | Emergency hospital admission (1 year)\(^{119}\) |                           |                             |
| RxRisk-V                | Emergency hospital admission (2 years), \(^{120}\) functional decline (2 years)\(^{120}\) |                           |                             |

Continued
Organ or system-based approaches

There were two instruments in this category. They were Cumulative Illness Rating Scale (CIRS)\(^{17, 18}\) and Organ Systems with Chronic Disease Count (Organ-CDC).\(^{19}\)

Weighted indices

There were 17 unique weighted instruments found in the included studies. The original CCI with its different modifications was the most frequently used instrument and was used in 29 studies. The CCI was based on Disease Count, but the 17 conditions were weighted originally based on their impact on 1-year mortality.\(^{20}\) The final score was derived by the summation of all the weighted conditions. There were many variations and modifications of the score including the addition of psychosocial factors. The CCI instrument was found to be associated with multiple outcomes other than 1-year mortality.

Most of the other weighted index instruments were novel, like the Multimorbidity-Weighted Index (MWI), in which the investigators built multivariable prognostic models from a set of potential predictor conditions and weighted the conditions based on an outcome of clinical interest. The most common outcomes chosen were mortality and physical function. Other outcomes included health expenditure,\(^{21}\) health utility index\(^{22}\) and severity of the most severe condition. The Multidimensional Multimorbidity Score (MDMS)\(^{24}\) was unique as it was weighted based on health behaviours and patient symptoms and not based on any specific outcome.

Other approaches to measuring multimorbidity

Other approaches included case-mix and pharmaceutical-based instruments. For case-mix approach, the ACG and Resource Utilisation Band were the most commonly used instruments.\(^{25}\) Most of the case-mix instruments required proprietary software licenses from the USA and obtained data from electronic medical records or administrative data. The Clinical Risk Groups instrument was similar but took into account the severity of individual conditions.\(^{26}\)

The second group of instruments in this category was related to pharmaceutical data. The most frequent type was the unweighted Drug Count. The other three (Chronic Disease Score, A Veterans Association adapted pharmacy-based case-mix instrument like RxRisk-V and modified Probability of repeated admission risk prediction tool using RxRisk-V) were all weighted indices. Except for the Drug Count that was based on a self-report questionnaire, the rest required a prescription drug database to obtain the data.

Table 3

| Multimorbidity measures | Association between outcomes and multimorbidity |
|-------------------------|-----------------------------------------------|
|                         | Evidence of an association | No evidence of an association |
| ACE-27, Adult Comorbidity Evaluation; ACG, Adjusted Clinical Groups; ADG, Aggregated Diagnosis Groups; ADL, Activities of Daily Living; CCC, Chronic Condition Count; CCI, Charlson Comorbidity Index; CDC, Chronic Disease Count; CDS, Chronic Disease Score; CIRS, Cumulative Illness Rating Scale; CLS, Comorbidity Linked Score; CRG, Clinical Risk Groups; DBIS, Disease Burden Impact Scale; DC, Disease Count; E1, Elixhauser Index; ERA, Elder Risk Assessment; HCC, Hierarchical Condition Categories; HM, Hybrid Model (MN Tier+ERA); HRQoL, health-related quality of life; HSMI, Health Search Morbidity Index; HUI, Health Utility Index; MDMS, Multidimensional Multimorbidity Score; M3 Index, Multimorbidity Measure (M3) Index; MM, Multimorbidity; MWI, Multimorbidity-Weighted Index; Pra tool, Probability of repeated admission risk prediction tool; QOF, Quality and Outcomes Framework; RxRisk-V, A Veterans Association adapted pharmacy-based case-mix instrument; SF-12, Short Form-12. |

Outcomes

We classified the 150 outcomes into 17 categories as reported in the core outcomes set of multimorbidity research (COSmm).\(^{10}\) The most commonly reported outcomes were healthcare use (n=45), mortality (n=18), health-related quality of life (n=18) and physical function (n=13). The different studies unanimously showed that higher levels of multimorbidity were associated with higher healthcare use and mortality, lower health-related quality of life and poorer physical function. Seven outcomes in the COSmm were not found in all the 96 studies. These were treatment burden, self-management behaviour, self-efficacy, adherence, communications, shared decision-making and prioritisation. There were 19 outcomes that were not described in the COSmm. These included cognitive function, risk of suicide, frailty and falls. The outcomes not found to have any association with the instruments for measuring the level of multimorbidity were preventive care,\(^{27}\) sickness absence episodes (female)\(^{24}\) and gait speed.\(^{28}\)

DISCUSSION

Summary of findings

Thirty-three unique instruments for measuring the level of multimorbidity were identified and categorised according to the classification by Sarfati.\(^{8}\) The most commonly used instrument was ‘Disease Count’. It was also the only instrument that was associated with the three essential outcomes from the core outcomes set of multimorbidity research (COSmm):\(^{10}\) that is, quality of life, mental health and mortality.

Comparison with previous research

Although the most common instrument identified in this systematic review was similar to that of Huntley et al.,\(^{12}\) several instruments including Duke Severity of Illness Checklist (DUSOI) and Functional Comorbidity Index identified in their article were not found in this systematic review. The possible reasons for not finding these instruments in this review could be due to the lack of interest in the instrument by the research community in recent years (to our knowledge, the last publication using DUSOI was
in 2004), or the exclusion of studies specifying an index condition.

Advantages and disadvantages of selected instruments

**Disease Count**
The advantage of using ‘Disease Count’ is its simplicity and the ease of data ascertainment with minimal resources required. However, using ‘Disease Count’ does not consider the severity of each condition where the complexity of multimorbidity may not be properly addressed. The other disadvantage noted was the lack of transparency in the operational definition of multimorbidity, especially regarding the list of conditions considered for multimorbidity and the cut-points used. Despite its simplicity, the level of multimorbidity measured using ‘Disease Count’ was the only instrument that was found to be associated with the three essential core outcomes (quality of life, mental health and mortality).

**Weighted indices**
The common weighted indices identified in this systematic review were CCI, Elders Risk Assessment (ERA), Elixhauser Index (EI) and MWI. These weighted indices were often used in prognostic models to build complex multivariable regression models in which the weights were calculated from hazard ratios, odds ratios or regression coefficients. The advantage of these weighted indices is that the weights allow the adaptation of an index to a specific outcome. An investigator could recalibrate the correct weight by creating a prognostic model to produce a contextualised instrument for a different setting. Prognostic models can provide clinically relevant risk stratification and help to allocate resources. The disadvantage of such indices is that calculated weights are greatly influenced by the population, outcomes used, and the instrument’s original conception and purpose, hampering the ability to compare across studies.

**Case-mix**
The ACG system has a good track record in the USA and several other countries, especially for measuring the outcomes of healthcare utilisation. However, the instrument is proprietary, and the exact algorithm of the instrument is not open to the public and may not be suitable in certain settings. The Clinical Risk Group (CRG) system has a good track record in Spain. It measures the severity of each condition and its algorithm is fully transparent. The common disadvantage of both systems is the financial costs involved in obtaining the license.

**Pharmaceutical-based instruments**
Medication-based indices include versions of the Chronic Disease Score, which later became known as the RxRisk and its adaptation for use in the veteran population, the RxRisk-V. Like the Disease Count, its main advantage is the ease of use with minimal resources required. However, many studies were not transparent regarding which type of drugs were included.

**Data sources**
Data sources used by these instruments included medical record information, patient self-report, clinical judgement and large administrative databases. Each data source has its inherent advantages and disadvantages. For patient self-report, patients with cognitive impairment may under-report symptoms and may be seen less frequently by their physicians, resulting in an under-recognition or undertreatment of conditions. It has also been shown that health administrative data based on billing system underestimated the prevalence of many chronic conditions.

The available data in a particular setting may strongly influence the ultimate instrument chosen for multimorbidity research. As there is currently no consensus on the gold standard for sources of data, it is difficult to assess which data source was superior from this review.

**Outcomes**
There were 17 multimorbidity outcomes identified by a Delphi process involving a panel of international experts in multimorbidity intervention studies. However, only 10 out of the 17 outcomes were reported in the 96 studies identified in this systematic review. The most common outcome that was investigated was healthcare use. The seven missing outcomes belong to ‘patient-reported impact and behaviours’ and ‘consultation-related’ outcome groups, most likely indicating that there is a dearth of multimorbidity studies looking at these two groups of outcomes measures.

**Clinical implications**
Ideally, a single instrument measuring the level of multimorbidity should be able to predict a variety of relevant outcomes. However, Byles et al reported that a single instrument could not be used to predict different outcomes, in different patient groups and settings, unless different weights were assigned to these factors in calculating a score. Such multiple-scoring instruments may be the way forward for validation of prognostic models for different outcomes and different populations with established multimorbidity instruments. For example, depending on the outcome, study population and setting, the choice of conditions included in the multiple-scoring instrument should include those with a high prevalence in that study population and the weights should be determined by their significant impact (ie, outcome) on the affected population.

For pragmatic reasons, the final selection of the conditions to be included in such a multiple-scoring instrument may still have to take into account the availability of relevant and reliable data. A certain degree of reductionism will also have to be accepted because a single instrument will not be able to encompass all the nuances of the different interactions of chronic conditions on an individual living in his/her unique milieu. We recommend that researchers perform validation studies using the instruments listed in this systematic review to adjust
the weights according to the specific outcome of interest for the study population relevant to their setting.

Strengths and limitations of the study
The main strengths of this systematic review were the involvement of a health science librarian in our search strategy, a published protocol, adherence to the protocol without major changes during the systematic review process,39 and the critical appraisal of all the primary studies with a risk of bias assessment tool.

The systematic review had several limitations. We excluded grey literature and included only studies that were published in the English language. We also did not contact authors directly for a suggestion of studies, nor identified a list of instruments from the preliminary search and then performed an additional search using the same databases.40 Additionally, this systematic review did not review the validity and reliability of all the instruments as it was beyond the scope of the intended work. We have, however, included the references of the original articles or validation studies in table 2 for each of the instrument where available. Finally, this review specifically aimed to look at the association of the level of multimorbidity as the main independent variable and excluded the level of multimorbidity as a mediating, confounding or effect-modifying variable. This strict criterion excluded 17 studies (figure 1) as a result. Excluding these 17 studies did not alter the findings as the instruments used in all the 17 studies were Disease Count (n=5), CIRS (n=3), CCI (n=3), EI (n=1) and Aggregated Diagnosis Groups (n=1) where no new instruments were identified.

CONCLUSIONS
In this systematic review, we found 33 instruments for measuring the level of multimorbidity in community-dwelling individuals that predict or explore the association of multimorbidity with at least one specified outcome. Disease Count and weighted indices like the CCI, the ERA and EI were commonly used for measuring the level of multimorbidity. Other approaches to measuring the level of multimorbidity included case-mix or pharmaceutical-based instruments.

We found continuing interest in measuring the level of multimorbidity with Disease Count and Drug Count. There has also been a rise in the development of novel weighted indices using prognostic models or validation of existing well-established instruments like the CCI over the last few years. There is currently an absence of a gold standard for where to obtain chronic disease information. The most suitable instrument will depend on the specified outcome of interest, the study population and the type of data and resources available.

Finally, there is still much work to improve on the body of knowledge of multimorbidity when most investigators in the last decade measured multimorbidity without including some of the important outcome measures of multimorbidity. We also suggest that a clear description of the instruments is required in the publication of multimorbidity studies to counter the frequent lack of information currently seen so as to contribute to robust multimorbidity research in future.
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