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REVIEW ARTICLE

A scoping review finds a growing trend in studies validating multimorbidity patterns and identifies five broad types of validation methods

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Abstract

Objectives: Multimorbidity, the presence of two or more long-term conditions, is a growing public health concern. Many studies use analytical methods to discover multimorbidity patterns from data. We aimed to review approaches used in published literature to validate these patterns.

Study Design and Setting: We systematically searched PubMed and Web of Science for studies published between July 2017 and July 2023 that used analytical methods to discover multimorbidity patterns.

Results: Out of 31,617 studies returned by the searches, 172 were included. Of these, 111 studies (64%) conducted validation, the number of studies with validation increased from 53.13% (17 out of 32 studies) to 71.25% (57 out of 80 studies) in 2017−2019 to 2022−2023, respectively. Five types of validation were identified: assessing the association of multimorbidity patterns with clinical outcomes ($n = 79$), stability across subsamples ($n = 26$), clinical plausibility ($n = 22$), stability across methods ($n = 7$) and exploring common determinants ($n = 2$). Some studies used multiple types of validation.

Conclusion: The number of studies conducting a validation of multimorbidity patterns is clearly increasing. The most popular validation approach is assessing the association of multimorbidity patterns with clinical outcomes. Methodological guidance on the validation of multimorbidity patterns is needed.

Keywords: Multimorbidity; Analytical method; Cluster analysis; Validation; Scoping review; Latent class analysis

1. Introduction

Multimorbidity, commonly defined to be when a patient develops two or more long-term conditions, is a growing public health concern, with a report from the UK's Academy of Medical Sciences highlighting that the number of patients affected by multimorbidity is increasing, and they often need complex care [1]. Multimorbidity has posed a significant burden on health-care sectors globally [2,3]. Analyzing multimorbidity can help to understand its nature and discover relationships between conditions.

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What is new?

Key findings

- The number of studies conducting a validation of data-derived multimorbidity patterns is increasing.
- Validation methods tend to fall into one of five broad categories: association with clinical outcomes; clinical plausibility; stability across subsamples; stability across methods; and exploring common determinants.

What this adds to what was known?

- Validation of multimorbidity patterns is conducted using different approaches with often incomplete reporting of the details.

What is the implication and what should change now?

- A consensus is needed on the appropriate methodology to validate multimorbidity patterns before they are being used in clinical practice or further research.
- Methodological and reporting guidelines for validation of multimorbidity patterns should be published to improve the quality and consistency of studies.

Multimorbidity often occurs in clusters of diseases that coexist in many patients [1]. Identifying such multimorbidity patterns, also known as clusters or profiles, can help to understand of the nature of multimorbidity, help in developing treatments, and reconfigure health services to better serve patients with multimorbidity [4].

Analytical methods are increasingly being used to identify multimorbidity patterns from health data [5–8]. Previous reviews, such as the one by Ng et al. [9] that identified the most common used methods. These methods were: factor analysis, hierarchical clustering, unified clustering, multiple correspondence analysis, and network analysis. The comparison analysis done in this review revealed variation in the multimorbidity patterns identified using the same data. Another review by Busija et al. [10] examined reliability and replicability of multimorbidity patterns, finding mental health conditions and cardio-metabolic conditions to be the most the most common and replicable patterns. Other patterns showed varying degrees of replicability across analytical methods. Additionally, they reported that studies often lacked details of the statistical methods used and it was not clear in some cases whether the identified multimorbidity patterns were validated.

The methods used to identify multimorbidity patterns typically fall into the broad class of unsupervised machine learning methods. Such methods can sometimes produce chance results or results that are aligned too closely to the data on which these clusters were derived from (overfitting). This can lead to clusters that do not accurately represent the broader population from which the dataset was sampled. It is essential for these clustering results to capture underlying patterns that are applicable to the population of origin, not just the sample data from which they were derived. The aim for clustering is to be robust and generalisable to the population from which the sample data were drawn, as this is integral to their utility and applicability. Therefore, it is important to validate these multimorbidity patterns before they are used to inform clinical practice or further research. However, a key challenge when applying such methods (whether in the context of multimorbidity research or not) is the principal absence of a known ground truth, which makes validation of these patterns particularly challenging.

To date, no published review has considered methods for validating multimorbidity patterns. Therefore, we aimed to conduct a methodology scoping review of validation approaches used in multimorbidity studies that applied analytical methods to identify multimorbidity patterns. Specific objectives were to review the current validation approaches used to determine the quality of multimorbidity patterns identified in multimorbidity research, and to provide recommendations for future research. Given that the concept of validation can vary depending on specific research areas, our secondary aim in this review was to assess how validation is typically defined and reported in the context of multimorbidity research. It is important to note that in this review, we did not confine ourselves to a specific type or definition of validation. Instead, we reviewed the literature to identify the methods and approaches that researchers report in their studies as validation of their results.

2. Methods

2.1. Search strategy and selection criteria

We searched the literature on multimorbidity to identify the validation approaches used in the published studies that applied analytical methods to find multimorbidity patterns using health data. We followed the recommendations published by Martin et al. [11] for conducting methodology scoping reviews.

All primary research articles published in peer-reviewed journals that applied analytical methods to identify multimorbidity patterns, were considered for inclusion. Studies were included if they use 10 long-term health conditions or more in their analyses. Other inclusion criteria were that studies had full text of the study available and were written in English. We excluded studies that identified their multimorbidity patterns without using any analytical methods (e.g., using only simple counts). Studies were also excluded

if their analysis was based only on patients aged 17 years or less, or a predefined health condition (i.e., index condition). Detailed inclusion and exclusion criteria are provided in the Supplementary Materials (p 3-4).

The literature search was conducted in July 2023 using PubMed and Web of Science with no time restriction on the publication date. We defined our search terms based on previous multimorbidity reviews [9,12,13]. These terms were broad enough and covered two sets of multimorbidity and analytical methods terms. Terms from both sets were combined with Boolean logic to search for relevant studies (Supplementary Table S1 and Supplementary Table S2). Identified studies were managed through EndNote 20. Any duplicates found were removed using the automatic deduplication feature on the same software.

To assess whether studies eligible for inclusion, titles were screened by one reviewer (TBD), after which abstracts were screened by four pairs of reviewers: (FJ & TBD); (AP & TBD); (RB & TBD); and (JR & TBD). The two reviewers in each pair blindly and independently screened the article for inclusion. If both reviewers in each pair decided that a study met the eligibility criteria, then the full text was screened by the reviewers. Any discrepancies were resolved through mutual discussion between the pair of reviewers; otherwise, an independent reviewer (GPM) was involved.

We selected publications from the six most recent years (between July 2017 and July 2023). To identify common types of validation, we grouped studies if the reported approach used for validation was similar. In other words, studies using the same type of validation approach were placed in the same group.

2.2. Data extraction and analysis

Data extraction was undertaken independently by five reviewers (TBD, FJ, NA, RB and JR) into a predesigned data extraction spreadsheet. The following information was extracted for studies included in the review: manuscript information; study type (i.e., cross-sectional or longitudinal); study aims; study data (i.e., sample size, age, setting); analysis methodology (i.e., number of conditions analyzed, clustering algorithm); validation approaches (Supplementary Materials p 3-4). After extracting the relevant information and to address the review objective, four reviewers (TBD, FJ, NA and NP) created groups of studies based on the validation approaches reported in the selected studies. The four reviewers compared these groups and resolved any discrepancies; if needed, a fifth reviewer (GPM) was involved.

3. Results

Our searches identified 31,617 studies. Study selection and reasons for exclusion are summarized in Fig. 1. A total of 172 studies were selected for our review (Table 1, Supplementary Table S3). Most studies were carried out in Europe (74 [42.8%]), Asia (56 [32.4%]) and North America (29 [16.8%]). Almost all studies were cross-sectional (146 [84.9%]) and only 26 (15.1%) were longitudinal. The sample size of the data used in studies varied widely, ranging from 247 patients [14] to over 22.1 million patients [15], with a median sample size of 13,144 (interquartile interval [IQI] 3,253−198,898.5). The most common data sources were prospective cohort studies (65 [37.8%]), followed by 57 (33.1%) studies using data from electronic health records (EHRs). We found more than half of studies (100 [58.2%]) focused on patients ≥40 years and 1 (1.4%) study focused on the very elderly (aged ≥80 years) [16]. The most common disease ascertainment method was through patient self-report or interviews (76 [44.2%]) or from patients medical records (71 [41.3%]). Half of studies (78 [45.3%]) used 10-20 conditions for assessing multimorbidity, while the rest used over 20 or all available conditions in data.

There were 26 (15.1%) studies implemented two clustering methods, and one study applied four clustering methods [17]. The majority applied only one method. Common methods were latent class analysis (56 [32.6%]), exploratory factor analysis (25 [14.5%]), network analysis (24 [14%]) and hierarchical clustering (17 [9.9%]). Variety of techniques were used to determine the optimal number of patterns (Supplementary Table S4).

With respect to validation of multimorbidity patterns in the selected studies, we found that 111 (64.5%) studies conducted validation in their analysis after identifying multimorbidity patterns, whereas 61 (35.5%) studies did not report any form of validation. Fig. 2 shows the number of studies included per year along with the proportions of studies that reported conducting validation of their results. Notably, from 2017 to 2019, 53.1% (17 out of 32 studies) conducted a validation, which increased to 61.7% (37 out of 60 studies) in the subsequent period of 2020-2021. This upward trend continued into 2021-2023, where 71.3% (57 out of 80 studies) reported validating multimorbidity patterns.

Five validation groups were identified in studies with validation (Table 2, see detailed definitions Supplementary Table S5). The most common type of validation was to assess association of patterns with clinical outcomes (79 [71.2%]), followed by stability across subsamples (26 [23.4%]), clinical plausibility (22 [19.8%]), stability across methods (7 [6.3%]) and exploring common determinants (2 [1.8%]). Overall, 136 validation analyses were performed in the 111 (64.5%) studies, where some studies used multiple types of validation. For example, both Grant et al. [40] and Marengoni et al. [109] assessed association with outcomes, clinical plausibility, and stability across subsamples or across different methods, while five studies [16,98,104,107,110] used two types of validity. Each of the five validation types was applied using different designs and metrics. The level of detail reported, both in

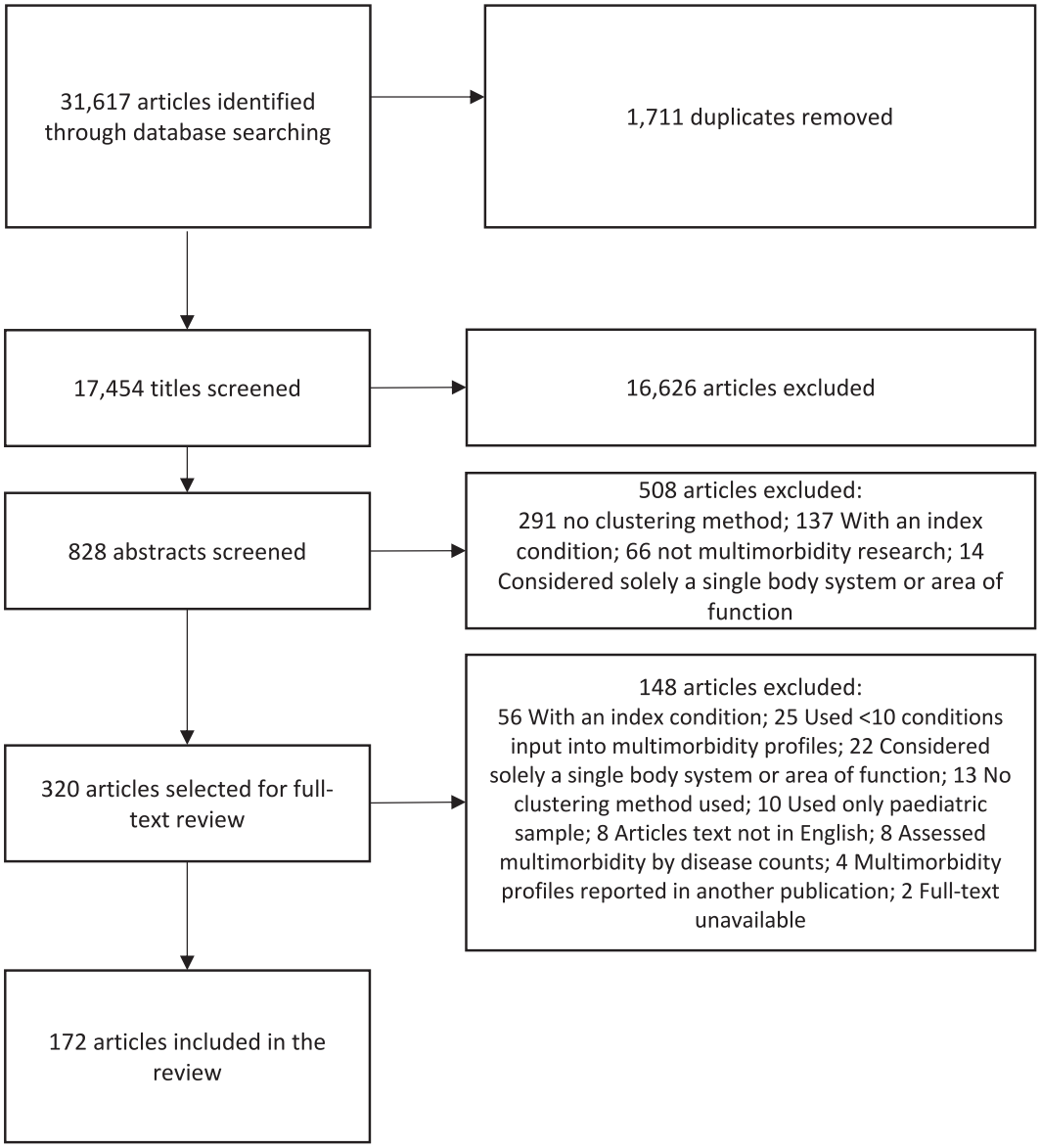

Fig. 1. Flowchart of the study selection process.

terms of methods used and validation findings, varied widely between studies.

Validation of multimorbidity patterns by assessing associations with clinical outcomes is done typically using regression analysis. For example, Zheng et al. [90] found five multimorbidity patterns (healthy, hypertensive, respiratory conditions, heart disease, and severely impaired) from patients in the USA. The logistic regression analysis showed elevated risk of visual impairment in diseases groups compared to the healthy group. Across studies using this type of validation, common clinical outcomes were health care utilisation, hospital admission, health-related quality of life, and death.

The second group of studies evaluated the stability of the derived multimorbidity patterns across different subsamples. Within this group, split sampling was used in 15 studies. For example, Zhu et al. [7] split their study dataset into a training set (80%) and a test set (20%) and assessed the consistency of clusterings derived from the training and test sets using the Jensen−Shannon distance [126] and the bivariate Pearson correlation coefficient [127]. Hu et al. [48] also used this design but split the data in a systematic way. They applied the analysis initially on the entire sample (age range 45−84 years), and then repeated it in two subsets with age ranges 45−64 and 65−85. By comparing the resulting patterns, they found consistent results from both analyses. Bootstrapping was used in eight studies. For instance, three studies [104,105,107] used the Jaccard coefficient [128] to assess stability of multimorbidity patterns that were derived over

Table 1. Characteristics of studies included in the scoping review

Study characteristics	Number of studies (n = 172)
Publication yr	
2017	7 (4.1%)
2018	15 (8.7%)
2019	10 (5.8%)
2020	32 (18.6%)
2021	28 (16.3%)
2022	61 (35.5%)
2023	19 (11.0%)
Regions and countries	
Europe	74 (42.8%)
Spain	25 (14.5%)
Italy	6 (3.5%)
UK	15 (8.7%)
Denmark	3 (1.7%)
Sweden	8 (4.6%)
Switzerland	4 (2.3%)
Other	13 (7.5%)
Asia	56 (32.4%)
China	36 (20.8%)
Korea	5 (2.9%)
Taiwan	4 (2.3%)
Other	11 (6.4%)
North America	29 (16.8%)
USA	24 (13.9%)
Canada	4 (2.3%)
Mexico	1 (0.6%)
Other	13 (7.5%)
Study design	
Cross-sectional	146 (84.9%)
Longitudinal	26 (15.1%)
Sample size	
<1,000	15 (8.7%)
1,000–10,000	54 (31.4%)
10,001–100,000	49 (28.5%)
100,001–500,000	24 (14.0%)
500,001–1,000,000	10 (5.8%)
>1,000,000	19 (11.0%)
Not reported	1 (0.6%)
Data source	
Electronic Health Records	57 (33.1%)
Cohort Study	65 (37.8%)
Registry/national audit	10 (5.8%)
Administrative data	8 (4.7%)
National survey data	31 (18.0%)
Data from multiple sources	1 (0.6%)
Age range (yr)	
Children to middle-aged adults (birth-65 yr)	5 (2.9%)
Young to older adults (age 15-85 yr)	8 (4.7%)
All adults (age ≥16 yr)	28 (16.3%)
Middle-aged adults (age 40–69 yr)	9 (5.2%)
Middle-aged and older adults (age ≥40 yr)	39 (22.7%)
Older adults (age ≥60 yr)	61 (35.5%)
All ages	15 (8.7%)
Not reported	7 (4.1%)
Disease ascertainment method	
Medical records	71 (41.3%)
Self-report or interviews with patients	76 (44.2%)
Self-report and medical records	8 (4.7%)
Clinical assessment and medical records	4 (2.3%)
Clinical assessment	1 (0.6%)
Self-report and Clinical assessment	7 (4.1%)
Clinical assessment; medical records; self-report or interviews with patients	3 (1.7%)
Not reported	2 (1.2%)
Number of conditions included in analysis	
10–20	78 (45.3%)
21–50	50 (29.1%)
51–100	20 (11.6%)
>100	18 (10.5%)
All available diagnosis codes in the data	6 (3.5%)
Clustering method[a]	
Latent class analysis	56 (32.6%)
Exploratory factor analysis	25 (14.5%)
Network analysis	24 (14.0%)
Hierarchical cluster analysis	17 (9.9%)
Association rule analysis	16 (9.3%)
Fuzzy C-means algorithm	16 (9.3%)
k-means clustering	11 (6.4%)
Principal component analysis	8 (4.7%)
Other	28 (16.3%)
With validation?	
Yes	111 (64.5%)
No	61 (35.5%)

[a] Percentages add to more than 100 as some studies use multiple clustering methods.

100 bootstrap samples. The last resampling design was cross-validation, which was used in three studies, but none of these studies reported which indices of stability they used, or presented the results obtained.

Clinical plausibility was the next type of validation in the included studies. An example of this validation was done by Grant et al. [40] where an interdisciplinary committee of 25 clinicians were involved to assess the derived multimorbidity patterns. The clinicians were split into groups to review the different patterns, based on their clinical expertise. Other studies looked at relevant published evidence or applied existing clinical criteria. In a study by Diaz-Santiago et al. [116] searches were performed using clinical databases such as PubMed to find the overlap

between the combinations of diseases mentioned in the literature and those found in the identified clustering. Another example was done in a study by Hassaine et al. [6], where their findings were validated by looking at two medical sources from published studies that provide lists of comorbid disease pairs [129,130].

Studies in this validation group often report few details on how the research team conducted the validation. For instance, reporting was limited to "Clinical criteria were used to evaluate the consistency and utility of the final cluster solution, based on clusters previously described in the literature and a consensus opinion drawn from the clinical experience of the research team (3 family physicians and 2 epidemiologists engaged in daily patient care)" [104] or "We based our evaluation of the consistency and significance of the final solution on clinical criteria" [110].

The fourth group of studies assess the stability of multimorbidity patterns by applying different analytical methods or measures. An example is the study by Grant et al. [40], who applied both latent class analysis and k-means clustering. Both clustering algorithms resulted in similar multimorbidity patterns with a high degree of overlap between them. Similarly, Craig et al. [121] found similar patterns with minor differences when applying latent class analysis and exploratory factor analysis on the same dataset. Roso-Llorach et al. [98] applied hierarchical clustering and exploratory factor analysis to their data. The results showed some differences in the identified multimorbidity patterns, but three combinations of diseases were observed consistently across both methods: hypertension and obesity, spondylopathies and deforming dorsopathies, and dermatitis eczema and mycosis.

Exploring common determinants was the least common validation type found in the selected studies. This was carried out in two studies [124,125] that looked for common determinants of the diseases within the derived multimorbidity patterns. For instance, Guo et al. [124] developed a disease comorbidity network from Chinese hospital admissions data using correlation analysis, and derived multimorbidity patterns from this network using network analysis and data mining methods. The patterns were subsequently validated by exploring shared molecular mechanisms using disease-gene associations and pathways.

4. Discussion

With the increasing number of multimorbidity patterns being identified through published studies, it is important to ensure the validity of such derived patterns. We used a methodology scoping approach to review the existing literature in the field of multimorbidity research and identified approaches used to validate multimorbidity patterns. We considered multimorbidity studies published within the last 6 years before the search date (July 2023). Earlier studies were not included in this review as they might have used outdated validation approaches, which may not align with contemporary analytical methods used for identification of multimorbidity patterns. There were 172 eligible studies published in this period. It was clearly noticeable that the number of studies performing a validation was increasing over time. This suggests a growing effort in the research community to validate findings, which is a positive sign for the reliability of research findings in this area. However, our review found that 61 (35.5%) of studies did not report any form of validation, while various studies that did include a validation often reported insufficient detail to understand what exactly happened.

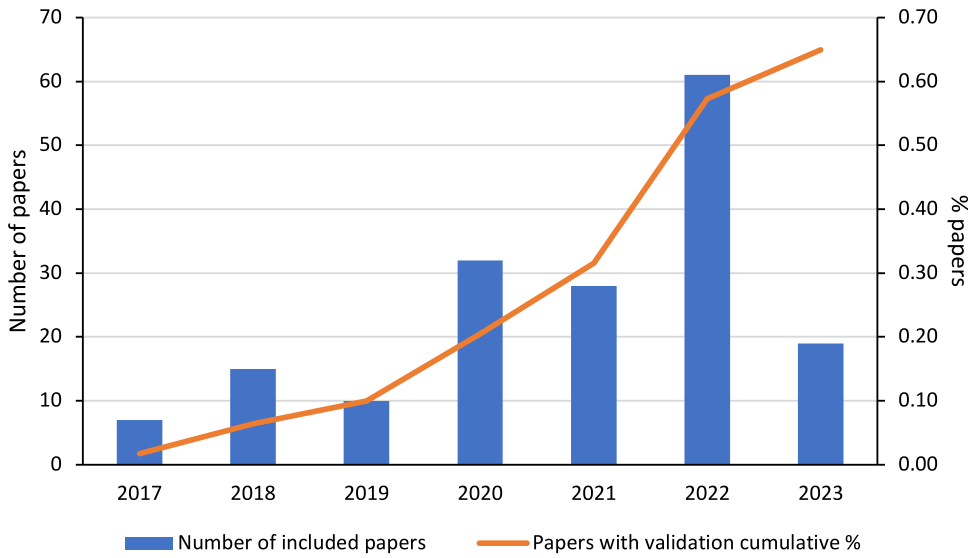

Fig. 2. The number of included studies since 2017 until 2023 with the proportions of studies that conducted validation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2. Details of five multimorbidity validation types (136 validation analyses in 111 studies)

Validation group	Reference, yr
1. Association with clinical outcomes (n = 79 [71.2%])	
Description: studies that evaluated the utility of derived multimorbidity profiles in terms of their associations with clinical outcomes of interest.	
Examining association of the derived multimorbidity profiles with outcomes using regression analysis	Akugizibwe et al. [18], 2020; Alvarez-Galvez et al. [19], 2022; Amirzada et al. [20], 2023; Aoki et al. [21], 2018; Aoki et al. [22], 2021; Bekic et al. [23], 2021; Bendayan et al. [24], 2021; Calvin et al. [25], 2022; Carrasco-Ribelles et al. [26], 2023; Carretero-Bravo et al. [27], 2022; Chen et al. [28], 2022; Corsonello et al. [29], 2022; Craig et al. [30], 2021; Craig et al. [31], 2023; Damiano et al. [32], 2022; DeCarvalho et al. [33], 2018; Eton et al. [34], 2022; Eyowas et al. [35], 2022; Fan et al. [36], 2022; Fehlberg et al. [37], 2023; Gates et al. [38], 2018; Grande et al. [39], 2021; Grant et al. [40], 2020; Gu et al. [41], 2018; Han et al. [42], 2022; Ho et al. [43], 2022; Ho et al. [44], 2022; Ho et al. [45], 2023; Honda et al. [46], 2022; Hsieh et al. [47], 2023; Hu et al. [48], 2022; Hunter et al. [49], 2021; Jacob et al. [50], 2020; Khondoker et al. [51], 2023; Khorrami et al. [52], 2020; Li et al. [53], 2021; Liu et al. [54], 2022; Lu et al. [55], 2021; Luo et al. [56], 2023; de Macedo Stumpf et al. [57], 2023; Marengoni et al. [58], 2021; Marengoni et al. [59], 2021; Møller et al. [60], 2020; Nguyen et al. [61], 2019; Nguyen et al. [62], 2020; Nunes et al. [63], 2017; Park et al. [64], 2019; Pati et al. [65], 2022; Puri et al. [66], 2022; Rodrigues et al. [67], 2022; Ronaldson et al. [68], 2021; Ronaldson et al. [69], 2022; Ronaldson et al. [70], 2023; Restocchi et al. [71], 2022; Shang et al. [72], 2022; Shi et al. [73], 2022; Sturmer et al. [74], 2022; Subedi et al. [75], 2022; Tazzeo et al. [76], 2021; Valletta et al. [77], 2023; Vetrano et al. [78], 2022; Wang et al. [79], 2019; Wang et al. [80], 2021; Wang et al. [81], 2022; Wartelle et al. [82], 2022; Yan et al. [83], 2022; Yao et al. [84], 2020; Yao et al. [85], 2020; Yao et al. [86], 2022; Zhai et al. [87], 2023; Zhang et al. [88], 2022; Zhao et al. [89], 2023; Zheng et al. [90], 2020; Zheng et al. [91], 2020; Zheng et al. [92], 2021; Zhong et al. [93], 2022; Zhong et al. [94], 2023; Zhou et al. [95], 2022; Zou et al. [96], 2022
2. Stability across subsamples (n = 26 [23.4%])	
Description: studies that evaluated the stability of the derived multimorbidity profiles by applying the same analytical method to different subsamples of their study data and assessing the consistency in derived profiles.	
Split sample	Gonsoulin et al. [97], 2017; Roso-Llorach et al. [98], 2018; Teh et al. [16], 2018; Zhu et al. [7], 2020; Bare et al. [99], 2021; Calvin et al. [25], 2022; Carrasco-Ribelles et al. [26], 2023; Khondoker et al. [51], 2023; Prasad et al. [100], 2022; Siah et al. [101], 2022; Arshadipour et al. [102], 2022; Hu et al. [48], 2022; Liu et al. [54], 2022; Robertson et al. [103], 2022; Shi et al. [73], 2022
Bootstrapping	Guisado-Clavero et al. [104], 2018; Machón et al. [105], 2020; Madlock-Brown et al. [106], 2021; Roso-Llorach et al. [98], 2018; Violán et al. [107], 2018; Alvarez-Galvez et al. [108], 2022; Nichols et al. [17], 2022; Rodrigues et al. [67], 2022
Cross-validation	Marengoni et al. [109], 2021; Vetrano et al. [110], 2020; Grande et al. [39], 2021
3. Clinical plausibility (n = 22 [19.8%])	
Description: studies that either involved clinical experts, used published evidence, or applied existing clinical criteria to assess the clinical relevance of identified profiles.	
Clinical experts	Grant et al. [40], 2020; Guisado-Clavero et al. [104], 2018; Menditto et al. [111], 2019; Roso-Llorach et al. [98], 2018; Teh et al. [16], 2018; Violán et al. [112], 2020; Carrasco-Ribelles et al. [26], 2023; Honda et al. [46], 2022; Ioakeim-Skoufa et al. [113], 2022; Martinez-Velilla et al. [114], 2022; Robertson et al. [103], 2022; Roso-Llorach et al. [115], 2022
Clinical literature/knowledge	Hassaine et al. [6], 2020; Diaz-Santiago et al. [116], 2020; Olaya et al. [117], 2017; Shi et al. [118], 2021; Violán et al. [119], 2019; Stafford et al. [120], 2021
Clinical criteria	Marengoni et al. [109], 2021; Vetrano et al. [110], 2020; Violán et al. [107], 2018; Grande et al. [39], 2021
4. Stability across methods (n = 7 [6.3%])	
Description: studies that assessed stability of profiles by applying different analytical methods and measures to the same data.	
Applied multiple methods	Grant et al. [40], 2020; Roso-Llorach et al. [98], 2018; Craig et al. [121], 2020; Franti et al. [122], 2022
Applied multiple measures	Arshadipour et al. [102], 2022; Monchka et al. [123], 2022; Robertson et al. [103], 2022

(*Continued*)

Table 2. Continued

Validation group	Reference, yr
5. Exploring common determinants (n = 2 [1.8%])	
Description: studies that looked for common determinants of the diseases within the derived multimorbidity profiles.	
Investigating shared molecular mechanisms using disease-gene associations and pathways	Guo et al. [124], 2019
Similarity-based evaluation method	Giannoula et al. [125], 2020

Of the 111 studies (64.5%) that reported validation in their analyses, the validation of the multimorbidity patterns varied in terms of the approaches used. In total, we found five broad types of validation approaches used throughout the selected studies: assessing the association of multimorbidity patterns with clinical outcomes (79 [71.2%]), stability across subsamples (26 [23.4%]), clinical plausibility (22 [19.8%]), stability across methods (7 [6.3%]) and exploring common determinants (2 [1.8%]). A number of studies applied more than one type of validation.

To the best of our knowledge, this is the first review of validation approaches used in multimorbidity profiling research. Previous reviews in this area of research only looked at the analytical methods used to identify multimorbidity patterns and not the validation approaches [9,10,12]. Validation is a challenging task, and as we found in this review, evaluating and validating the identified multimorbidity patterns is not often carried out. Similar issues regarding validation were also reported in studies in other clinical areas. Particularly, in studies that used unsupervised machine learning methods to derive subphenotypes of clinical conditions [131,132]. This was demonstrated in a review by Horne et al. [133] where only a third of studies which used clustering methods to identify asthma subtypes evaluated the clustering results. The review also found that the reporting of the clustering analysis and its evaluation was generally poor. Using unsupervised machine learning methods has the potential to identify robust subphenotypes and provide better understanding of the diseases. Many studies utilized such methods in their analysis; however, with the lack of validating and assessing these subphenotypes, such potential remains limited.

A key strength of this review is the systematic and robust approach taken to search and screen studies for inclusion and reviewing the selected studies. We used predefined search terms and eligibility criteria to include relevant studies. There was an overall agreement between the reviewers regarding the selection of eligible studies. This was demonstrated by engaging them in two rounds of screening and extracting an initial batch of studies. Such level of agreement between the reviewers should limit the selection and extraction bias. A limitation is that we restricted our search period to the most recent 6 years leading up to the search date, after finding that the previous studies may have used outdated validation methods. It is unlikely that this impacted our findings because most multimorbidity profiling studies were published in recent years. We also excluded studies with an index condition and studies that used a study sample with a predefined health condition. We may, therefore, have missed validation methods that are relevant to multimorbidity in the presence of an index condition. Studies that involved only nonadult patients were also excluded. This is in line with common practice in multimorbidity literature, which focuses on long-term conditions in the adult population. We believe this choice did not influence our findings. A final limitation is that information extracted from studies may have been incomplete because authors left it implicit that they were aiming to validate their multimorbidity patterns.

The concept of validation is inherently problematic for studies that use unsupervised machine learning methods, because these methods are characterized by the absence of a ground truth in the data. Our review aimed to summarize what published studies report about their efforts to validate multimorbidity patterns, and not to critically appraise whether those efforts should or should not count as proper 'validation'. Specifically, we note that a number of included studies [73,102,103,134] repeated their analysis using different methods and/or subsamples and referred to this activity as a means of validating their results. However, one could argue that such checks are better reported as sensitivity analyses aiming to assess the robustness of findings rather than validating them.

It is worth noting that the five types of validation identified in this review concur with commonly made distinctions in the field of measurement theory regarding the scientific concept of 'validity' [135]. In criterion validity the driving question is whether the results of an analysis correlate with certain variables or predict an outcome of interest. In the context of our review, this corresponds to assessing the association of multimorbidity patterns with clinical outcomes, and to exploring common determinants of multimorbidity patterns. Content validity, also known as face validity, is a subjective form of validity which seeks opinions from a panel of informed individuals regarding the results from an analysis. It corresponds to the 'clinical plausibility' group in our review. Lastly, construct validity asks whether the results of an analysis are reproducible when experimenting with other methods or data. In our review,

studies that assessed stability across subsamples or across methods explored this type of validity.

We identified that a notable number of studies did not report much detail regarding the validation design, or in other cases, did not conduct or report any validation. At a minimum, we believe that all studies using analytical methods to identify multimorbidity patterns need to explicitly and clearly report: the validation design with sufficient information of the approaches and the metrics used; when involving a group of domain experts, their number, expertise and role of each member, as well as a report of their discussions and decisions; and a priori clinical criteria to determine the clinical utility of the identified patterns. In addition, to improve the quality and consistency of published studies, we recommend that methodological and reporting guidelines be published for the development and validation of multimorbidity patterns. This has the potential to achieve uniformity between multimorbidity profiling studies allowing them to be more easily comparable. Furthermore, in future studies, it would be valuable to assess the strength and limitations of the current validation methods. This assessment can provide insights into ways to improve the process of validation, particularly in the context of identifying multimorbidity patterns.

5. Conclusion

In conclusion, this review provides a synthesis of 172 published studies in the area of multimorbidity research. We found that 35.5% of these studies did not report any form of validation. However, our review shows a clear upward trend that more studies are conducting validation of multimorbidity patterns over the years. Among the 64.5% of studies that did conduct a validation, there was variation in the approaches used and discrepancies in reported methodologies. We identified five complementary types of validation (association with clinical outcomes, clinical plausibility, stability across subsamples, stability across methods, and exploring common determinants), with several studies applying more than one type of validation. A consensus is needed on the appropriate methodology to validate multimorbidity patterns.

CRediT authorship contribution statement

Thamer Ba Dhafari: Conceptualization, Methodology, Data curation, Formal analysis, Writing − original draft. **Alexander Pate:** Data curation, Writing − review & editing. **Narges Azadbakht:** Data curation, Writing − review & editing. **Rowena Bailey:** Data curation, Writing − review & editing. **James Rafferty:** Data curation, Writing − review & editing. **Farideh Jalali-najafabadi:** Data curation, Writing − review & editing. **Glen P. Martin:** Methodology, Data curation, Writing − review & editing. **Abdelaali Hassaine:** Data curation, Writing − review & editing. **Ashley Akbari:** Writing − review & editing, Project administration. **Jane Lyons:** Methodology, Writing − review & editing. **Alan Watkins:** Methodology, Writing − review & editing. **Ronan A. Lyons:** Writing − review & editing, Funding acquisition. **Niels Peek:** Conceptualization, Methodology, Writing − original draft, Supervision, Funding acquisition.

Data availability

No data was used for the research described in the article.

Declaration of competing interest

None declared.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2023.11.004.

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