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REVIEW

Do replicable profiles of multimorbidity exist? Systematic review and synthesis

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Abstract

This systematic review aimed to synthesise multimorbidity profiling literature to identify replicable and clinically meaningful groupings of multimorbidity. We searched six electronic databases (Medline, EMBASE, PsycINFO, CINAHL, Scopus, and Web of Science) for articles reporting multimorbidity profiles. The identified profiles were synthesised with multidimensional scaling, stratified by type of statistical analysis used in the derivation of profiles. The 51 studies that met inclusion criteria reported results of 98 separate analyses of multimorbidity profiling, with a total of 407 multimorbidity profiles identified. The statistical techniques used to identify multimorbidity profiles were exploratory factor analysis, cluster analysis of diseases, cluster analysis of people, and latent class analysis. Reporting of methodological details of statistical methods was often incomplete. The discernible groupings of multimorbidity took the form of both discrete categories and continuous dimensions. Mental health conditions and cardio-metabolic conditions grouped along identifiable continua in the synthesised results of all four methods. Discrete groupings of chronic obstructive pulmonary disease with asthma, falls and fractures with sensory deficits and of Parkinson's disease and cognitive decline where partially replicable (identifiable in the results of more than one method), while clustering of musculoskeletal conditions and clustering of reproductive systems were each observed only in one statistical approach. The two most replicable multimorbidity profiles were mental health conditions and cardio-metabolic conditions. Further studies are needed to understand aetiology and evolution of these multimorbidity groupings. Guidelines for strengthening the reporting of multimorbidity profiling studies are proposed.

Keywords Multimorbidity · Exploratory factor analysis · Cluster analysis · Latent class analysis · Multidimensional scaling

Introduction

Multimorbidity is defined as the presence of more than one chronic conditions within one person [1], where each condition is either a non-communicable disease, a mental health disorder, or an infectious disease of long duration [2]. Multimorbidity is estimated to affect almost a quarter of the adult population in developed countries [3–5] and is a significant and growing public health burden due to its association with an increased risk of premature death, high level of disability, and high use of health care [5]. Cost of health care increases almost exponentially with the increasing number of health conditions [6]. While clinicians are well aware of the challenges in the treatment of individuals with multiple chronic conditions [7, 8], clinical guidelines, medical training and many aspects of health management remain focused on separate illnesses [7], despite the growing number of individuals presenting with multiple health conditions [9, 10].

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A major challenge in developing therapeutic guidelines for managing multimorbidity is the absence of agreed upon standards for identifying and classifying multimorbidity subtypes. The two broad approaches currently used to capture multimorbidity are disease counts (weighted or unweighted) [11, 12] and statistical classification of multimorbidity profiles [12]. The counts-based methods of measuring multimorbidity provide means of identifying individuals who might be in need of complex health care [13], but their utility in informing clinical guidelines is limited by the inability to distinguish between individuals with the same number but different types of diseases. In contrast to counts-based methods, the statistically-derived profiles of multimorbidity classify individuals into qualitatively distinct classes based on the specific combinations of diseases. Identifying the diseases that reliably occur together has great potential to provide critical insights into the underlying pathological processes that give rise to specific patterns of multimorbidity thus facilitating the development of guidelines targeted to the specific profiles of multimorbidity. However, reliable information on the replicable profiles of multimorbidity that exist in the population is currently absent. We are aware of only one systematic review of multimorbidity classification studies [14], that identified 97 multimorbidity profiles reported in 14 separate studies. The review identified three groups of partially replicable patterns, one of which was characterised by a combination of cardiovascular and metabolic diseases, the second one captured mental health problems, and the third one comprised musculoskeletal disorders. However, the review utilised a solely qualitative approach to data synthesis and hence it is not possible to disentangle spurious associations reported in the literature from the associations that identify reliable profiles of multimorbidity. Given the increasing incidence of both multimorbidity and multimorbidity profile studies, quantitative synthesis of multimorbidity profiles is well overdue.

The aims of this systematic review were to (1) synthesise results of multimorbidity studies to gain a greater understanding of reliable and replicable multimorbidity profiles that exist in the population and (2) provide guidance on optimising methodological quality of multimorbidity profiling studies with the goal of increasing comparability of results across the studies.

Methods

Search strategy

Articles for this systematic review were identified by searches of Medline (on EBSCOhost platform), EMBASE (on OVID platform), PsycINFO (on EBSCOhost platform), CINAHL (on EBSCOhost platform), Scopus, and Web of Science on 13 March, 2018. The search strategy was based on an earlier systematic review [14] and was adapted for this study in consultation with a research librarian. The search comprised terms for multimorbidity (e.g. 'multiple diagnoses') and statistical methods (e.g. cluster analysis [CA], latent class analysis [LCA]), and excluded clinical trials and in vitro and ex vivo studies. As we sought to synthesise current research on multimorbidity rather than to develop a definition of multimorbidity, we accepted definitions of multimorbidity as used by the study authors. Examples of two search strategies (Medline and EMBASE) are provided in Supplementary Data 1. Results were limited to papers published from 1 January 2000 and in the English language. We also undertook manual searching of reference lists of the studies included in the review to identify any additional potentially relevant articles.

Selection of articles

Abstracts of all articles identified through searches of electronic databases were downloaded to a reference management software (EndNote X7; Thompson Scientific, New York, NY, US) and checked for duplication. After the removal of duplicates, the remaining articles were transferred to an online systematic review platform, Covidence (www.covidence.org, Vertitas Health Innovation Ltd, Melbourne, Australia). Titles and abstracts were reviewed against predefined inclusion criteria: (a) original research (not a review paper, case study, or editorial); (b) studied patterns of co-occurring diseases (e.g. did not solely use disease counts or bivariate associations between disease pairs); (c) included at least 10 long-term health conditions in their analyses (following recommendations of a previous review [14]); and (d) studies were carried out with adults (18 years and above). Where a study included individuals under 18 years of age, it was only included in our review if separate results were reported for individuals aged 18 years and above [15–17]. Studies that included signs and symptoms ("abnormalities that can indicate a potential medical condition", https://www.nature.com/subjects/signs-and-symptoms) alongside the diagnosed conditions were considered eligible for the study.

Studies were excluded if they: (a) described the frequency of disease combinations without applying any statistical technique to identify patterns of co-occurring diseases; (b) selected the study population based on the presence of a pre-defined health condition; (c) included risk factors (e.g. smoking) alongside diseases in identifying multimorbidity profiles; (d) analysed conditions that focused on single body system or area of function (e.g., solely psychiatric disorders; solely musculoskeletal conditions); (e) focused on comorbidities of an index condition; or (f) reported data that were already presented in another (included) publication.

Consideration for the exclusion of studies that analysed conditions from single body system (criterion d) was based on prior evidence indicating that multimorbidity patterns do not neatly correspond with the current classification of disease categories [7]. For the purposes of our review, we used World Health Organisation (WHO) definition of a risk factor as "an attribute, characteristic or exposure that increases the likelihood of developing a disease or injury" (https://www.who.int/topics/risk_factors/en/). Where insufficient information was available in the title and abstract, we retrieved and examined full texts to determine whether the study met the inclusion criteria.

To optimise the accuracy of screening process, the first (LB) and second (KL) authors screened the first 100 titles and any disagreements were resolved through discussion. Screening of the remaining articles was performed by KL and adjudicated by LB.

Data extraction

For each article that met the inclusion criteria, we extracted information on study characteristics (authors, publication year, country, sample size, study design); participant characteristics (gender, age [mean (SD) and range]); morbidity measures (source of data, clinical verification of diagnoses, criteria for inclusion/exclusion of diseases); analysis (number of diseases/conditions analysed, type of classification technique, proximity measures used, disease grouping algorithm, use of stratification, criteria to determine number of morbidity profiles extracted); and results (number of profiles identified, researcher-allotted names of profiles, diseases associated with each profile). Data were extracted into an Access 2010 database (Microsoft Corporation, Redmond, WA, US). Data extraction was performed by the second author (KL) and independently verified by the first author (LB).

Data synthesis

As there was substantial variability across the studies in the types of conditions included in the analyses, prior to data synthesis, sparsely mentioned conditions were consolidated into more general groupings (based on ICD10 codes) to optimise consistency of morbidity data across the studies. Details of how conditions were consolidated for this review are provided in Supplementary Data 2.

Synthesis of multimorbidity profiles recorded in the reviewed studies was carried out with multidimensional scaling (MDS) analysis. MDS is a data-exploratory technique that aims to visually represent the level of similarity between objects. It makes no underlying assumptions about causes of observed associations but is able to identify the discrete groupings of conditions (clusters) as well as arraying of condition along some underlying continuum (axes). Since critical aspects of multimorbidity profiles, such as causality of associations and whether multimorbidity profiles reflect discrete or continuous underlying processes, are not well understood at present, these properties of MDS make it well-suited to the exploration of commonalities in multimorbidity profiles reported in the literature.

Given that different statistical approaches used in multimorbidity profiling studies make different assumptions about the nature of underlying multimorbidity patterns, MDS analyses were stratified by analysis type. For each statistical technique of multimorbidity profiling identified in this review, we constructed a similarity matrix of health conditions by recording the number of times a given condition appeared in the same multimorbidity group with any other condition. Matrix diagonals represented the total number of multimorbidity profiles that contained a given condition. The similarity matrices were input into MDS to derive distances between health conditions, which were then plotted in two-dimensional space to create a bivariate point map of disease proximities. The more frequently any two conditions co-occurred within the same multimorbidity profile, the closer they would appear on the point map.

Unlike other dimension-reduction methods, such as principal component or exploratory factor analysis (EFA) for example, dimensions in MDS analyses have no intrinsic meaning. The meaningfulness of an MDS solution is inferred from the examination of positioning of observations relative to each other. The MDS point maps were examined qualitatively to identify clusters of conditions and axes. Clusters are groups of conditions that occur closer to each other than to other conditions and meaningful clusters were considered to be conditions with known common pathways (e.g., the hypothalamic–pituitary–adrenal axis disorders [18]), recognised complications (e.g., renal disease and anaemia), or previously documented associations (e.g., hypertension, obesity, insulin resistance, and dyslipidaemia as constituents of metabolic syndrome [19]). Axes represent ordering of conditions on the map along a continuum and capture differences in the level of a particular attribute (e.g., ordering of conditions from low to high severity). The axes need not correspond to MDS dimensions and can vary in the positioning from right to left, top to bottom, or diagonally at any angle across the map.

The similarity matrices were constructed in Microsoft Excel (2016) software and imported into IBM SPSS Statistics version 25 (IBM, Armonk, NY, US) for two-dimensional MDS using the PROXSCAL command. Kruskal's Stress formula I values were used as an indicator of goodness of fit between raw similarities and MDS-derived distances [20]. Stress values capture the proportion of variance in similarities that is not explained by the MDS solution, with values ranging from 0 (perfect correlation between similarities and distances) to 1 (no correlation between similarities and distances) [20]. MDS analyses reported here utilised Torgerson as initial configuration. The choice of initial configurations for the MDS solutions was based on the lowest stress values and conceptual interpretability of the solutions [21].

Results

Selection of studies

As displayed in Fig. 1, our search strategy yielded 19,568 records. After the removal of duplicates, 8693 unique articles remained, with 176 selected for full-text review after the screening of titles and abstracts. Following full-text review, 51 articles were included in our systematic review [4, 15–17, 22–68]. The process of article selection and reasons for exclusion are summarised in Fig. 1.

Characteristics of the reviewed studies

Characteristics of the 51 studies included in our systematic review are shown in Table 1. Sample sizes used for multimorbidity analyses ranged from 328 [30] to 1.9 million [15] adult participants, with a median of 3583 (interquartile range [IQR] 1213–34,886). The majority of studies were cross-sectional (n = 33) or utilised cross-sectional data from either prospective (n = 11) or retrospective (n = 6) longitudinal studies. One additional study was case–control, with controls-only data included in multimorbidity profiling. The most common method of ascertainment of chronic conditions was unverified self-report (n = 23), followed by administrative health records (n = 17), self-report with clinical assessment (n = 7), and clinical assessment (n = 4). The number of conditions included in the multimorbidity analyses ranged from 10 [40] to 99 [29], with a median of 16 (IQR 12–31). The majority of studies were carried out in Europe (n = 25) or North America (n = 12).

Among the 51 articles included in this review, one publication applied two separate statistical techniques of multimorbidity profiling [53], one publication applied three techniques [34] and one publication [40] applied four statistical techniques. The statistical techniques used in the resultant 57 analyses of multimorbidity profiling are outlined in Table 2. The most frequently utilised statistical technique was EFA (n = 26 including eight studies that applied principal component analysis), followed by CA of diseases (n = 13), LCA (n = 11), and CA of individuals (n = 7).

Results of multimorbidity profiling analyses reported in the reviewed studies are summarised in Supplementary

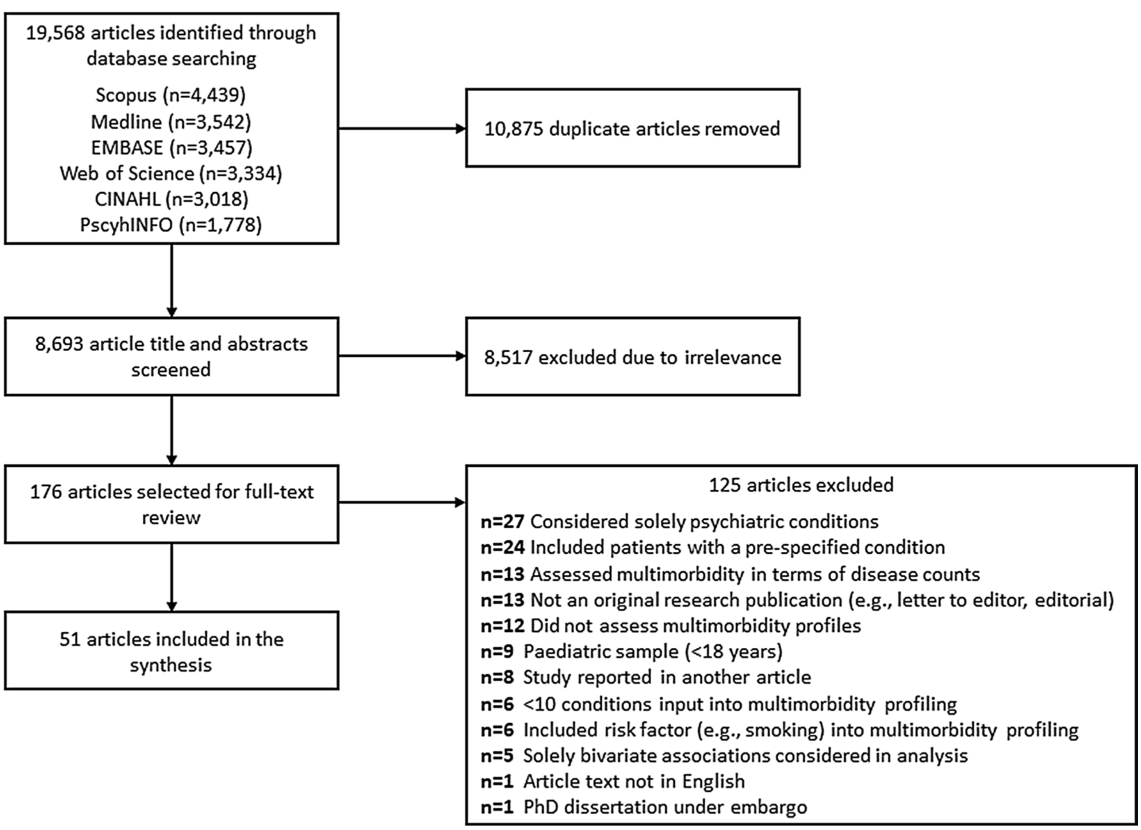

Fig. 1 Flowchart of study search and selection

Table 1 Characteristics of the reviewed studies (n = 51)

References	Country	Sample size	Sex composition	Age range (years)	Study design	Study population	Disease ascertainment method	Diagnosis classification tool	Disease inclusion criteria	No. conditions in analysis
Aoki et al. [22]	Japan	3256	50% F; 50% M	18–84	Cross-sectional	General population	Self-report (unverified)	Researcher-generated ad hoc list (17 items)	Not stated	17
Barile et al. [23]	US	4184	51% F; 49% M	18–65+	Longitudinal (a cross-section of data analysed)	General population	Self-report (unverified)	Researcher-generated ad hoc list (34 items)	Not stated	27
Cigolle et al. [24]	US	11,113	Not reported	65+	Longitudinal (a cross-section of data analysed)	General population	Self-report (unverified)	Not stated	Not stated	12
Clerencia-Sierra et al. [25]	Spain	924	57% F; 43% M	65+	Cross-sectional	Hospital outpatients	Medical records	EDCs of the ACG system	Prevalence > 5% per stratum	31
Collerton et al. [26]	UK	658	60% F; 40% M	85	Longitudinal (a cross-section of data analysed)	General practice patients	Clinical assessment and medical records	Researcher-generated ad hoc list (20 items)	Prevalence > 3% at baseline and < 10% missing data	20
Cornell et al. [27]	US	1,327,382	5% F; 95% M	Not reported	Cross-sectional	Veterans attending a VHA care facility	Medical records	ICD-9-CM codes	High prevalence in the population of interest	45
Diaz et al. [15]	Norway	1,920,125	Range from 44% F (Eastern European 45–64 years) to 63% F (Western European 65+ years)	15+	Cross-sectional	General population of Norwegian citizens and immigrants	Medical records	EDCs of the ACG system	Prevalence ≥ 1% per stratum	Range from 9 (Eastern European M 45–64 years) to 32 (Norwegian-born M 65+ years)
Dong et al. [28]	Sweden	496	76% F; 24% M	85	Cross-sectional	Residents of Linköping municipality born in 1922	Medical records	ICD-10 codes	Prevalence > 5%	16 for F, 13 for M
Foguet-Boreu et al. [29]	Spain	322,328	57% F; 44% M	65+	Cross-sectional	General practice patients	Medical records	ICD-10 codes	Prevalence > 1% per stratum	Range from 88 (M 65–69 years) to 99 (M and F 80+ years)

Table 1 (continued)

References	Country	Sample size	Sex composition	Age range (years)	Study design	Study population	Disease ascertainment method	Diagnosis classification tool	Disease inclusion criteria	No. conditions in analysis
Formiga et al. [30]	Spain	328	62% F; 38% M	85	Longitudinal (a cross-section of data analysed)	Community-dwelling residents of Barcelona born in 1924	Self-report and clinical assessment	Researcher-generated ad hoc list (16 items)	Not stated	16
Garin et al. [31]	Spain	3625	55% F; 45% M	50+	Cross-sectional	General population	Self-report (unverified)	Researcher-generated ad hoc list (11 items)	Not stated	11
Garin et al. [4]	China, Finland, Ghana, India, Mexico, Poland, Russia, South Africa, Spain	41,909	Not reported	50+	Cross-sectional	General population	Self-report (unverified)	Researcher-generated ad hoc list (12 items)	High prevalence and high impact on health	12
Gellert et al. [32]	Germany	1121	91% F; 9% M	100–109	Cross-sectional	Individuals 100+ years with health insurance at AOK Nordost	Medical records	ICD-10 codes	10 most prevalent conditions	10
Goldstein et al. [33]	US	3498	3% F; 97% M	18+	Cross-sectional	Veterans attending outreach programs	Clinical interview	Researcher-generated ad hoc list (16 items)	Not stated	15
Gomez-Rubio et al. [34]	Spain, UK, Germany, Ireland, Italy, Sweden	1084 in control group	48% F; 52% M	18+	Case–control (only controls data analysed)	Combination of hospital patients and general population	Self-report (unverified)	Researcher-generated ad hoc list (25 items)	Prevalence ≥ 2%	17
Gonsoulin et al. [35]	US	38,597	100% F	65+	Cross-sectional	Female Veterans attending a VHA care facility	Medical records	ICD-9-CM codes	20 most prevalent conditions; A priori exclusion of sex-specific disorders (e.g., prostate and menstrual disorders)	20

Table 1 (continued)

References	Country	Sample size	Sex composition	Age range (years)	Study design	Study population	Disease ascertainment method	Diagnosis classification tool	Disease inclusion criteria	No. conditions in analysis
Gu et al. [36]	China	2452	49% F; 51% M	60–93	Cross-sectional	Community-dwellers who had resided in Nanjing, Jiangsu province for 2+ years	Self-report and clinical assessment	Researcher-generated ad hoc list (13 items)	Not stated	13
Guisado-Clavero et al. [37]	Spain	190,108	60% F; 40% M	65+	Longitudinal (a cross-section of data analysed)	General practice patients residing in Catalonia	Medical records	ICPC-2 codes	Prevalence > 1%	Range from 80 (F 65–79 years) to 84 (F 80+ years)
Holden et al. [38]	Australia	1494	65% F; 35% M	18–70	Cross-sectional	Employees of 58 large companies taking part in 'Australian Work Outcomes Cost–benefit project'	Self-report (unverified)	WHO Health and Productivity Questionnaire and K6	Not stated	23
Islam et al. [40]	Australia	4574	Not reported	50+	Cross-sectional	Members of National Seniors Australia (subscription-based lobbying group; 285,000 members)	Self-report (unverified)	Researcher-generated ad hoc list (11 items)	Prevalence ≥ 2%	10
Islam et al. [39]	Australia	2540	53% F; 47% M	Not reported	Cross-sectional	Members of 3 national organisations: National Seniors Australia, the National Diabetes Services Scheme and Lung Foundation Australia	Self-report (unverified)	Researcher-generated ad hoc list (12 items)	Not stated	12

Table 1 (continued)

References	Country	Sample size	Sex composition	Age range (years)	Study design	Study population	Disease ascertainment method	Diagnosis classification tool	Disease inclusion criteria	No. conditions in analysis
Jackson et al. [42]	Australia	7270	100% F	76–81	Longitudinal (a cross-section of data analysed)	Community-dwelling women	Self-report (unverified)	Researcher-generated ad hoc list (31 items)	Not stated	31
Jackson et al. [41]	Australia	4896	100% F	59–64	Longitudinal (a cross-section of data analysed)	Community-dwelling women	Self-report (unverified)	Researcher-generated ad hoc list (31 items)	Not stated	31
John et al. [43]	US	1039	59% F; 41% M	60+	Cross-sectional	American Indian elders identified from Indian Health Service records	Self-report (unverified)	Researcher-generated ad hoc list (11 items)	Not stated	11
Jovic et al. [44]	Serbia (excl. Kosovo and Metohia)	13,103	52% F; 48% M	20+	Cross-sectional	General population	Self-report (unverified)	Researcher-generated ad hoc list (16 items)	Prevalence ≥ 1%	13
Kirchberger et al. [45]	Germany	4127	51% F; 49% M	65–94	Cross-sectional	Community dwelling adults aged 65–94 years living in Southern Germany	Self-report (unverified)	Researcher-generated ad hoc list (13 items)	Not stated	13
Kuwornu et al. [46]	Canada	3284	18–54 years: 61% F; 39% M 55+ years: 58% F; 42% M	18+	Cross-sectional	General population	Self-report (unverified)	List based on population prevalence (15 items)	Prevalence ≥ 5% per stratum	15
Lenzi et al. [47]	Italy	1,373,037	55% F; 45% M	18+	Longitudinal (a cross-section of data analysed)	Residents of the Emilia-Romagna region with 1+ conditions	Medical and pharmacy records	ICD-9-CM and ATC codes	Not stated	26
Marengoni et al. [50]	Sweden	1099	77% F; 33% M	77+	Cross-sectional	Residents of Stockholm aged 75+ years	Medical records and clinical assessment	ICD-9, ATC, and DSM-IV codes	Prevalence > 3%	15

Table 1 (continued)

References	Country	Sample size	Sex composition	Age range (years)	Study design	Study population	Disease ascertainment method	Diagnosis classification tool	Disease inclusion criteria	No. conditions in analysis
Marengoni et al. [48]	Italy	1332	54% F; 46% M	65+	Cross-sectional	Hospital internal medicine and geriatric outpatients	Clinical assessment	ICD-9 codes	Prevalence ≥ 5%	19
Marengoni et al. [49]	Italy	Wave 1: 1155; Wave 2: 1173	Wave 1: 54% F; 46% M Wave 2: 48% F; 52% M	65+	Longitudinal (cross-sectional analysis of two waves of data)	Hospital internal medicine and geriatric outpatients	Clinical assessment	ICD-9 codes	Prevalence ≥ 5%	19
Marventano et al. [52]	Spain	2818	76% F; 24% M	65+	Cross-sectional	Community-dwelling people aged 65+ years	Self-report and medical records	Researcher-generated ad hoc list (11 items)	Insufficient information	11
Marventano et al. [51]	Spain	891	79% F; 21% M	65+	Cross-sectional	Institutionalised older adults	Medical records	Researcher-generated ad hoc list (11 items)	Insufficient information	11
Mino-Leon et al. [53]	Mexico	77,573	58% F; 42% M	60+	Retrospective cohort (a cross-section of data analysed)	General practice patients	Medical records	ICD-10 codes	Not stated	11
Newcomer et al. [54]	US	15,480	59% F; 41% M	Not reported	Retrospective cohort (a cross-section of data analysed)	Health insurance members	Medical records	ICD-9 codes	Insufficient information	17
Nunes et al. [55]	Brazil	2927	59% F; 41% M	20+	Cross-sectional	General population	Self-report (unverified)	Researcher-generated ad hoc list (11 items)	Not stated	11

Table 1 (continued)

References	Country	Sample size	Sex composition	Age range (years)	Study design	Study population	Disease ascertainment method	Diagnosis classification tool	Disease inclusion criteria	No. conditions in analysis
Nunes et al. [56]	Brazil	60,202	55% F; 45% M	18–101	Cross-sectional	General population	Self-report (unverified)	Ad hoc list predetermined for national survey (22 items)	Not stated; final model excluded schizophrenia, OCD, 'other mental disease' and 'other heart disease' to improve model fit.	16
Olaya et al. [57]	Spain	3541	55% F; 45% M	50+	Longitudinal (a cross-section of data analysed)	General population	Self-report (unverified)	Researcher-generated ad hoc list (11 items)	Not stated	11
Poblador-Plou et al. [16]	The Netherlands	79,291	52% F; 48% M	15+	Retrospective cohort (a cross-section of data analysed)	General practice patients	Medical records	EDCs of the ACG system	Prevalence ≥ 1% per stratum	Range from 41 (M 45–64 years) to 54 (M 65+ years)
Prados-Torres et al. [17]	Spain	275,682	57% F; 43% M	15+	Retrospective cohort (a cross-section of data analysed)	General practice patients	Medical records	EDCs of the ACG system	Prevalence ≥ 1% per stratum	Range from 23 (F 45–64 years) to 39 (M 65+ years)
Prazeres et al. [58]	Portugal	1993	64% F; 36% M	Not reported	Cross-sectional	General practice patients	Medical records and self-report	ICPC-2 codes	Prevalence > 5%	16
Pugh et al. [59]	US	191,797	Not reported	Not reported	Retrospective cohort (a cross-section of data analysed)	Veterans receiving medical care through Veterans Affairs	Medical and pharmacy records	ICD-9-CM codes	Not stated	32
Schafer et al. [60]	Germany	149,280	42% F; 58% M	65+	Cross-sectional	Health insurance members	Health insurance claims data	ICD-10 codes	Prevalence ≥ 1%	46

Table 1 (continued)

References	Country	Sample size	Sex composition	Age range (years)	Study design	Study population	Disease ascertainment method	Diagnosis classification tool	Disease inclusion criteria	No. conditions in analysis
Sibley et al. [61]	Canada	16,357	55% F; 45% M	65+	Cross-sectional	Community-dwelling adults who experienced at least one fall in the prior year	Self-report (unverified)	Researcher-generated ad hoc list (13 items)	Prevalence ≥ 2%	11
Simões et al. [62]	Portugal	23,754	59% F; 41% M	35–54	Cross-sectional	General population	Self-report (unverified)	Researcher-generated ad hoc list (11 items)	Not stated	11
Teh et al. [63]	New Zealand	888	55% F; 45% M	Maori: 80–90 Non-Maori: 85	Cross-sectional	Population based sample of Maori and Non-Maori older people in the North Island, NZ	Self-report, medical records, and clinical assessment	Researcher-generated ad hoc list (14 items)	Not stated	14
Van Cleave et al. [64]	US	470	71% F; 29% M	60+	Longitudinal (a cross-section of data analysed)	Older adults residing in long-term aged care	Self-report and medical records	ICD-10 codes	Used in the calculation of Charlson Comorbidity Index	11
Walker et al. [65]	France	5647	52% F; 49% M	55+	Cross-sectional	Community-dwelling older adults	Self-report (unverified)	Researcher-generated ad hoc list (19 items)	High impact on health status	19
Wang et al. [66]	China	1480	59% F; 41% M	60+	Cross-sectional	Residents aged 60+ living in Shandong, China	Self-report, medical records, and clinical assessment	Not stated	Not stated	16
Wang et al. [67]	China	2705	58% F; 42% M	60+	Cross-sectional	Residents aged 60+ living in Shenzehen City	Self-report (unverified)	Researcher-generated ad hoc list (17 items)	Not stated	17
Whitson et al. [68]	US	14,052	57% F; 44% M	65+	Retrospective cohort (a cross-section of data analysed)	Community-dwelling older adults	Self-report (unverified)	Researcher-generated ad hoc list (13 items)	Not stated	13

Table 1 (continued)

ACG adjusted clinical groups, *ATC* anatomical therapeutic chemical classification system, *DSM* diagnostic and statistical manual of mental disorders, *EDC* expanded diagnosis clusters, *ICD* International Statistical Classification of Diseases and Related Health Problems, *ICPC* International Classification of Primary Care, *WHO* World Health Organization, *VHA* Veterans Health Administration, *K6* Kessler Psychological Distress Scale (6-item)

Data 3. Fifteen studies (29%) utilised stratification in their analyses: 9/26 EFA; 4/13 CA of diseases; 1/7 CA of people analyses; and 1/11 LCA studies. This produced 98 analyses of multimorbidity profiling, with a total of 407 multimorbidity profiles identified, including 206 profiles identified in EFA studies, 97 in CA of disease studies, 30 in CA of people studies, and 74 in LCA studies. The number of profiles identified in a given stratum ranged from 2 to 11 (median 5, IQR 3–5) overall, 2 to 6 in EFA studies (median 3, IQR 2–4), 3 to 11 in CA of diseases (median 5, IQR 4–6), 4 to 10 in CA of people (median 4, IQR 4–8.5), and 3 to 7 in LCA studies (median 6, IQR 4–7). Broadly, there was reasonable comparability in multimorbidity profiles derived from analyses stratified by sex and ethnicity within a given study. However, analyses stratified by age group tended to identify greater number and higher complexity of multimorbidity profiles in the older age groups.

Multidimensional scaling: co-occurring conditions

The MDS solutions displaying pooled co-locations of chronic conditions identified in each analysis technique are presented in Figs. 2, 3, 4, and 5. Stress values were 0.33 for EFA, 0.35 for CA of disease, 0.28 for CA of people, and 0.33 for LCA, indicating that MDS solutions gave a reasonable representation of similarities for each statistical technique. The total number of conditions for MDS analyses was 84 in EFA studies, 66 in CA of diseases studies, 41 in LCA studies, and 34 in CA of people studies.

Exploratory factor analysis

Tetrachoric correlations matrix was used to capture disease proximity in 18/26 EFA studies and the remaining studies did not state proximity measure used (n = 8). Twelve studies applied principal factor extraction, eight studies applied principal component extraction, one study applied multidimensional item-response theory extraction, and five studies did not state the type of extraction used. Type of rotation was reported in 25/26 reviewed studies, with oblique oblimin (n = 14) and orthogonal varimax (n = 7) rotations used most frequently. Eleven studies used only one criterion to determine the number of factors to retain, namely eigenvalues > 1 (n = 7) or scree plot (n = 4). Two studies did not state the criteria used to determine the number of multimorbidity profiles and the remaining studies used multiple criteria. In all studies, allocation of conditions to factors was based on the magnitude of factor loadings, with cut off values ranging from 0.20 to 0.40. Only 10 studies reported using clinical assessment to determine meaningfulness of the derived profiles. Of these, only two provided explicit a priori criteria used in clinical assessment of the derived profiles.

Table 2 Details of statistical techniques used to identify multimorbidity profiles, by analysis technique (57 analyses in 51 studies)

Author, year	Stratification variable(s)	Assessment of disease proximities	Aggregation method	Criteria for allocating conditions to profiles	Assessment of dimensionality	Assessment of clinical interpretability
Exploratory factor analysis ($n=26$)						
Aoki et al. [22]	None	Not stated	Multidimensional item response theory-based extraction with promax rotation	Factor loadings > 0.30	Parallel analysis	None stated
Clerencia-Sierra et al. [25]	Gender	Tetrachoric correlations	Principal factor method; rotation not stated	Factor loadings ≥ 0.25	Scree plot	Five medical doctors assessed clinical relevance of the profiles identified (first independently and then together)
Diaz et al. [15]	Gender, age group (15–44, 45–64, 65+), place of birth status (Norway, Eastern Europe, Western Europe, other)[a]	Tetrachoric correlations	Principal factor method with oblique oblimin rotation	Factor loadings ≥ 0.25	Scree plot	Clinical assessment by the author team to determine the solution that produced pathophysiologically most plausible profiles
Garin et al. [31]	None	Tetrachoric correlations	Extraction method not stated; oblique rotation	Factor loadings > 0.25	Eigenvalue ≥ 1	None stated
Garin et al. [4]	Country	Tetrachoric correlations	Extraction method not stated; oblique rotation	Factor loadings > 0.25	Parallel analysis and scree plot	None stated
Gomez-Rubio et al. [34]	Country	Tetrachoric correlations	PCA with orthogonal varimax rotation	Factor loadings ≥ 0.30	Scree plot and eigenvalue > 1	Biological plausibility of multimorbidity profiles, as determined by the research team
Gomez-Rubio et al. [34]	Country	Tetrachoric correlations	Principal factor method with orthogonal varimax rotation	Factor loadings ≥ 0.30	Scree plot and eigenvalue > 1	Biological plausibility of multimorbidity profiles, as determined by the research team
Gu et al. [36]	None	Tetrachoric correlations	PCA with oblique oblimin rotation	Factor loadings ≥ 0.25	Eigenvalue > 1	None stated
Holden et al. [38]	None	Tetrachoric correlations	Extraction method not stated; orthogonal quartimin rotation	Factor loadings ≥ 0.40	Scree plot, eigenvalue > 1, SRMR < 0.05, CFI and TLI > 0.95, > 2 items per factor	None stated
Islam et al. [40]	None	Tetrachoric correlations	PCA with orthogonal varimax rotation	Factor loadings ≥ 0.30	Scree plot, eigenvalue > 1, SRMR, CFI, TLI	None stated

Table 2 (continued)

Author, year	Stratification variable(s)	Assessment of disease proximities	Aggregation method	Criteria for allocating conditions to profiles	Assessment of dimensionality	Assessment of clinical interpretability
Jackson et al. [42]	None	Tetrachoric correlations	Principal factor method with varimax rotation	Factor loadings ≥ 0.30	Scree plot and eigenvalue > 1	Assessment of clinical interpretability of solutions with different number of factors by the author team
Jackson et al. [41]	None	Tetrachoric correlations	Extraction method not stated; varimax rotation	Factor loadings > 0.20	Scree plot and eigenvalue > 1	Assessment of clinical interpretability of solutions with different number of factors by the author team
Jovic et al. [44]	Age group (20–44, 45–64, 65+) and gender	Not stated	PCA with orthogonal varimax rotation	Factor loadings > 0.25	Scree plot, parallel analysis, eigenvalue > 1, > 2 items per factor	None stated
Kirchberger et al. [45]	None	Tetrachoric correlations	Principal factor method with oblique oblimin rotation	Factor loadings ≥ 0.25	Eigenvalue ≥ 1	None stated
Lenzi et al. [47]	None	Tetrachoric correlations	Principal factor method with oblique oblimin rotation	Factor loadings ≥ 0.30	Eigenvalue ≥ 1	None stated
Marventano et al. [52]	None	Tetrachoric correlations	PCA with oblique oblimin rotation	Factor loadings ≥ 0.40	Not stated	None stated
Marventano et al. [51]	None	Tetrachoric correlations	PCA with oblique oblimin rotation	Factor loadings ≥ 0.40	Not stated	None stated
Mino-Leon et al. [53]	None	Not stated	PCA with varimax rotation	Factor loadings ≥ 0.30	CFI, TLI, eigenvalue > 1	None stated
Nunes et al. [55]	None	Tetrachoric correlations	Principal factor method with oblique oblimin rotation	Factor loadings ≥ 0.30	Scree plot, eigenvalue ≥ 1, minimum explained variance > 10% for each component, total explained variance > 70%, ≥ 2 variables per factor	None stated
Nunes et al. [56]	None	Tetrachoric correlations	Principal factor method with oblique oblimin rotation	Factor loadings ≥ 0.30	Scree plot, eigenvalue ≥ 1, minimum explained variance > 10% for each component, total explained variance > 70%, ≥ 2 variables per factor	None stated

Table 2 (continued)

Author, year	Stratification variable(s)	Assessment of disease proximities	Aggregation method	Criteria for allocating conditions to profiles	Assessment of dimensionality	Assessment of clinical interpretability
Poblador-Plou et al. [16]	Age group (15–44, 45–64, 65+) and gender[a]	Tetrachoric correlations	Principal factor method with oblique oblimin rotation	Factor loadings > 0.25	Scree plot	None stated
Prados-Torres et al. [17]	Age group (15–44, 45–64, 65+) and gender[a]	Tetrachoric correlations	Principal factor method with oblique oblimin rotation	Factor loadings ≥ 0.25	Scree plot	Clinical plausibility of multimorbidity profiles reviewed by physicians (independently and as a group)
Schafer et al. [60]	Gender	Tetrachoric correlations	Principal factor method with oblique oblimin rotation	Factor loadings ≥ 0.25	Eigenvalue ≥ 1	None stated
Walker et al. [65]	None	Tetrachoric correlations	Principal factor method with oblique oblimin rotation	Factor loadings > 0.25	Scree plot and eigenvalue > 1	None stated
Wang et al. [66]	None	Tetrachoric correlations	Extraction method not stated; oblique oblimin rotation	Factor loadings ≥ 0.25	Eigenvalue > 1	None stated
Wang et al. [67]	None	Tetrachoric correlations	PCA with oblique oblimin rotation	Factor loadings ≥ 0.35	Eigenvalue > 1	None stated
Cluster analysis of diseases (n = 13)						
Cornell et al. [27]	None	Jaccard coefficient	Lance-Williams flexible beta clustering	N/A	Dendogram and agglomerative coefficient	Clinical assessment by health researcher and clinicians of meaningfulness of the identified profiles, based on known epidemiology and importance to clinical co-management
Dong et al. [28]	Gender	Yule's Q	Average linkage	N/A	Dendogram and agglomerative coefficient	Clinical assessment by the research team of meaningfulness of the identified profiles
Foguet-Boreu et al. [29]	Age group (65–79, 80+) and gender	Jaccard coefficient	Ward's minimum variance clustering	N/A	Highest adjusted Rand index and a high pseudo T2 statistic	Clinical meaningfulness based on prior research and clinical experience of the research team
Formiga et al. [30]	None	Yule's Q	Average linkage	N/A	Dendogram	None stated
Gomez-Rubio et al. [34]	None	Yule's Q	Average linkage	N/A	Dendogram	Biological plausibility of multimorbidity profiles, as determined by the research team

Table 2 (continued)

Author, year	Stratification variable(s)	Assessment of disease proximities	Aggregation method	Criteria for allocating conditions to profiles	Assessment of dimensionality	Assessment of clinical interpretability
Islam et al. [40]	None	Yule's Q	Average linkage	N/A	Dendogram and agglomerative coefficient	None stated
John et al. [43]	None	Yule's Q	Complete linkage	N/A	Dendogram and Goodman and Kruskal's gamma	None stated
Marengoni et al. [50]	None	Yule's Q	Average linkage	N/A	Dendogram	None stated
Marengoni et al. [48]	None	Yule's Q	Average linkage	N/A	Dendogram	None stated
Marengoni et al. [49]	Survey wave (first or second)	Yule's Q	Average linkage	N/A	Dendogram	None stated
Mino-Leon et al. [53]	None	Yule's Q	Average linkage	N/A	Dendogram and agglomerative coefficient	None stated
Prazeres et al. [58]	None	Yule's Q	Average linkage	N/A	Dendogram	None stated
Teh et al. [63]	Maori status (Maori/Non-Maori)	Not stated	Ward's minimum variance clustering	N/A	Dendogram and scree plot of cluster distances	Informed judgements and consensus of health researchers (geriatricians, cardiologist, general practitioner, biostatisticians, and epidemiologist)
Latent class analysis (n = 11)						
Barile et al. [23]	None	N/A	N/A	Highest prevalence	AIC, BIC, and best class separation based on average posterior probabilities of class membership	Subjective assessment of meaningfulness and distinctiveness of classes
Cigolle et al. [24]	None	N/A	N/A	Highest prevalence	Not stated	None stated
Gellert et al. [32]	None	N/A	N/A	Highest prevalence	BIC	None stated
Gonsoulin et al. [35]	None	N/A	N/A	High item-response probability in a given class (Rho > 0.45)	AIC and BIC	None stated
Islam et al. [40]	None	N/A	N/A	Relatively higher item-response probabilities (Rho values)	Likelihood ratio and BIC, no classes with near-zero probability of membership	Subjective assessment of distinguishability and meaningfulness of each class
Kuwornu et al. [46]	Age group (18–54, 55+) and Aboriginal status (yes/no)	N/A	N/A	High item-response probability in a given class (Rho ≥ 0.40)	AIC and BIC	Subjective assessment of model interpretability
Olaya et al. [57]	None	N/A	N/A	Higher than average prevalence in a given class	Adjusted BIC and consistent AIC	Subjective assessment of model interpretability
Pugh et al. [59]	None	N/A	N/A	Not stated	AIC and BIC	None stated

Table 2 (continued)

Author, year	Stratification variable(s)	Assessment of disease proximities	Aggregation method	Criteria for allocating conditions to profiles	Assessment of dimensionality	Assessment of clinical interpretability
Simões et al. [62]	None	N/A	N/A	Relatively higher item-response probabilities	BIC and higher discrimination between classes.	Subjective judgment of pathophysiologic plausibility
Van Cleave et al. [64]	None	N/A	N/A	Relatively higher prevalence	Likelihood ratio test and AIC	Subjective judgment of conceptual clarity
Whitson et al. [68]	None	N/A	N/A	Relatively higher prevalence	BIC	Subjective assessment of clinical significance of the resulting classes
Cluster analysis of people (n = 7)						
Collerton et al. [26]	None	Jaccard coefficient	Not stated	Observed/expected ratio 1:1.2	Calinski-Harabasz pseudo-F index	Subjective review by the research team
Goldstein et al. [33]	None	Jaccard coefficient	Lance-Williams flexible beta clustering	Not stated	Scree plot of cluster distance	None stated
Guisado-Clavero et al. [37]	Age group (65–79, 80+) and gender	Distances derived from multiple correspondence analysis	k-means clustering	Observed/expected ratio 1:1.2	Calinski-Harabasz pseudo-F index	None stated
Islam et al. [40]	None	Yule's Q	k-medoids partial clustering	Not stated	Calinski-Harabasz pseudo-F index	None stated
Islam et al. [39]	None	Yule's Q	k-medoids partial clustering	Not stated	Calinski-Harabasz pseudo-F index	None stated
Newcomer et al. [54]	None	Jaccard coefficient	Ward's minimum variance clustering	Not stated	Calinski-Harabasz pseudo-F index, pseudo-T, and R-squared	Subjective assessment of clinical relevance
Sibley et al. [61]	None	Jaccard coefficient	Ward's minimum variance clustering	Prevalence > 70% in a cluster	Calinski-Harabasz pseudo-F index, pseudo-T, agglomerative schedule, and dendogram	None stated

PCA principal component analysis, *SRMR* standardised root mean-square residual, *CFI* comparative fit index, *TLI* Tucker–Lewis Index, *BIC* Bayesian information criterion, *AIC* Akaike information criterion

[a]Data from the youngest group are not included in the synthesised results

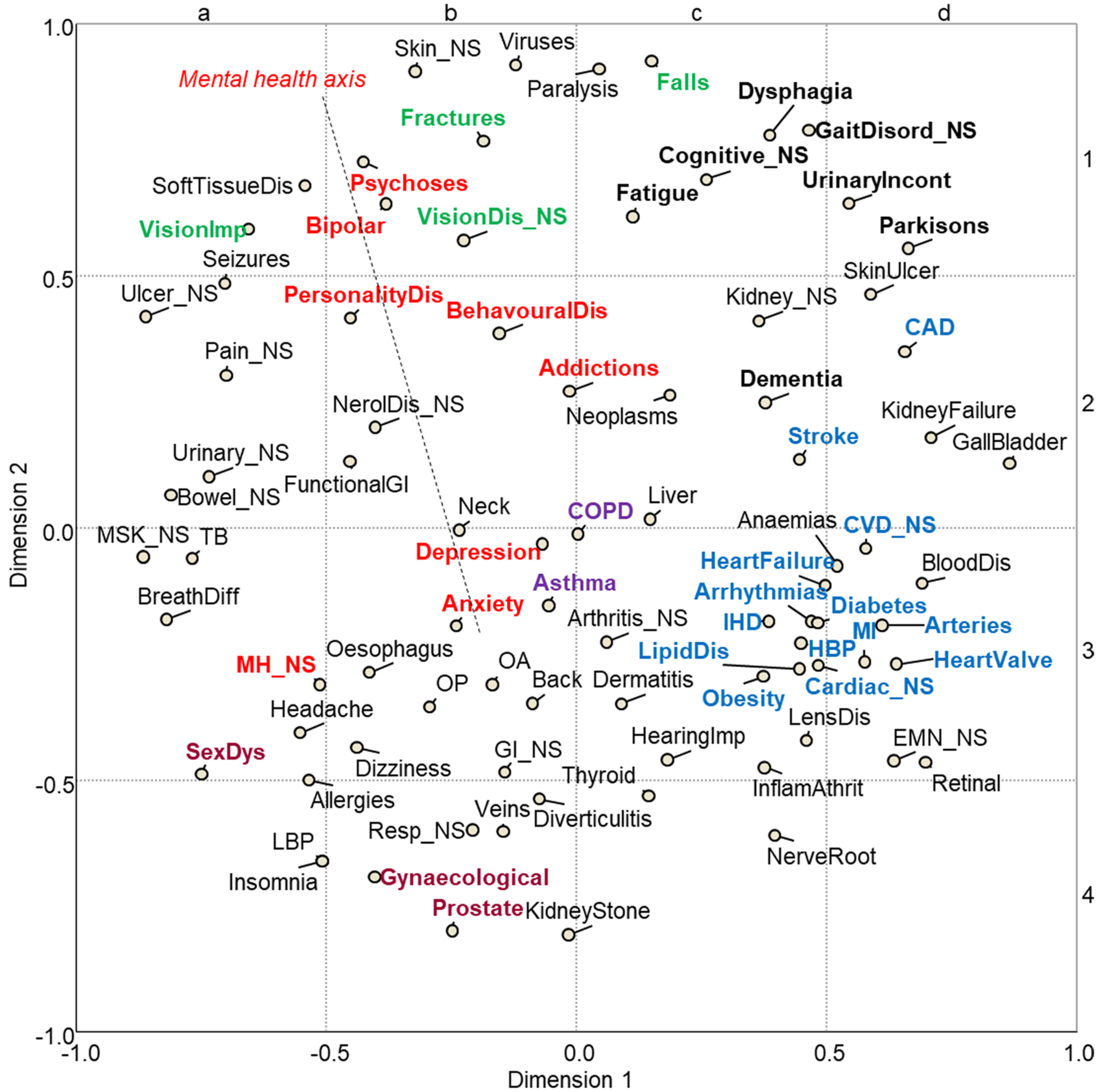

Fig. 2 Multidimensional scaling solution (two dimensional) for multimorbidity profiles identified in exploratory factor analysis studies. Addictions = addictive & substance use disorders; Arthritis_NS = arthritis, not specified; Back = back problems; BehavouralDis = behavioural disorders; Bipolar = bipolar disorder; BloodDis = blood disorders, not specified; BreathDiff = breathing difficulties; COPD = bronchitis/chronic obstructive pulmonary disease/emphysema; Arrhythmias = cardiac arrhythmias; Cardiac_NS = cardiovascular disorders, not specified; CVD_NS = cerebrovascular disorders not specified; Pain_NS = chronic pain, not specified; Cognitive_NS = cognitive impairment, not specified; CAD = coronary artery disease; Dermatitis = dermatitis and eczema; Skin_NS = dermatological disorders, not specified; Bowel_NS = disorders of large intestine, not specified; Oesophagus = disorders of oesophagus; Veins = disorders of veins; Arteries = disorders of arteries or arterioles; LipidDis = disorders of lipid metabolism; NerveRoot = disorders of nerve root, plexus or peripheral nerves; Diverticulitis = diverticular disease; EMN_NS = endocrine/metabolic/nutritional disorders, not specified; Fatigue = fatigue/Fatigue syndromes; FunctionalGI = functional gastrointestinal disorders; GallBladder = gall bladder disorders; GI_NS = gastrointestinal disorders, not specified; Gynaecological = gynaecological conditions; Hearing = hearing impairment; HeartFailure = heart failure; HeartValve = heart valve disorders; Prostate = hyperplasia of prostate; HBP = hypertension; LBP = hypotension; IHD = ischemic heart disease; InflamAthrit = inflammatory arthropathies; Kidney_NS = kidney disorders, not specified; KidneyFailure = kidney failure; KidneyStone = kidney stones; LensDis = lens disorders; Liver = liver disorders; MH_NS = mental health disorders, not specified; Headache = migraine/Severe headache; GaitDisord_NS = mobility/gait disorders, not specified; MSK_NS = musculoskeletal disorders, not specified; MI = myocardial infarction; Neck = neck pain; NerolDis_NS = neurologic disorders, not specified; OA = osteoarthritis; OP = osteoporosis; Obesity = overweight or obesity; Parkisons = Parkinson's disease; PersonalityDis = personality disorders; Resp_NS = respiratory conditions, not specified; Retinal = retinal disorders; Psychoses = schizophrenia or psychosis; Seizures = seizure disorders; SexDys = sexual dysfunction; SkinUlcer = skin ulcer; SoftTissueDis = soft tissue disorders; Thyroid = thyroid disorders; TB = tuberculosis; Ulcer_NS = Ulcer, not specified; Urinary_NS = Urinary conditions, not specified; UrinaryIncont = Urinary incontinence; Dizziness = vertiginous syndromes/Dizziness; Viruses = viral infections; VisionDis_NS = vision and eye disorders, not specified; VisionImp = vision impairment

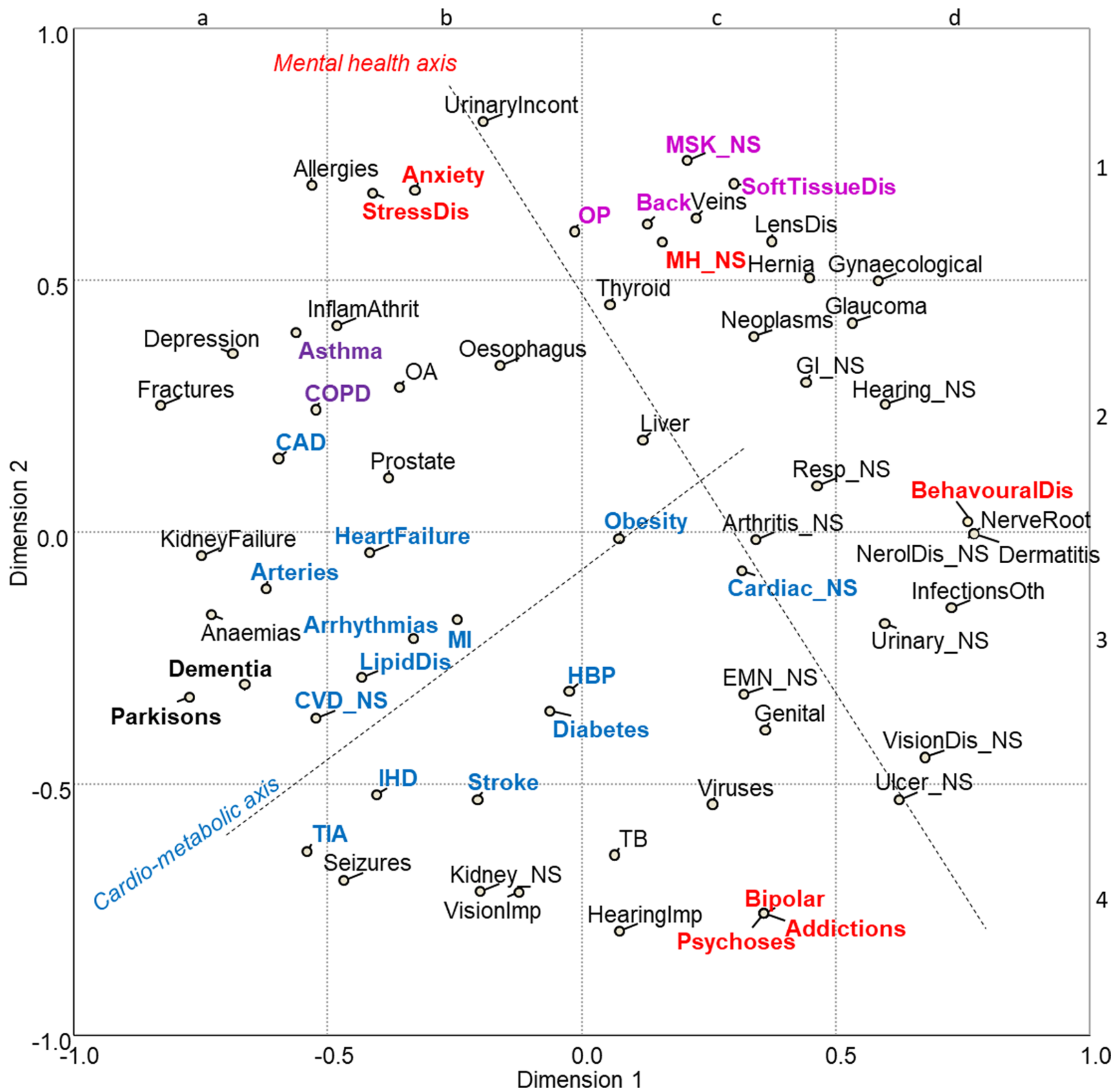

Fig. 3 Multidimensional scaling solution (two dimensional) for multimorbidity profiles identified in cluster analysis of diseases studies. Abbreviations: Addictions = addictive and substance use disorders; Arthritis_NS = arthritis, not specified; Back = back problems; BehavouralDis = behavioural disorders; Bipolar = bipolar disorder; COPD = bronchitis/Chronic obstructive pulmonary diseases/Emphysema; Arrhythmias = cardiac arrhythmias; Cardiac_NS = cardiovascular disorders, not specified; CVD_NS = cerebrovascular disorders, not specified; CAD = coronary artery disease; Dermatitis = dermatitis and eczema; Oesophagus = disorders of oesophagus; Veins = disorders of veins; Arteries = disorders of arteries or arterioles; LipidDis = disorders of lipid metabolism; NerveRoot = disorders of nerve root, plexus or peripheral nerves; EMN_NS = endocrine/metabolic/nutritional disorders, not specified; Genital = genital disorders, not specified; GI_NS = gastrointestinal disorders, not specified; Gynaecological = gynaecological conditions; Hearing_NS = hearing and ear disorders, not specified; HearingImp = hearing impairment; HeartFailure = heart failure; Prostate = hyperplasia of prostate; HBP = hypertension; IHD = ischemic heart disease; InflamAthrit = inflammatory arthropathies; Kidney_NS = kidney disorders, not specified; KidneyFailure = kidney failure; LensDis = lens disorders; Liver = liver disorders; MH_NS = mental health disorders, not specified; MSK_NS = musculoskeletal disorders, not specified; MI = myocardial infarction; NerolDis_NS = neurologic disorders, not specified; OA = osteoarthritis; OP = osteoporosis; InfectionsOth = other infections; Obesity = overweight or obesity; Parkisons = Parkinson's disease; Resp_NS = respiratory conditions, not specified; Psychoses = schizophrenia or psychosis; Seizures = seizure disorders; SoftTissueDis = soft tissue disorders; StressDis = stress and trauma disorders; Thyroid = thyroid disorders; TIA = transient ischemic attack; TB = tuberculosis; Ulcer_NS = Ulcer, not specified; Urinary_NS = urinary conditions, not specified; UrinaryIncont = urinary incontinence; Viruses = viral infections; VisionDis_NS = vision and eye disorders, not specified; VisionImp = vision impairment

Examination of co-locations of chronic conditions in multimorbidity profiles derived from EFA studies identified one axis and five meaningful clusters of health conditions (Fig. 2). The discernible axis was defined by mental health conditions, with depression and anxiety at the one end (b3) and psychoses (b1) at the other. One of

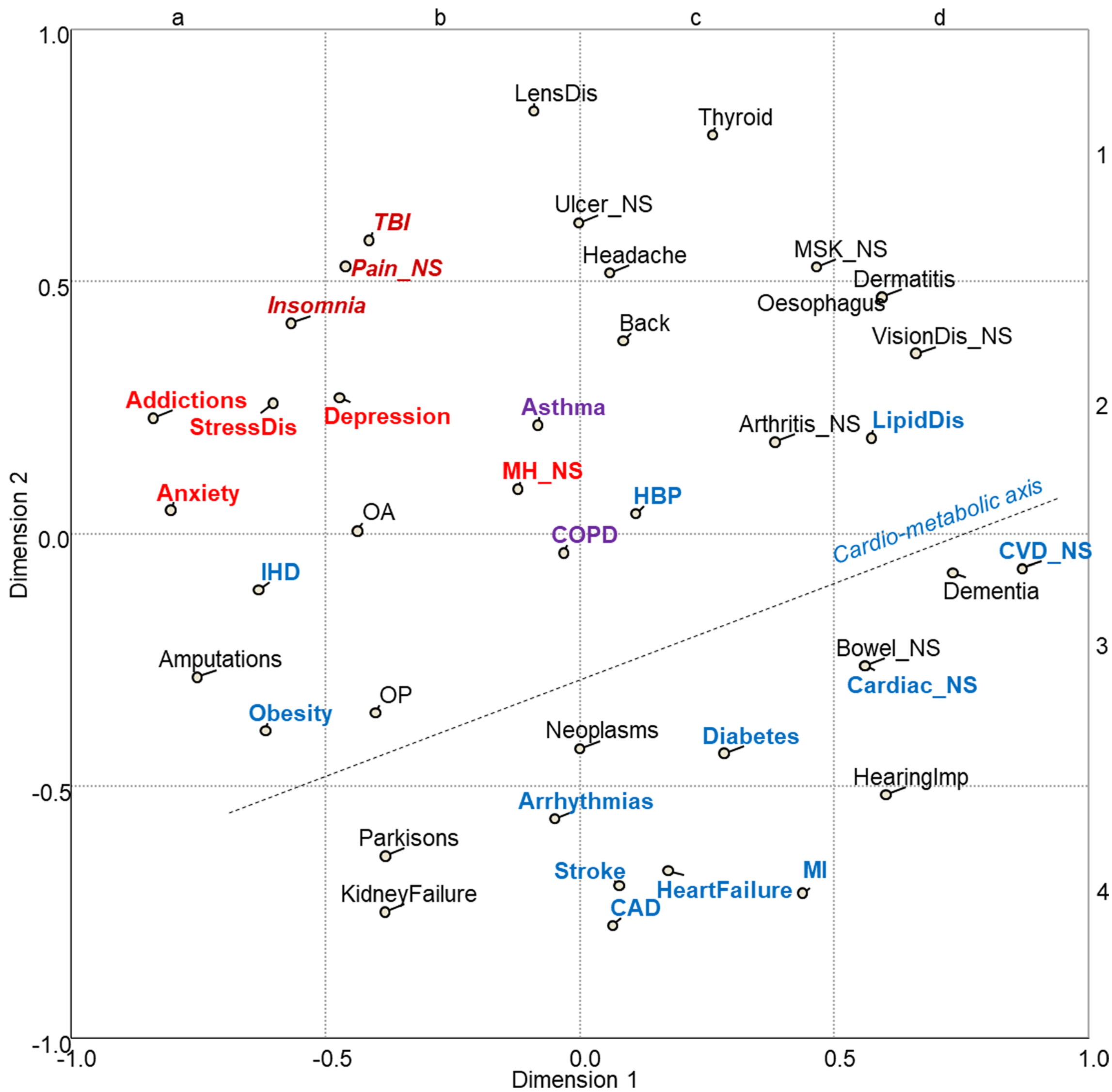

Fig. 4 Multidimensional scaling solution (two dimensional) for multimorbidity profiles identified in latent class analysis studies. Abbreviations: Addictions = addictive and substance use disorders; Arthritis_NS = arthritis, not specified; Back = back problems; COPD = bronchitis/chronic obstructive pulmonary disorders/Emphysema; Arrhythmias = cardiac arrhythmias; Cardiac_NS = cardiovascular disorders, not specified; CVD_NS = cerebrovascular disorders, not specified; Pain_NS = chronic pain, not specified; CAD = coronary artery diseases; Dermatitis = dermatitis and eczema; Bowel_NS = disorders of large intestine, not specified; Oesophagus = disorders of oesophagus; LipidDis = disorders of lipid metabolism; HearingImp = hearing impairment; HeartFailure = heart failure; HBP = hypertension; IHD = ischemic heart disease; KidneyFailure = kidney failure; LensDis = lens disorders; MH_NS = mental health disorders, not specified; Headache = migraine/Severe headache; MSK_NS = musculoskeletal disorders, not specified; MI = myocardial infarction; Neoplasms = neoplasms; OA = osteoarthritis; OP = osteoporosis; Obesity = overweight or obesity; Parkisons = Parkinson's disorders; StressDis = stress and trauma disorders; Thyroid = thyroid disorders; TBI = traumatic brain injury; Ulcer_NS = ulcer, not specified; VisionDis_NS = vision and eye disorders, not specified

the clusters encompassed falls and fractures, vision disorders, and cognitive impairment (quadrants b1 and c1 of the MDS map) and this pattern is consistent with prior research [69, 70]. Other interpretable clusters included reproductive system (gynaecological and prostate) disorders and sexual dysfunction (a3) (b4); Parkinson's disease with urinary incontinence, gait disorders, dysphagia, fatigue, and cognitive decline (c1–d1) [71]; and chronic obstructive pulmonary disease (COPD) (c3) with asthma (b3). The clustering of cardiovascular disease, diabetes, hypertension, lipid metabolism disorders, and obesity/overweight (c3–d3) is consistent with cardio-metabolic syndrome (obesity, insulin resistance, dyslipidaemia and hypertension) and its known association with heart disease and diabetes [19].

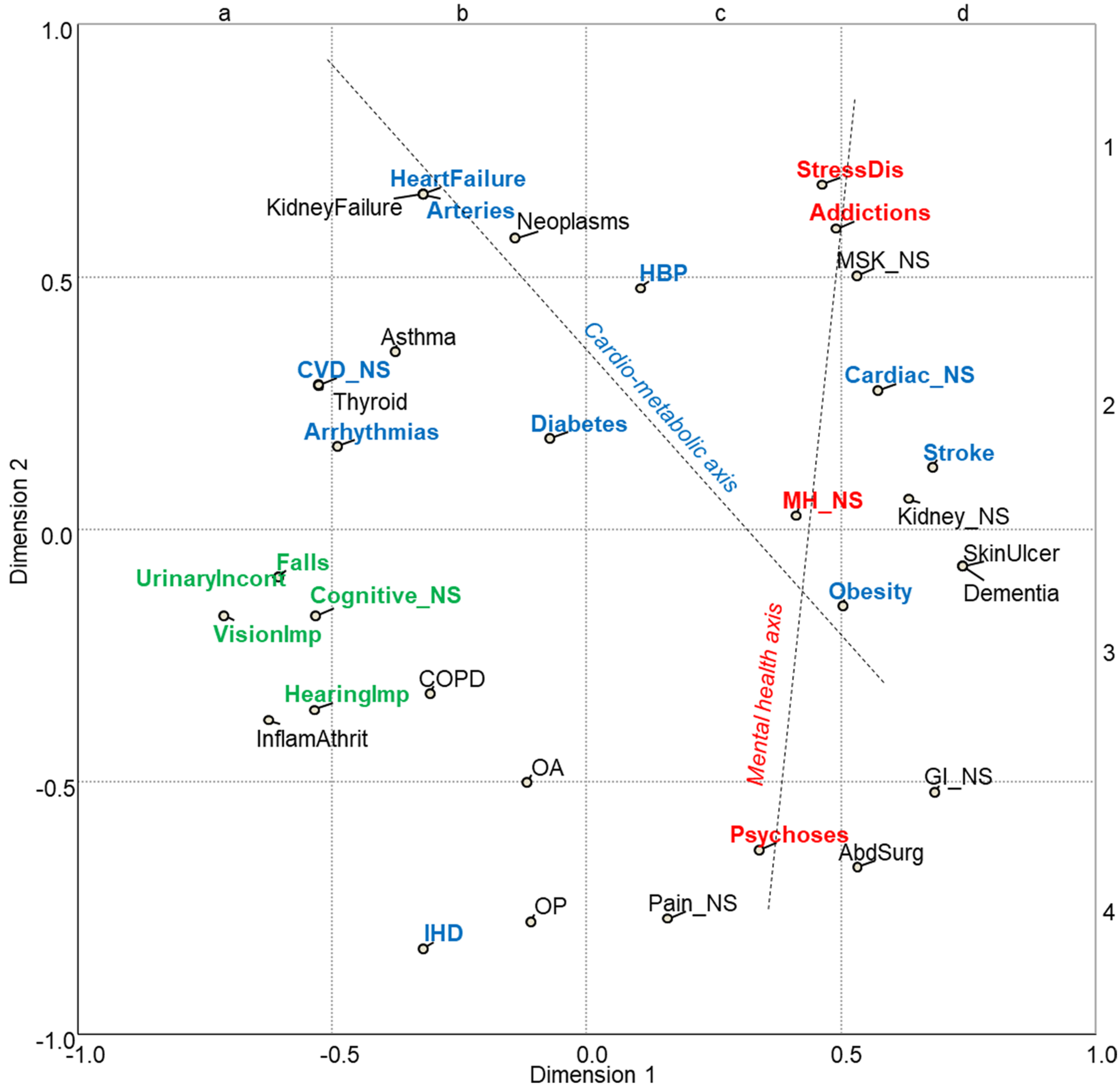

Fig. 5 Multidimensional scaling solution (two dimensional) for multimorbidity profiles identified in cluster analysis of people studies. Abbreviations: AbdSurg = abdominal surgery, not specified; Addictions = addictive and substance use disorders; COPD = bronchitis/Chronic obstructive pulmonary disease/emphysema; Arrhythmias = cardiac arrhythmias; Cardiac_NS = cardiovascular disorders, not specified; CVD_NS = cerebrovascular disorders, not specified; Pain_NS = chronic pain, not specified; Cognitive_NS = cognitive impairment, not specified; Arteries = disorders of arteries or arterioles; GI_NS = gastrointestinal disorders, not specified; HearingImp = hearing impairment; HeartFailure = heart failure; HBP = hypertension; IHD = ischemic heart disease; InflamAthrit = inflammatory arthropathies; Kidney_NS = kidney disorders, not specified; KidneyFailure = kidney failure; MH_NS = mental health disorders, not specified; MSK_NS = musculoskeletal disorders, not specified; OA = osteoarthritis; OP = osteoporosis; Obesity = overweight or obesity; Psychoses = schizophrenia or psychosis; SkinUlcer = skin ulcer; StressDis = stress and trauma disorders; Thyroid = thyroid disorders; UrinaryIncont = urinary incontinence; VisionImp = vision impairment

Cluster analysis of diseases

Proximity measures utilised in the 13 CA of disease analyses were Yule's Q (n = 10) and Jaccard coefficient (n = 2); one study did not state proximity measure used. Most studies (n = 9) used average linkage method to aggregate diseases into clusters. Optimal number of clusters was determined by a dendogram (n = 6) or a combination of dendogram and agglomerative coefficient (n = 4). Clinical assessment of interpretability of the derived solution was mentioned in five studies only. However, there was insufficient information to determine the cogency of clinical assessment in any of these studies.

Synthesised results of CA of diseases (Fig. 3) produced three interpretable clusters and two axes. Clusters included COPD and asthma (a2); osteoporosis, back pain, musculoskeletal disorders, and soft tissue disorders (c1); and Parkinson's disease and dementia (a3). One axis corresponded to the conditions associated with cardio-metabolic syndrome and another axis represented mental health disorders, with stress and anxiety disorders at one end and psychoses at the other end.

Latent class analysis

LCA was used to derive multimorbidity profiles in 11 studies. LCA utilises maximum likelihood estimation to identify groups of cases with similar probabilities of a particular diagnosis and uses raw data as input. Hence, similarity measures and aggregation algorithms are not relevant to LCA. A combination of Akaike Information Criterion (AIC) and Bayesian-Schwarz Information Criterion (BIC) was the most frequent method of determining the number of classes to retain (n = 5). The remaining studies used BIC alone (n = 2) or in combination with other methods (n = 2). One study utilised AIC and likelihood ratio test and one study did not state the method of dimensionality assessment. Criteria for assigning diseases to classes were high prevalence in a cluster (n = 6) or high item-response probabilities (n = 4). Clinical interpretability of solutions was assessed in seven studies, but was not reported in sufficient detail.

Synthesis of the results of LCA studies identified two interpretable clusters (Fig. 4): mental health disorders (addictive and substance use disorders, anxiety, stress and trauma disorders, and depression [a2–b2]) and chronic pain, traumatic brain injury, and insomnia (a2–b1); and asthma (b2) and COPD (b3). The solution also produced a discernible cardio-metabolic axis.

Cluster analysis of people

Proximity measures in the seven studies that utilised CA of people were Jaccard coefficient (n = 4), Yule's Q (n = 2), and distances between conditions derived from a multiple correspondence analysis. Most frequently used clustering algorithms were k-medoid clustering (n = 2) and Ward's minimum variance linkage (n = 2). The most frequent criterion for identifying optimal number of clusters was Calinski-Harabasz pseudo-F index, either alone (n = 4) or in combination with other methods (n = 2). Statistical criteria used to allocate conditions to clusters were not stated in four studies. The remaining studies allocated conditions to clusters based on high prevalence in a cluster. Clinical assessment of interpretability of the derived profiles was either not mentioned (n = 5) or was reported in insufficient detail (n = 2).

Only one interpretable cluster was identifiable in the pooled results of CA of people (Fig. 5) and was characterised by falls, vision impairment, cognitive impairment, urinary incontinence, and hearing impairment (a3). CA of people also produced two discernible axes, namely cardio-metabolic and mental health. Consistent with the results of EFA and CA of disease, mental health axis was represented by stress disorders at one end and psychoses at the other.

Discussion

Our systematic review synthesised data from 51 multimorbidity profiling studies published since year 2000. Cumulatively, the reviewed studies reported 407 profiles of multimorbidity. The most common statistical approach used in the classification of multimorbidity profiles was EFA, followed by CA of diseases, LCA, and CA of people. Synthesised results of EFA produced the most discernible groupings of health conditions (n = 6), followed by CA of people (n = 5), and CA of diseases (n = 3) and LCA (n = 3). Two groupings of conditions (mental health and cardio-metabolic) were identifiable in the synthesised results of all four methods, three groupings were partially replicable (COPD and asthma; falls and fractures with sensory deficits; Parkinson's disease with cognitive decline), and two groupings (musculoskeletal conditions and reproductive system disorders) each emerged in the synthesised results of one statistical approach only. Our synthesised results also revealed that multimorbidity patterns took the form of both discrete categories and continuous dimensions.

The most replicable groupings of conditions in our synthesised results were axes of mental health conditions and cardio-metabolic conditions. Given the differences in theoretical and mathematical underpinnings of the four statistical approaches used in multimorbidity profiling, such robust replication would be unlikely if the observed associations were purely artefactual. Furthermore, our findings accord well with the published literature (e.g. [72–76]) and hence, we are confident that our results capture meaningful associations. Clustering of falls and fractures with sensory deficits and of Parkinson's disease and cognitive decline each occurred in the synthesised results of two methods (EFA and CA of people, and EFA and CA of disease, respectively), while clusters of musculoskeletal conditions and of reproductive system disorders were each observed in one statistical approach (CA of disease and EFA, respectively). An earlier systematic review of 14 multimorbidity profiling studies found three multimorbidity profiles that were relatively recurrent, including cardiovascular and metabolic diseases, mental health problems, and musculoskeletal disorders [14]. However, these findings were based on a qualitative review of the observed multimorbidity profiles, whereas we performed a quantitative synthesis of published results from 51 studies. Furthermore, our approach to the synthesis of the results using MDS allowed us to identify continuous dimensions of multimorbidity in addition to qualitatively distinct groupings. Specifically, our results show that mental health conditions consistently group along a continuous axis, with depression and anxiety at the one end and psychoses at the opposite end. The consistency of positioning of mental health disorders along a continuum appears to suggest that what is currently conceptualised as separate disorders might be 'symptoms' of the same underlying pathology. Given the well-documented co-morbidity of mental health conditions (e.g., [72, 77]), the 'unifying pathology' hypothesis warrants consideration in future studies. Likewise, cardiovascular disease, diabetes, and metabolic conditions formed discernible axes in the pooled results of three statistical approaches, although positioning of conditions along the continuum varied between the approaches.

To the best of our knowledge, our study is the first systematic attempt to quantitatively synthesise the results of multimorbidity profiling studies. A recent systematic review of multimorbidity was focused on identifying multimorbidity definitions rather than on identifying qualitatively distinct, replicable groupings of multimorbidity [78]. The agreement between the results of our study and an earlier qualitative review of multimorbidity profiles [14] provides a good indication that replicable profiles of multimorbidity exist in a population. Given that multimorbidity profiling studies attempt to identify disease grouping of unknown number and type, replicability of results between studies that utilise different methodologies is an important step towards moving from exploratory to confirmatory approaches. The consistencies in co-locations of certain conditions across different methods of multimorbidity profiling provide avenues for exploration of possible common underlying causes or shared risk pathways and can potentially provide insights into mechanisms that give rise to multimorbidity and identify opportunities for prevention. Increased understanding of pathological processes that underlie profiles of multimorbidity can also potentially optimise the treatment of multimorbidity by targeting the underlying pathology, as opposed to the treatment of each separate disease or even the treatment of each separate multimorbidity profile. However, it is important to note that our findings are based on the results of cross-sectional observational studies and the development of specific profiles of multimorbidity requires further studies using longitudinal data.

One of the unintended findings of this systematic review was that very few studies included in the review offered an explicit theoretical rationale for their selection of analytical approach to identifying multimorbidity profiles. This is an important omission, since the observed groupings of multimorbidity can arise through a number of mechanisms, including a unifying cause, iatrogenic morbidity, and even spurious association. Lack of reliable knowledge about how or why diseases group together has been identified as one of the impediments to the development of guidelines for the clinical management of multimorbidity [79]. An explicit rationale for the selection of a statistical technique utilised to classify multimorbidity is key to understanding the nature of multimorbidity as it will provide context for the interpretation of results in light of underlying statistical assumptions.

Differences in the general methodological aspects of multimorbidity studies, including population characteristics, methods of ascertaining the presence of health conditions (e.g. self-report vs. medical records), criteria for disease inclusion, and statistical approach used to classify multimorbidity have already been noted as being likely sources of variability in multimorbidity profiles reported in the literature [14]. Another factor that could potentially explain the between-study variability in multimorbidity profiles is the use of stratification [14]. Qualitative examination of profiles derived from stratified analyses (Supplementary Data 3) from the reviewed studies shows reasonable concordance in multimorbidity profiles across subpopulations defined by gender and ethnicity within a given study. However, the number and complexity of multimorbidity profiles tends to be greater among older subpopulations and this is consistent with findings of past studies [4, 17]. Hence, it is possible that MDS analyses stratified by age might have identified different configurations of multimorbidity groupings. Subpopulation analyses were beyond the scope of this study and the subpopulations effect, particularly with respect to age, warrants further examination.

In our study, we also found that within each major statistical approach, there were notable differences in how a given approach was implemented across the studies. Specifically, exploration of an optimal number of profiles was not adequate overall, with almost half of all analyses relying upon a single criterion to determine the number of multimorbidity patterns to extract. Moreover, of the 26 EFA analyses, a quarter ($n = 7$) based their decisions regarding the number of factors to extract solely on eigenvalues > 1 criterion, despite the evidence that this method is the least reliable for identifying the number of underlying dimensions (e.g. [80]). Only a few studies reported clinical assessment of meaningfulness of the emerged profiles and then in insufficient detail. Hence, clinical utility of multimorbidity profiles reported in the literature to date is unclear. Since none of the studies included in our review had explicit hypotheses about the number of underlying multimorbidity profiles, lack of adequate assessment of the number and meaningfulness of the derived profiles is a critical weakness of multimorbidity profiling studies to date.

Multimorbidity of health conditions is becoming increasingly recognised as one of the most pressing challenges facing the twenty-first century health care [81–83]. Although a number of guidelines for the management of multimorbidity have been developed [84–87], it has been previously noted that these tend to be focused on an additive definition of multimorbidity [88]. This is not surprising given that guidelines are generally based on the results of RCTs and these study designs either exclude individuals with complex comorbidity profiles or use additive definition of multimorbidity (e.g., [89]). Yet, two individuals with the same number but different combinations of chronic conditions are likely to have different risk profiles, varying treatment needs, and experience disparate outcomes [23]. Not surprisingly, studies that defined multimorbidity in additive terms found no evidence to support the effectiveness of a particular treatment approach in improving outcomes for patients with multiple chronic conditions [89–91]. Understanding which chronic conditions frequently co-occur can facilitate person-centred care tailored to the needs of individuals with specific profiles of multimorbidity. One of the first steps towards identifying distinct and reliable profiles of multimorbidity that can be used to inform clinical guidelines is to enhance methodological rigour and clinical meaningfulness of studies that focus on statistical profiling of multimorbidity. The following sections summarise our recommendations for strengthening the design of multimorbidity profiling studies.

Guidelines for multimorbidity profiling studies

Definition of multimorbidity

While review of definitions of multimorbidity was not in the scope of our study, and has been addressed elsewhere [78], we recommend that future studies of multimorbidity profiling utilise a standardised definition of multimorbidity. This will increase comparability between studies and facilitate communication and interpretation of results of multimorbidity research. We recommend the following definition of multimorbidity, adopted by the leading health organisations such as The Academy of Medical Sciences and WHO [2, 92]:

"The co-existence of two or more chronic conditions, each one of which is either:

- A physical non-communicable disease of long duration, such as a cardiovascular disease or cancer.
- A mental health condition of long duration, such as a mood disorder or dementia.
- An infectious disease of long duration, such as HIV or hepatitis C." (p. 22, [2])

Theoretical rationale

We recommend that studies focusing on statistical identification of multimorbidity profiles explicitly state the theoretical rationale for the selection of a given statistical approach. Specifically, future studies seeking to identify profiles of multimorbidity should select the method that is theoretically consistent with their conceptualisation of processes that generate multimorbidity profiles, at least in terms of underlying causality and structure of multimorbidity profiles (continuous/discrete).

The goal of EFA is to identify underlying continuous variables that explain the correlations between the observed variables. The factors are seen as continuous normal variables and are assumed to be the underlying causes of the observed correlations. Applied to multimorbidity profiling, a given multimorbidity pattern identified with EFA is conceptualised as a continuum of underlying pathological process(es) that manifest in a specific pattern of diseases for each person. Since factors are assumed to be continuous variables, individuals would be expected to vary in the degree to which pathological process represented by a given factor is expressed or active. Individuals can have high scores on some factors, indicating that these pathological processes are highly characteristic of this individual, and low scores on other factors, indicating that the pathological processes are less characteristic of this individual.

Similar to EFA, application of LCA to multimorbidity profiling assumes that multimorbidity groupings are caused by underlying latent variables. However, latent classes are conceptualised as discrete pathological processes, with individuals having high or low probability of belonging to a given latent class. Classes are formed in the basis of probability of co-occurrence of various chronic conditions. Like LCA, CA also conceptualises multimorbidity profiles as discrete categories. However, in contrast to EFA and LCA, CA aims to identify homogenous groups of observations, without making assumptions about causal links between the observations. CA aims to separate the conditions or people into clusters in a way that maximises similarity within clusters and difference between clusters. Applied to multimorbidity profiling, CA of diseases would identify homogenous groupings of conditions while CA of individuals would identify groups of people who present with similar disease profiles. Unlike EFA and LCA, CA approaches classify individuals into mutually exclusive groupings.

Given theoretical differences in conceptualisation of causality and nature (discreet group vs continuum) of multimorbidity profiles, we recommend the application of EFA (common factor extraction) when multimorbidity profiles are (1) assumed to capture common pathology that is causal to the observed correlations between health conditions and (2) expected to vary along some continuum. LCA should be the preferred approach when multimorbidity profiles are conceptualised as discrete categories that are reflections of a single underlying cause. CA is a suitable approach when multimorbidity profiles are expected to represent discrete categories that do not necessarily share an underlying cause (Fig. 6). Our synthesised results show that discernible groupings of multimorbidity appeared both in a form of clusters (discrete categories) and axes (continuum). Hence, we recommend that future studies apply at least one statistical approach

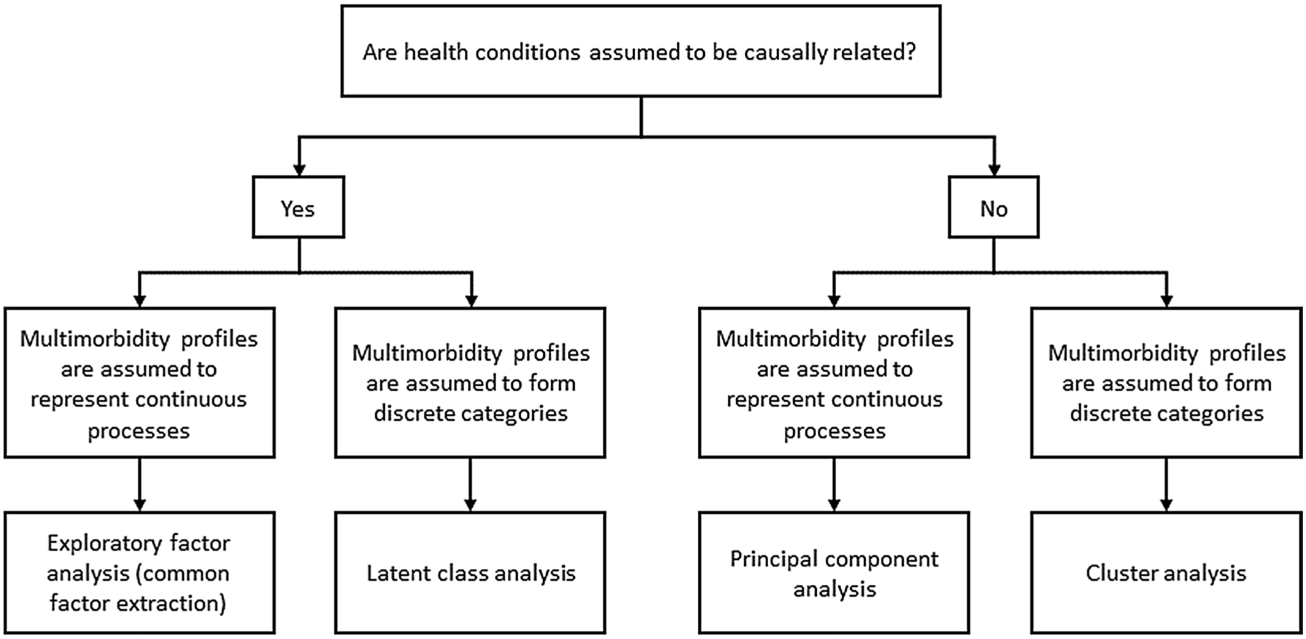

Fig. 6 Decision chart for the selection of a statistical approach in multimorbidity profiling studies, based on causality and hypothesised structure of the underlying profiles

designed to identify continuous profiles and one approach designed to identify discrete categories of multimorbidity profiles.

Number and type of conditions

We found that the number and type of conditions varied greatly between the studies. The use of heterogeneous lists of chronic diseases or level of disaggregation of chronic conditions has been identified as one of the main factors that vitiate the interpretation of the results of multimorbidity studies [79]. The number and type of conditions included in analyses should be sufficient to provide adequate granularity in the identified multimorbidity profiles but not so great that it compromises interpretation of results. While optimal levels of diagnostic codes and the number of conditions to be included in multimorbidity studies is not known at present, we recommend the use of three- or four-digit ICD-11 codes and the inclusion of at least 20 conditions.

Number of potential profiles

Inadequate assessment of the number of potential multimorbidity profiles present in the dataset can introduce random error into the results of a study. The result can be either the identification of artefactual multimorbidity profiles (false positives) due to the extraction of too many profiles, or missing potentially clinically important profiles (false negatives) due to the extraction of too few profiles. Given that 'true number of multimorbidity patterns is not known, it is at present not possible to provide a guideline for estimating the numbers of false positives and false negatives in the results of multimorbidity profiling studies. We therefore recommend the use of at least two different methods of identifying optimal number of multimorbidity profiles in a given study. These methods must be explicitly reported and criteria for reconciling conflicting results from different criteria should also be explicated. Furthermore, appropriately designed simulation studies are urgently needed to better understand the ability of different statistical methods to 'correctly' identify the number of multimorbidity groupings under different conditions.

Interpretability of profiles

To facilitate interpretability of identified profiles of multimorbidity for analyses that aim to classify people (e.g., EFA, LCA, CA of people), we recommend that the researchers give clear and explicit a priori criteria for allocating conditions to clusters. We also recommend that future studies of multimorbidity profiling include assessment of clinical meaningfulness of the identified profiles. This should ideally be done through a discussion between clinical and statistical members of the research team and also utilise explicit a priori criteria to determine clinical utility of the identified profiles.

Inclusion of healthy individuals

Another point to be considered in future studies of multimorbidity profiles is whether healthy individuals and/or those with a single diagnosis should be included in analysis. Inclusion of these groups in analyses has the potential to dilute the associations between health conditions and add extra random error into the classification, leading to spurious profiles being uncovered. On the other hand, the inclusion of healthy and single-diagnosis individuals might help to identify shared risk factors that predate the development of multimorbidity. There is currently no evidence to support recommendations in this area and this question remains to be explored in future studies.

The role of age

Previous research reported increasing number and complexity of multimorbidity profiles among older age groups [16, 17, 44] and this was also evident in the descriptive results of multimorbidity profiles from stratified analyses of studies included in this review (Supplementary data 3). To gain a better understanding of the evolution of multimorbidity over a life span, we recommend that future studies either stratify multimorbidity profiling by age group or, when this is not feasible, restrict their analyses to pre-specified age groups.

Limitations and strengths

One of the limitations of our systematic review is that we did not assess quality of included publications. Variations in the methodological quality of statistical analyses are likely to add to random variability to the synthesised results of MDS. Furthermore, in order to be able to synthesise the results of different studies, we assumed that, within each study, the conditions listed as part of the same multimorbidity profile all contributed equally to that profile. This was a necessary assumption to make, since information about the relative contribution of conditions to their profiles was (1) not reported systematically, (2) not reported in a form that can be easily pooled across different studies and (3) not available for all statistical approaches (i.e., cluster analysis). Hence, co-locations of conditions on synthesised MDS maps need to be interpreted with a degree of caution. The effect of study characteristics on the results of different analytical approaches was not in the scope for our review and is a question for future studies. Additionally, we based our systematic review on published literature only. Since studies that did not find discernible profiles of multimorbidity are unlikely to be published, the extent to which reported profiles are artefactual is not known. However, given that at least two groupings of conditions (mental health and cardio-metabolic) were identifiable within all four statistical approaches used to classify multimorbidity, artefactual explanation for the results observed in our systematic review is unlikely. A strength of our study is that we reviewed the largest number of multimorbidity studies to date and hence our synthesised results provide insights into replicable grouping of multimorbidity that would not be possible to derive from a single study.

Conclusions

This systematic review provides a synthesis of published multimorbidity groupings and offers guidance to increase methodological rigour and consistency of studies focused on statistical identification of multimorbidity profiles. Knowledge of stable and replicable multimorbidity profiles is needed to facilitate a shift from additivity-focused conceptualisation of multimorbidity to the study of outcomes, needs, and risk profiles of individuals with qualitatively different profiles of multimorbidity. In the longer term, better understanding of needs and outcomes of individuals with different profiles of multimorbidity will enable the transition from disease-centred to person-centred health care for individuals with multiple chronic conditions.

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Compliance with ethical standards

Conflict of interest Monash University received consultancy fees from Charité – Universitätsmedizin Berlin and Jesuit Social Services (Richmond, Victoria, Australia) for the statistical consultancy work undertaken by LB. The consultancy fees were unrelated to this project. The remaining authors have no conflict of interest to declare.

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