Multimorbidity of non-communicable diseases in low-income and middle-income countries: a systematic review and meta-analysis

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ABSTRACT

Introduction Multimorbidity is a major public health challenge, with a rising prevalence in low/middle-income countries (LMICs). This review aims to systematically synthesise evidence on the prevalence, patterns and factors associated with multimorbidity of non-communicable diseases (NCDs) among adults residing in LMICs.

Methods We conducted a systematic review and meta-analysis of articles reporting prevalence, determinants, patterns of multimorbidity of NCDs among adults aged >18 years in LMICs. For the PROSPERO registered review, we searched PubMed, EMBASE and Cochrane libraries for articles published from 2009 till 30 May 2020. Studies were included if they reported original research on multimorbidity of NCDs among adults in LMICs.

Results The systematic search yielded 3272 articles; 39 articles were included, with a total of 1 220 309 participants. Most studies used self-reported data from health surveys. There was a large variation in the prevalence of multimorbidity: 0.7%–81.3% with a pooled prevalence of 36.4% (95% CI 32.2% to 40.6%). Prevalence of multimorbidity increased with age, and random effect meta-analyses showed that female sex, OR (95% CI): 1.48, 1.33 to 1.64, being well-off, 1.35 (1.02 to 1.80), and urban residence, 1.10 (1.01 to 1.20), respectively were associated with higher odds of NCD multimorbidity. The most common multimorbidity patterns included cardiometabolic and cardiorespiratory conditions.

Conclusion Multimorbidity of NCDs is an important problem in LMICs with higher prevalence among the aged, women, people who are well-off and urban dwellers. There is the need for longitudinal data to access the true direction of multimorbidity and its determinants, establish causation and identify how trends and patterns change over time. PROSPERO registration number CRD42019133453.

INTRODUCTION

Although the burden of diseases in low/middle-income countries (LMICs) has classically been infectious, changes in demographic patterns as a result of the interplay between urbanisation, lifestyle and culture, has led to emerging non-communicable diseases (NCDs) in LMICs.1 3 The NCD burden is estimated to increase by 27% in the African region in the next 10 years, while Western Pacific and South-East Asia will account for the highest absolute number of deaths from NCDs.3 Coexistence of one or more chronic diseases in an individual is commonly denoted as multimorbidity.4 5 With the increasing prevalence of NCDs in LMICs,6 many of which share common risk factors, the prevalence of multimorbidity of NCDs will continue to rise. There is, however, a substantial difference in the burden of NCDs between LMICs and high-income countries (HICs) due to the difference in drivers, such as promotion of healthier lifestyles and providing equitable healthcare by instituting appropriate government policies.7 While research investigated common pathways on NCD multimorbidity in HICs, it is unclear if this is also valid for...
LIMCs. It is therefore important to identify common NCD multimorbidity patterns and pathways that are specific to LIMCs.

Studies undertaken so far predominantly used self-reported measures and show multimorbidity to be associated with decreased quality of life, increased healthcare utilisation and costs in primary, secondary and tertiary healthcare settings. Just as reported in HICs, there is also limited information on the distribution of patterns of multimorbidity, their size, their drivers and their risk factors in LIMCs. There are a few studies indicating that multimorbidity in LIMCs is more frequent in women and that it starts at an earlier age than in HICs, but these studies are scattered. In order to address and manage the increasing number of people with multimorbidity, it is important to assess the burden of multimorbidity as well as the combinations of NCDs and their patterns in LIMCs. A recent scoping review of of that summarised the prevalence and determinants of multimorbidity chronic NCDs in LIMCs reported prevalence ranging from 3.2% to 90.5%. This review builds on the previous scoping review by adopting systematic methods and meta-analysis to synthesise the evidence on the prevalence, patterns and factors associated with multimorbidity of NCDs among adults residing in LIMCs. We further showed the prevalence and patterns of multimorbidity of NCDs according to country’s income level classification by the World Bank.

METHODS

Review framework and patient and public involvement

This systematic review and meta-analysis was reported according to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (online supplemental file 1).

Patient and public involvement

This is a meta-analysis based on study-level data and no individual-level data were involved in the study or in defining the research question or outcome measures. It was not possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Search strategy

A structured search was done in the following databases: PubMed, EMBASE and Cochrane library for articles published in English from 2009 until April 2020. Keywords and Medical Subject Headings (MeSH) terms and their combinations used in the searches included “Multiple Chronic Conditions”, “Multimorbidity”, “Comorbidity”, “Non-Communicable Diseases”, “Developing Countries”, “Cardiovascular Diseases”, “Neoplasms”, “Lung Diseases, Obstructive”, “Diabetes Mellitus” and “Mental Disorders”, “Hypertension”. In addition, the reference lists and bibliographies of the included articles were examined to identify any other relevant article. The detailed search strategy is provided as online supplemental file 2.

Inclusion and exclusion criteria

Studies were included if they (i) reported original research on multimorbidity of NCDs, (ii) included adults aged 18 years and above and residing in LIMCs, (iii) conducted in any of these study settings; community, residential care homes, primary care, secondary care, tertiary care and specialised care centres/institutions; or at the regional level using data from primary research, demographic and health surveys, or demographic and health surveillance systems. We defined LIMCs according to the World Bank’s Country and Lending Group List. We excluded studies conducted in HICs. Studies published in languages other than English and studies on comorbidity (studies that recruited patients based on an index disease or primary disease of interest) were also excluded. However, we included comorbidity in the search strategy to enable us to capture and scrutinise studies that used the terms comorbidity and multimorbidity interchangeably or incorrectly.

Definition of terms/concepts

We defined multimorbidity of NCDs as co-occurrence of two or more chronic non-communicable health conditions in the same individual. Prevalence of multimorbidity of NCDs was defined as the proportion of people with two or more chronic NCDs in the study population. Patterns of multimorbidity NCDs were assessed by considering the frequencies and distributions of NCDs among individuals, regions and countries.

Data extraction

Two reviewers (OAA, AMF) extracted data from the included articles. In case of divergent opinions, KK-G and DB were consulted. Information extracted included author(s) name, year of publication and study country, survey/source of data, sample size, method of data collection, number of NCDs, multimorbidity definition, prevalence and factors associated with multimorbidity. The following summary measures were included: prevalence, odds ratio (OR), prevalence risk ratios and relative risk ratio with their 95% CI for the association between risk factors/determinants and NCD multimorbidity.

Quality assessment

The risk of bias in the included studies was assessed using the National Institute of Health Quality Assessment Tool for Observational Cohort and Cross-sectional Studies. This tool was used to appraise the reliability, validity, generalisability and overall quality of the included studies using 14 criteria. This included clearly stated research question and objective, clearly specified study population, adequate participation rate, similar subject selection/recruitment and uniform application of eligibility to all participants, sample size estimation, exposure measurement before outcome, sufficient time frame to detect an association, examination of different levels of exposure.
multiply exposure measurement over time, valid outcome assessment, detection bias, loss to follow-up and adjustment of confounding variables. The tool provides general guidance to determine the overall quality of the studies and to grade their level of quality as good, fair or poor.

Data synthesis and analysis

Studies that provided sufficient data were used in the meta-analyses using Cochrane Review Manager (RevMan) software. For multi-country studies with sufficient analysis of country level data, findings from individual countries were included separately in the meta-analyses. Findings of the remaining studies were presented in a narrative format. We pooled the OR (95% CI) for the association between sex, education, income, residence (rural/urban) and multimorbidity. A pooled OR of the association between age and multimorbidity was not estimated due to the variation in reference age categories whereas smoking, physical activity and alcohol consumption were not meta-analysed due to the limited number of studies that reported on them. The log OR and SEs were combined in RevMan using the generic inverse-variance. We performed a random effect analysis, and heterogeneity was assessed using the Cochrane’s Q and degree of inconsistency ($I^2$). The pooled prevalence of multimorbidity was estimated using Open Meta (analyst) software. The pooled prevalence was further stratified according to different regions in LMICs. The robustness of the pooled estimates was assessed by conducting a leave-one-out sensitivity analysis. All analyses were considered statistically significant at the two-sided 5% level ($p<0.05$).

RESULTS

The electronic database and reference list search yielded 3272 articles, while 3134 articles remained after removal of duplicates. After the title and abstract screening, 68 articles were deemed potentially relevant. Twenty-nine articles were further excluded because they were conducted on communicable diseases ($n=18$), in non-LMICs ($n=2$), had poor quality ($n=1$) or based on other reasons such as presence of an index disease, or assessed multimorbidity in all ages without a separate report for adult above 18 years ($n=8$). We included 39 studies for the current review (figure 1). Some of the studies reported results from multiple countries, which were included individually in the analyses. For example, Bao et al included analyses from seven countries; Cuba, Dominican Republic, Puerto Rico, Peru, Venezuela, Mexico, China. Agrawal and Agrawal, Garin et al and Christian et al each reported findings from six countries; China, India, Mexico, Russia, South Africa and Ghana. Zhou et al reported findings from India, China, and Bangladesh while Kuma et al assessed multimorbidity in China and India. Table 1 shows all the countries or regions where multimorbidity of NCDs were conducted.

All included articles were cross-sectional except two studies that were cohort studies. A total of 1,220,309 individuals were included and the sample size ranged from 380 to 60,209. NCDs were assessed through self-report in all included studies, or in combination with a health insurance database, or medication use and clinical test. One study assessed based on the Anatomical Therapeutic Chemical Classification System. The number of self-reported NCDs ranged from 3 to 22. All studies defined multimorbidity as coexistence of two or more chronic NCDs, except one study which defined multimorbidity as a count of 21 chronic health conditions (table 1).

Most of the studies were of good quality. Three included articles were judged to be of fair quality. One study was excluded because of having a small sample size, and a lack of data or non-robust methods. Twenty-one of the included studies did not give information about missing data handling. Online supplemental file 3.

The overall prevalence of multimorbidity of NCD varied from 0.7% (in a population aged ≥20 years in a rural community in Western India) to 81.3% (in an elderly population aged ≥60 years in Southern Brazil). A study that assessed prevalence of multimorbidity among adults ≥18 years in 27 LMICs using the World Health Surveys reported a mean prevalence ranging from 1.7% (95% CI 1.4 to 2.0) in Myanmar to 15.2% (95% CI 14.3 to 16.0) in Nepal. In studies that combined self-reported diseases with symptom based diagnosis, medication use/medical card review, prevalence varied between 4.0% and 72% in people ≥18 years. The overall prevalence of multimorbidity was 36.4% (95% CI 32.2% to 40.6%) as shown in figure 2. In a subgroup analysis, the pooled prevalence according to the countries’ income levels was 39.3% (95% CI 34.5% to 44.1%) for upper middle-income countries (MICs) (online supplemental figure 1a) and 29.2% (95% CI 23.0% to 35.4%) for lower MICs (online supplemental figure 1b). We did not pool the prevalence for low-income countries (LICs) because there were only three studies, with prevalence ranging from as low as 4.0% in Malawi to 65.0% in Burkina Faso. Subgroup analysis according to the World Bank regions of LMICs was 26.2% (95% CI 18.9% to 33.5%) for sub-Saharan Africa (SSA); 29.5% (95% CI 20.9% to 38.1%) for Asia; 31.8% (95% CI 25.7% to 37.8%) for East Asia; 33.1% (95% CI 10.4% to 55.8%) for Middle-East and North Africa (MENA); for Europe and Central Asia (excluding high income) 44% (95% CI 32.7% to 55.3%) and 50.4% (95% CI 35.6% to 65.2%) for Latin America and the Caribbean (LAC). According to the leave-one-out sensitivity analysis, no single study had a substantial influence on the overall prevalence of NCD multimorbidity (online supplemental figure 2).
Age, sex, education, wealth/income, urban/rural setting and marital status were the most studied factors associated with multimorbidity of NCDs (online supplemental table 1). ORs for the association between major predictors and multimorbidity are shown in online supplemental table 2. Age was positively associated with multimorbidity of NCDs in 22 studies, whereas 3 studies found no association.

Figure 3 shows a forest plot of pooled OR for the association between major predictors and multimorbidity; details of the meta-analysis for the individual predictors are shown in online supplemental figure 3a–d). Women had significantly higher odds of multimorbidity compared with men in 11 studies, whereas 8 studies showed a non-significant association (online supplemental table 2). Fourteen studies (one study included six different country level results) were meta-analysed and the pooled OR for female sex and NCD multimorbidity was 1.48 (95% CI 1.33 to 1.64) (figure 3a). The association between education and multimorbidity was assessed in 31 studies. In most studies, the risk of multimorbidity was higher among those with a lower educational status, while four studies reported a lower risk of lower education status. A meta-analysis of 13 studies (one study included six different country level results) showed an OR of 1.22 (95% CI 1.00 to 1.49) for those with no formal education or lower educational attainment (figure 3, online supplemental figure 3b).

The association between socioeconomic status (income/wealth) and multimorbidity was determined in 14 studies; 7 studies found an association with higher odds/risk/prevalence of multimorbidity for people in the most well-off class, while in 3 studies the odds/prevalence of multimorbidity was higher for people considered to be poor. The pooled OR from 10 studies (one study included six different country level results; one study included results for males and females) showed increased odds of NCD multimorbidity among people who are well-off, OR 1.35 (95% CI 1.02 to 1.80) (figure 3, online supplemental figure 3c). There were...
| Author                   | Country/region                          | Inclusion criteria                                                                 | Study design            | Survey/source of data | Sampling characteristics | Field year | Sample size | Age range (years) | Data collection | No of NCDs | Multimorbidity definition | Prevalence (%) | Quality of included studies |
|-------------------------|----------------------------------------|-----------------------------------------------------------------------------------|-------------------------|-----------------------|--------------------------|------------|-------------|-------------------|----------------|------------|------------------------|----------------|-----------------------------|
| Afshar et al (27 LMIC)   | Africa, Central and South America, Eastern Europe and Central Asia, South Asia, South East Asia | Prevalence and determinants                                                       | Cross-sectional        | WHS                   | Probabilistic            | 2001–2004  | 25,761      | ≥18               | Self-report     | 6          | ≥2                     | Ranges from 1.7 to 15.2; Africa (3.6–11.2) Central and South America (5.7–13.4) Eastern Europe and Central Asia (7.6–15.0) South Asia (3.9–7.8) Southeast Asia (1.7–15.2) Mean global prevalence (95 CI) 7.8 (7.8 to 7.8)* | Good            |                             |
| Agrawal and Agrawal      | China                                  | Prevalence and determinants                                                       | Cross-sectional        | WHO SAGE              | Probabilistic            | 2007–2010  | 42,236      | ≥18               | Self-report+medication use+SBD | 9          | ≥2                     | 22.0–50.0; China (22.0); Mexico (27.0); Russia (50.0); South Africa (32.0); Ghana (23.0) | Good            |                             |
| Arokiasamy et al         | China, Ghana, India, Mexico, South Africa, Russia | Prevalence and determinants                                                       | Cross-sectional        | WHO SAGE              | Probabilistic            | 2007–2010  | 42,236      | ≥18               | Self-report+medication use+SBD | 9          | ≥2                     | 21.9                  | Good            |                             |
| Aye et al                | Myanmar                                | Prevalence, patterns and determinants                                             | Cross-sectional        | Household survey      | Probabilistic            | 2016       | 4,859       | ≥60               | Self-report     | 14         | ≥2                     | 33.2                  | Good            |                             |
| Bao et al                | Cuba, Dominican Republic, Puerto Rico, Peru, Venezuela, Mexico, China              | Prevalence                                                                      | Population based Cohort | Household survey      | NR                       | 2003–2010  | 15,027      | ≥65               | Self-report+physical examination | 15         | ≥2                     | Ranges from 31.0 to 68.0; China (31.0); Peru (49.0); Cuba (58.0); Venezuela (60.0); Mexico (60.0); Dominican Republic (68.0) | Fair            |                             |
| Chen et al               | China                                  | Prevalence and determinants                                                       | Cross-sectional        | CHARLS                | Probabilistic            | 2011–2012  | 3,737       | ≥45               | Self-report     | 16         | ≥2                     | 46.0                  | GOOD           |                             |
| Christian et al          | China, Ghana, India, Mexico, South Africa, Russia                                | Prevalence                                                                      | Cross-sectional        | WHO SAGE              | Probabilistic            | 2007–2010  | 42,487      | ≥50               | Self-report     | 8          | ≥2                     | Ranges from 8.8 to 50.2; Ghana (8.8), India (16), China (20.3), Mexico (20.8), South Africa (20.8%), Russia (50.2) | Good            |                             |
| Author            | Country/region                  | Inclusion criteria                          | Study design                  | Survey/source of data | Sampling characteristics | Field year | Sample size | Age range (years) | Data collection                          | No of NCDs | Multi-morbidity definition | Prevalence (%) | Quality of included studies |
|-------------------|--------------------------------|---------------------------------------------|-------------------------------|-----------------------|--------------------------|------------|-------------|-------------------|------------------------------------------|------------|--------------------------|----------------|--------------------------|
| Ebrahimoghli et al<sup>12</sup> | Iran                           | Prevalence                                | Retrospective cohort study    | IHIO                  | All beneficiaries of IHIO | 2013–2016  | 481 733     | ≥18                | ATC CS                                    | 18         | ≥2                       | 21.5           | Fair                     |
| Garin et al<sup>23</sup>  | China, Ghana, India, Mexico, South Africa, Russia | Prevalence and determinants and patterns | Cross-sectional               | WHO SAGE              | Probabilistic            | 2007–2010  | China (131,577), Ghana (43,058), India (66,560), Mexico (23,081), South Africa (37,683), Russia (3836) | 12         | ≥2                       | Ranges from 45.1 to 72.0: China (45.1), Ghana (48.3), India (67.9), Mexico (64.0), South Africa (63.4), Russia (72.0) | Good       |
| Hen et al<sup>33</sup>  | Burkina Faso                   | Prevalence and determinants                | Cross-sectional               | Household survey      | Probabilistic            | 2012       | 389         | ≥60                | Self-report†clinical examination†medical record review | 16         | ≥2                       | 65.0           | Good                     |
| Jawed et al<sup>36</sup> | Pakistan                       | Prevalence and determinants                | Cross-sectional               | The IMPACT study      | Probabilistic            | 2015–2016  | 1500        | ≥30                | Self-report†medication use†SBD            | 16         | ≥2                       | 48.6           | Good                     |
| Jerliu et al<sup>46</sup> | Kosovo                         | Prevalence and determinants                | Cross-sectional               | Community survey      | Probabilistic            | 2011       | 2265        | ≥65                | Self-report†SBD                          | 7          | ≥2                       | 45.0           | Good                     |
| Jovic et al<sup>42</sup> | Serbian                        | Prevalence, patterns and determinants      | Cross-sectional               | NHS-Serbia            | Probabilistic            | 2013       | 131 035     | ≥20                | Self-report†SBD                          | 12         | ≥2                       | 26.9           | Good                     |
| Jankovic et al<sup>43</sup> | Serbian                        | Prevalence, patterns and determinants      | Cross-sectional               | NHS-Serbia            | Probabilistic            | 2013       | 13 765      | ≥20                | Self-report†SBD                          | 13         | ≥2                       | 30.2           | Good                     |
| Khan et al<sup>46</sup>  | Bangladesh                      | Prevalence, patterns and determinants      | Cross-sectional               | Household survey      | Probabilistic            | 2014–2016  | 12 338      | ≥35                | Self-report†medication use†SBD            | 6          | ≥2                       | 8.4            | Good                     |
| Khanam et al<sup>48</sup> | Bangladesh                      | Prevalence and determinants                | Cross-sectional               | HDSS                  | Probabilistic            | 2003–2004  | 452         | ≥60                | Self-report†physical examination†blood test | 9          | ≥2                       | 53.7           | Good                     |
| Kumar et al<sup>47</sup>  | India                          | Prevalence                                | Cross-sectional               | Household survey      | NR                       | 2012–2013  | 58 590      | ≥20                | Self-report†SBD                          | 5          | ≥2                       | 0.7            | Fair                     |
| Kunna et al<sup>51</sup>  | China, Ghana                   | Prevalence and determinants                | Cross-sectional               | WHO SAGE              | Probabilistic            | 2007–2010  | China (11 814); Ghana (4050) | 7          | ≥2                       | China (29.7); Ghana (30.2) | Good       |
| Koyanagi et al<sup>51</sup> | China, Ghana, India, Mexico, South Africa, Russia | Prevalence and determinants              | Cross-sectional               | WHO SAGE              | Probabilistic            | 2007–2011  | 32 715      | ≥50                | Self-report†SBD                          | 10         | ≥2                       | 49.8           | Good                     |
| Lee et al<sup>53</sup>   | China, Ghana, India, Mexico, South Africa, Russia | Prevalence and determinants              | Cross-sectional               | WHO SAGE              | Probabilistic            | 2007–2010  | 39 213      | ≥18                | Self-report†SBD                          | 9          | ≥2                       | Varies from 3.9 in Ghana-33.6 in Russia | Good       |
| Mini and Thankappan<sup>50</sup> | India                          | Prevalence, patterns and determinants      | Cross-sectional               | UNFPA                 | Probabilistic            | 2011       | 9852        | ≥60                | Self-report†SBD                          | 12         | ≥2                       | 30.7           | Good                     |
| Author          | Country/region                        | Inclusion criteria             | Study design          | Survey/source of data | Sampling characteristics | Field year | Sample size | Age range (years) | Data collection | No of NCDs | Multi-morbidity definition | Prevalence (%) | Quality of included studies |
|-----------------|--------------------------------------|---------------------------------|------------------------|-----------------------|--------------------------|------------|-------------|-------------------|----------------|-----------|-----------------------------|----------------|--------------------------|
| Nugraha et al  | Indonesia                            | Prevalence and patterns        | Cross-sectional       | Community survey      | Probabilistic            | 2018       | 427         | ≥60               | Self-report     | 15        | ≥2                          | 60.7            | Good                     |
| Nunes et al     | Brazil                               | Prevalence and patterns        | Cross-sectional       | Household survey      | Probabilistic            | 2008       | 1593        | ≥60               | Self-report     | 17        | ≥2                          | 81.3            | Good                     |
| Nunes et al     | Brazil                               | Prevalence, patterns and        | Cross-sectional       | PNS                   | Probabilistic            | 2013       | 60 202      | ≥18               | Self-report     | 22        | ≥2 or ≥3                    | 22 for ≥2 and 10.2 for ≥3 | Good                     |
| Pati et al      | India                                | Prevalence and determinants    | Cross-sectional       | WHO SAGE              | Probabilistic            | 2007       | 10 973      | ≥18               | Self-report     | 9         | ≥2                          | 8.9             | Good                     |
| Pati et al      | India                                | Prevalence and patterns        | Cross-sectional       | Primary healthcare    | Probabilistic            | 2013       | 1649        | ≥18               | Self-report     | 21        | ≥2                          | 28.3            | Good                     |
| Pengpid and Peltzer | Mekong                             | Prevalence, determinants       | Cross-sectional       | Primary healthcare    | Probabilistic            | 2013       | 6 236       | ≥18               | Self-report     | 21        | ≥2                          | 72.6 (28.6 had 2, 22.4 had 3 and 21.6 had ≥24 chronic conditions) | Good                     |
| Phaswana-        | South Africa                         | Prevalence                      | Cross-sectional       | WHO SAGE              | Probabilistic            | 2008       | 3 840       | ≥50               | Self-report     | 8         | ≥2                          | 22.5            | Good                     |
| Matuya et al    | Malawi                               | Prevalence and patterns        | Cross-sectional       | Household survey      | No sampling: all adults  | 2013–2016  | 28 891      | ≥18               | Self-report+medication use+patient health record+clinical test | 3         | ≥2                          | 4.0             | Good                     |
| Price et al     | Northern Jordan                      | Prevalence, patterns and       | Cross-sectional       | UNHCR                 | Probabilistic            | 2016       | 8 041       | ≥18               | Self-report     | 6         | ≥2                          | 44.7            | Good                     |
| Rzewuska et al  | Brazil                               | Prevalence, patterns and       | Cross-sectional       | PNS                   | Probabilistic            | 2013       | 60 202      | ≥18               | Self-report+SBD | 14        | ≥2                          | 24.2            | Good                     |
| Sum et al       | China, Ghana, India, Mexico, South    | Prevalence and patterns        | Cross-sectional       | WHO SAGE              | Probabilistic            | 2007–2010  | 41 557      | ≥18               | Self-report+SBD | 9         | ≥2                          | 18.9            | Good                     |
| Vadrevu         | India                                | Prevalence and patterns        | Cross-sectional       | Household survey      | Probabilistic            | 2009       | 815         | ≥40               | Self-report+SBD | 6         | ≥2                          | 44.1            | Good                     |
| Vancampfort et al | China, Ghana, India, Mexico, South   | Prevalence                      | Cross-sectional       | WHO SAGE              | Probabilistic            | 2007–2010  | 34 129      | ≥50               | Self-report+SBD | 11        | ≥2                          | 45.5            | Good                     |
| Vancampfort et al | China, Ghana, India, Mexico, South   | Prevalence                      | Cross-sectional       | WHO SAGE              | Probabilistic            | 2007–2010  | 34 129      | ≥50               | Self-report+SBD | 11        | ≥2                          | 45.5            | Good                     |

Continued
| Author | Country/region | Study design | Sample size | Quality of included studies | Multi-morbidity definition | No. of NCDs | Age range (years) | Data collection | Prevalence and determinants | Inclusion criteria |
|--------|----------------|--------------|-------------|-----------------------------|---------------------------|-------------|------------------|----------------|------------------------|------------------|
| Vancampfort et al | China, Ghana, India, Mexico, South Africa, Russia | Cross-sectional | WHO SAGE | Good | WHO SAGE | 11 | ≥65 | Self-report+SBD | 60.2 | Good |
| Waterhouse et al | Ethiopia | Cross-sectional | WHO SAGE | Good | WHO SAGE | 8 | ≥2 | Self-report+medical | 17.8 | Good |
| Zhou et al | Bangladesh, India, China | Cross-sectional | WHS | Good | WHO SAGE | 9 | ≥2 | Self-report | 17.4 | Good |

Three of the seven studies that assessed the association between multimorbidity of NCDs and physical activity/exercise showed significantly higher odds for those that do little or no physical activity, while the other five showed no significant relationship.

Eight studies examined the relationship between obesity and multimorbidity; five articles found higher a positive association between multimorbidity of NCDs and obesity. Eight studies assessed the association between smoking and multimorbidity, with a study conducted among the elderly from seven Indian urban and rural states reporting a positive association when compared with no NCD (OR: 1.22, 95% CI 1.08 to 1.37).

The patterns of reported NCD multimorbidity are shown in Table 2. Seventeen studies assessed patterns of multimorbidity of NCDs using factor analysis, cluster analysis or descriptive methods. Sixteen out of the 17 studies that reported on patterns of multimorbidity were conducted in LMICs, while only one study was conducted in LIC. Cardiometabolic and cardiorespiratory conditions were the most identified patterns seen in MICs, while cardiovascular, musculoskeletal system diseases and endocrine system diseases were observed in the only one study in LMICs (Table 2). The highest prevalence of cardiometabolic pattern was 70.3% and 60.7% among males and females aged 20–40 years, respectively in MICs. Cardiometabolic, mental and respiratory conditions were present in both men and women in two MICs studies that stratified by sex. Mental disorder was also reported to cluster with other conditions such as cardiometabolic, respiratory and musculoskeletal conditions in studies conducted in Brazil, Serbia and a multi-country study in South Africa, Ghana, Mexico, Russia, Bangladesh, India and China.

**DISCUSSION**

This systematic review with meta-analyses of 39 studies shows that the overall prevalence of NCD multimorbidity in LMICs was 36% with substantial variation between studies. Prevalence differed by region and was observed to be lowest in SSA and highest in LAC region. According to income levels of countries, the prevalence of NCD multimorbidity was higher among upper MICs and as compared with lower-middle income countries. Older age,
female sex, higher income and urban residence increased the odds of having NCD multimorbidity. Cardiometabolic and cardiopulmonary patterns of multimorbidity of NCDs were most common; in addition, multimorbidity of mental disorders with respiratory, musculoskeletal and cardiometabolic conditions was observed.

An important finding from our review is the large variation in the estimates of prevalence of multimorbidity in LMICs. This may be explained by differences in definition/measurement of multimorbidity, study populations, demographics, study settings, self-reported diseases and the number of NCDs included. Similar variation was seen in reviews that focused on South Asia\(^6\) and HICs.\(^62\)\(^63\) A recent scoping review of multimorbidity of chronic NCDs in LMICs also found a wide variation in the prevalence of multimorbidity in LMICs (3.2%–90.5%), depending on population age and the number of conditions considered.\(^6\) Since prevalence estimates depend on the number and the type of chronic conditions included in the measurement of multimorbidity, there might be underreporting due to lack of data or undiagnosed conditions. To date, there is no valid standard measurement of

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**Figure 2** Forest plot of pooled prevalence of multimorbidity in low/middle-income countries.
multimorbidity indicating a need for a uniform definition and a reporting system for multimorbidity, as suggested by the Academy of Medical Science.8

The positive association of multimorbidity with age and female sex is consistent with a study comparing 27 LMICs and 1 HIC using the World Health Survey,16 other reviews on multimorbidity in South Asia and LMICs,6 39 as well as reviews from HICs.62 63 The meta-analyses showed higher odds of multimorbidity among women compared with men. While the association between these factors and multimorbidity is inconsistently reported, the sex-related differences in multimorbidity could be related to context related proxy for behavioural characteristics such as care seeking, that might influence the detection of multimorbidity.8 Women are more likely to have frequent healthcare consultations than men64 65 and might be able to self-report their health status than men. In addition, sex differences in socioeconomic status could also account for the discrepancy observed. Socioeconomic status affects general health functioning, including mental and physical health. Research show that women, in general, have lower socioeconomic status than men, which is in part related to gender inequality and could negatively affect health outcomes.66

In LMICs, people who are well-off in terms of income seem to be most affected by multimorbidity, in contrast with evidence from HICs that shows an inverse association. Few studies from HIC have, however, reported higher prevalence among people who are well-off.9 16 59 Contextually, people who are well-off in LMICs are generally less physically active and consume more fats, salt and processed food which could partly explain the higher prevalence of NCD multimorbidity.62 Further, they might be better educated, informed and have greater access to medical care and are more likely to receive disease diagnosis. The significantly higher odds for multimorbidity of NCDs seen in the urban areas may be due to under-reporting in rural areas as a result of poorer access to healthcare and healthcare insurance.58 In most LMICs, healthcare services are paid out of pocket for every inpatient and outpatient visit.9 People living in rural areas are less likely to have long-term healthcare insurance and also less likely to be provided with adequate healthcare.60 Furthermore, regional differences in lifestyle could also explain higher odds of multimorbidity of NCDs in people living in urban areas as residence in urban areas is associated with unfavourable diets and lower physical activity levels.70 71 This review identified various patterns of NCD multimorbidity across different regions in LMICs. Cardiometabolic and cardiorespiratory patterns of multimorbidity were most common and shared major pathophysiological pathways and common risk factors such as smoking.72 73 partly explaining their clustering together. The frequent co-occurrence of cardiometabolic conditions and mental disorders among studies in LMICs as shown in this review is consistent with findings from HICs62 74 75 and highlights the importance of prevention and management policies addressing environmental and living conditions.76

Current evidence suggests a poorer health-related quality of life, worse clinical outcomes and an increased risk of premature mortality among patients with concurrent physical and mental health conditions than those who have physical conditions alone.77–79 Individuals with concurrent physical and mental health conditions are also found to have challenges with medication adherence, compromised self-management,80 high risk of adverse drug events,81 higher rates of healthcare utilisation. They are however at a risk of receiving suboptimal care for coexisting health conditions, leading to poorer health outcomes and increased mortality.82

### Strength and limitations

A strength of this review is that most of the included studies from the database search were from the WHO Study on global AGing and adult health (SAGE), which ensured standardisation of methods of measurements and data collection. This review provides worldwide prevalence rates and predictors for multimorbidity. The standardised methods and large sample sizes of the underlying studies ensure a high qualitative standard of the report.

A main limitation of this review is that all studies included self-reported measures for data collection of multimorbidity, and very few collected physical or biochemical data. Self-reported disease is fairly accurate, and may be subject to recall and self-declaration bias, under or over reporting of outcome of interest.83 84 This may result in under/over estimation of the true prevalence of multimorbidity. The restriction of inclusion criteria to only studies conducted in English might have also led to studies from other LMICs, especially South America where Spanish dominates, leading to potential bias in the estimates. Generally, studies that assessed determinants of multimorbidity did not take the heterogeneity and clusters of conditions into consideration. The observational studies summarised involved patients with
Table 2 Patterns of multimorbidity reported in included studies

| Pattern       | Study                          | Economy status | Diseases                                                                 | Prevalence % (95% CI) |
|---------------|--------------------------------|----------------|--------------------------------------------------------------------------|-----------------------|
| Cardiometabolic | Garin et al<sup>28</sup> (China) | MIC            | Diabetes, obesity, hypertension, angina, stroke, cataract                 | NR                    |
|               | Garin et al<sup>28</sup> (Ghana, India, Mexico) | MIC            | Diabetes, obesity, hypertension                                           | NR                    |
|               | Garin et al<sup>28</sup> (Russia) | MIC            | Diabetes, obesity, hypertension, angina, stroke, cataract, arthritis, edentulism, depression | NR                    |
|               | Garin et al<sup>28</sup> (South Africa) | MIC            | Diabetes, obesity, hypertension, angina, stroke, arthritis, edentulism     | NR                    |
|               | Jovic et al<sup>42</sup>        | MIC            | Male (age 20–44 years): Cardiometabolic Age 45–64 years: Cardiometabolic Age 65+ years: Cardiometabolic | 70.3, 39.2, 29.5       |
|               |                                |                | Female (Age 20–44 years): Cardiometabolic Age 45–64 years: Cardiometabolic Age 65+ years: Cardiometabolic | 60.7, 53.2, 33.2       |
|               | Khan et al<sup>46</sup>         | MIC            | Hypertension, diabetes, CVD; Hypertension, diabetes, stroke; Hypertension, diabetes, cancer; Hypertension, CVD, stroke; | 0.6, 0.4, 0.0, 0.3     |
|               |                                |                | Hypertension, diabetes, CVD; Hypertension, diabetes, stroke               | 0.3                   |
|               |                                |                | Hypertension, diabetes, CVD, stroke                                       | 0.6                   |
|               | Mini and Thankappan<sup>50</sup> | MIC            | High blood pressure, diabetes                                            | 4.7                   |
|               | Nunes et al<sup>34</sup>        | MIC            | High blood pressure, heart attack, angina, heart failure, stroke, hypercholesterolaemia, diabetes, arthritis/rheumatism | NR                    |
|               | Rehr et al<sup>51</sup>         | MIC            | Diabetes and hypertension; Diabetes, hypertension and CVD; Diabetes, hypertension and CVD; Diabetes, hypertension and thyroid disease | 17.6 (15.9 to 19.5), 8.1 (6.9 to 9.7), 7.1 (5.9 to 8.4), 1.3 (0.9 to 2.0) |
|               |                                |                | Hypertension and CVD                                                      | 1.3                   |
| Cardiovascular | Aye et al<sup>54</sup>          | MIC            | Coronary heart disease, Heart failure                                     | NR                    |
|               | Jovic et al<sup>42</sup>        | MIC            | Male (age 45–64 years): cardiovascular Age >65 years: cardiovascular Female (45–64 years): cardiovascular Age >65 years: cardiovascular | 22.8, 28.7, 29.6, 18.9 |
|               | Rehr et al<sup>51</sup>         | MIC            | Hypertension and CVD                                                      | 7.1 (5.9 to 8.4)      |
|               | Woldesemayat et al<sup>60</sup> | LIC            | Cardiovascular and endocrine system diseases                             | 2.4                   |
| Cardiorespiratory | Aye et al<sup>54</sup>          | MIC            | Asthma, COPD, hypertension, diabetes, stroke                             | NR                    |
|               | Garin et al<sup>28</sup> (China) | MIC            | Angina, asthma, COPD                                                      | NR                    |
|               | Garin et al<sup>28</sup> (Ghana) | MIC            | Angina, asthma, COPD                                                      | NR                    |
|               | Garin et al<sup>28</sup> (India) | MIC            | Angina, asthma, COPD                                                      | NR                    |
|               | Garin et al<sup>28</sup> (Mexico) | MIC            | Angina, asthma, COPD, stroke, depression, arthritis, cataract             | NR                    |
|               | Garin et al<sup>28</sup> (South Africa) | MIC            | Angina, asthma, COPD, stroke, depression, arthritis, cataract             | NR                    |
|               | Rehr et al<sup>51</sup>         | MIC            | Hypertension and chronic respiratory condition                           | 1.3 (0.8 to 1.9)      |
|               | Khan et al<sup>50</sup>         | MIC            | Hypertension, diabetes, COPD                                              | 0.1                   |

Continued
| Pattern                      | Study                     | Economy status | Diseases                                                                 | Prevalence % (95% CI) |
|------------------------------|---------------------------|----------------|---------------------------------------------------------------------------|-----------------------|
| Mental                       | Aye et al<sup>14</sup>    | MIC            | Depression, mental illness                                                NR                    |
| Respiratory                  | Garin et al<sup>28</sup> (Russia) | MIC            | Asthma, COPD, cataract                                                    NR                    |
|                              | Jovic et al<sup>42</sup>  | MIC            | Male (age 45–64): respiratory, Age 65+ years: respiratory                13.7                  |
|                              |                           |                | Female (age 45–64 years): respiratory 16.6                               14.5                  |
|                              | Rzewuska et al<sup>45</sup> | MIC            | Male and female: Asthma, chronic obstructive pulmonary disease             NR                    |
| Musculoskeletal              | Aye et al<sup>14</sup>    | MIC            | Arthritis, osteoporosis                                                   NR                    |
| Ocular+musculoskeletal +cardiorespiratory | Aye et al<sup>14</sup>    | MIC            | Arthritis, COPD, cataract, arthritis, osteoporosis, asthma, COPD, hypertension, diabetes, stroke | NR                    |
|                              | Mini and Thankappan<sup>30</sup> | MIC            | Arthritis, hypertension; Arthritis, cataract                               7.5                    |
|                              | Nunes et al<sup>30</sup>  | MIC            | Hypertension+APD+diabetes, Hypertension+APD+CBA; Hypertension+arthritis+diabetes+CBA; Arthritis+CBA+CLD; Arthritis+CBA+visual impairment | 10.6 to 5.5           |
|                              | Pati et al<sup>39</sup>   | MIC            | Hypertension+visual impairment/CBA/arthritis/diabetes/CBA/deafness | NR                    |
|                              | Sum et al<sup>44</sup>    | MIC            | Arthritis+visual impairment/CBA/diabetes                                  NR                    |
|                              |                           |                | Age 18–49 years: Hypertension+arthritis, Hypertension+angina, Hypertension+CLD, Age 50–64 years: Hypertension+arthritis, Hypertension+angina, Hypertension+CLD, Age >64 years: Hypertension+arthritis, Hypertension+angina, Hypertension+CLD, Hypertension+cataract, Hypertension+cataract | 4.99 4.13 4.99 19.08 17.08 9.79 33.77 29.73 16.44 15.27 |
| Mental+musculoskeletal       | Garin et al<sup>28</sup> (China) | MIC            | Arthritis, depression, stroke, cataract                                    NR                    |
|                              | Garin et al<sup>28</sup> (Ghana) | MIC            | Arthritis, depression                                                     NR                    |
|                              | Garin et al<sup>28</sup> (India) | MIC            | Arthritis, depression, cataract, angina                                    NR                    |
|                              | Jovic et al<sup>42</sup>  | MIC            | Male age ≥65 years: mechanical/mental/metabolic                             25.8                  |
|                              |                           |                | Female age ≥65 years: mechanical/mental/metabolic                           32.3                  |
|                              | Nunes et al<sup>44</sup>  | MIC            | Arthritis/rheumatism, spinal column problem, spinal column problem, asthma/wheezy bronchitis, COPD, work-related muscle-skeletal disorders, depression, bipolar disorder, kidney problem | NR                    |
### Table 2  Continued

| Pattern | Study | Economy status | Diseases | Prevalence % (95% CI) |
|---------|-------|----------------|----------|-----------------------|
| Rzewuska et al<sup>15</sup> | MIC | Male and female: Arthritis or rheumatism, high blood cholesterol, MSK-D related to work, any chronic back problem, chronic renal insufficiency, schizophrenia, bipolar, obsessive-compulsive disorder, depression | NR |
| Sum et al<sup>14</sup> | MIC | Age: 18–49 years: Hypertension+arthritis, Hypertension+angina, Hypertension+CLD, Hypertension+depression | 4.99, 4.13, 1.90, 1.67 |
| Cardio metabolic+musculoskeletal | Mini and Thankappan<sup>80</sup> | MIC | Arthritis, hypertension | 7.5 |
| Nunes et al<sup>80</sup> | MIC | HBP, rheumatism, spinal column disease; HBP, heart problem, spinal column disease; HBP, heart problem, cognitive impairment; HBP, spinal column, falls | 10.6 to 5.7 |
| Pati et al<sup>39</sup> | MIC | Hypertension, arthritis, diabetes/CBA | |
| Woldesemayat et al<sup>80</sup> | LIC | Cardiovascular and musculoskeletal system diseases | 1.2 |
| Cardio metabolic+musculoskeletal +mental | Nunes et al<sup>80</sup> | MIC | HBP, heart problem, cognitive impairment, depression | 10.6 to 5.2 |
| Jovic et al<sup>42</sup> | MIC | Male: Age 45–64 years: Aggregate pattern, such as degenerative joint disease/arthrosis, depression, cardiovascular, kidney disease, stroke and malignancy Female: Aged 20–44 years: non-communicable pattern such as degenerative joint disease/arthrosis, depression, cardiovascular and malignancy | 24.3, 13.3 |
| Jovic et al<sup>42</sup> | MIC | Male: Age 20–44 years: non-communicable pattern such as degenerative joint disease/arthrosis, depression, cardiovascular, respiratory, kidney disease and malignancy | 29.7 |
| Pati et al<sup>39</sup> | MIC | Arthritis+CBA/visual impairment/chronic lung disease | NR |
| Sum et al<sup>14</sup> | MIC | Age 18–49 years: Hypertension+arthritis, Hypertension+angina, Hypertension+CLD, Hypertension+depression | 4.99, 4.13, 1.90, 1.67 |
| | | Age 50–64 years: Hypertension+arthritis, Hypertension+angina, Hypertension+CLD | 19.08, 17.08, 9.79 |

APD, acid peptic disease; CBA, chronic back pain; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; CRD, cardiorespiratory disease; CVD, cardiovascular disease; LIC, low-income country; MIC, middle-income country; MSK-D, musculoskeletal disorder.
varied characteristics and from a wide range of settings contributing to substantial heterogeneity, which could affect the reliability of the findings. The use of cross-sectional design in almost all studies limits the ability to assess the outcome over a longer period and therefore makes it impossible to draw a causal relationship between the various determinants and multimorbidity. In the absence of intervention studies, the meta-analysis of the observational studies provides insight into the direction and strength of the association between the various risk factors and NCD multimorbidity. We did not include MeSH terms related to metabolic diseases such as obesity/overweight, metabolic syndrome and osteoarthritis mainly because they are risk factors of major NCDs. We believe, however, that our search strategy was able to cover these risk factors since most of the major NCDs are assessed together with these in most multimorbidity studies.

Implications of findings

The rising burden of multimorbidity in LMICs indicates the urgent need to strengthen the healthcare system to accommodate for the diagnosis and management of multiple chronic conditions. Available evidence shows that patients with multimorbidity have significantly higher outpatient and inpatient visits, resulting in higher out-of-pocket expenditure. Increased healthcare utilisation among patients with multimorbidity poses challenges to the patients, health providers and the healthcare system.

Evidence from HIC shows diverse challenges when dealing with patients with multimorbidity, including the complexity of multiple guidelines which focus on the management of single conditions and challenges in delivering patient-centred care. This emphasises the need to develop context-specific guidelines on how to diagnose and deal with multiple chronic conditions and to ensure better health service provision, health management and resource deployment to manage the increasing number of people with multimorbidity. Exploring the economic burden of multimorbidity across different settings and populations in LMICs will be crucial in informing policy decisions about service provision and resource allocation.

Despite the clear rise of multimorbidity in LMICs, there is a challenge in explaining the factors behind this rising burden given inconsistencies in findings. This is partly due to the lack of longitudinal studies providing strong evidence on the determinants and the differences in patterns of multimorbidity among different age groups as well as factors that influence variation in clusters of multimorbidity. The acceptance of a standard definition of multimorbidity will provide more clarity on the burden and epidemiology of multimorbidity.

CONCLUSION

In conclusion, this review shows a high burden of multimorbidity in LMICs, especially among women, the people who are well-off, and people residing in urban areas, with cardiometabolic and cardiorespiratory profiles being the most prevalent patterns of multimorbidity. There are however major gaps in epidemiological research on this topic, including the need for longitudinal data to access the true direction of the multimorbidity and its determinants, to establish causation and to identify how trends and patterns change over time.
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