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Prevalence of multimorbidity in community settings: A systematic review and meta-analysis of observational studies

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Abstract

Background: With ageing world populations, multimorbidity (presence of two or more chronic diseases in the same individual) becomes a major concern in public health. Although multimorbidity is associated with age, its prevalence varies. This systematic review aimed to summarise and meta-analyse the prevalence of multimorbidity in high, low- and middle-income countries (HICs and LMICs).

Methods: Studies were identified by searching electronic databases (Medline, Embase, PsycINFO, Global Health, Web of Science and Cochrane Library). The term 'multimorbidity' and its various spellings were used, alongside 'prevalence' or 'epidemiology'. Quality assessment employed the Newcastle-Ottawa scale. Overall and stratified analyses according to multimorbidity operational definitions, HICs/LMICs status, gender and age were performed. A random-effects model for meta-analysis was used.

Results: Seventy community-based studies (conducted in 18 HICs and 31 LMICs) were included in the final sample. Sample sizes ranged from 264 to 162,464. The overall pooled prevalence of multimorbidity was 33.1% (95% confidence interval (CI): 30.0–36.3%). There was a considerable difference in the pooled estimates between HICs and LMICs, with prevalence being 37.9% (95% CI: 32.5–43.4%) and 29.7% (26.4–33.0%), respectively. Heterogeneity across studies was high for both overall and stratified analyses (I^2 > 99%). A sensitivity analysis showed that none of the reviewed studies skewed the overall pooled estimates.

Conclusion: A large proportion of the global population, especially those aged 65+, is affected by multimorbidity. To allow accurate estimations of disease burden, and effective disease management and resources distribution, a standardised operationalisation of multimorbidity is needed.

Keywords
Multimorbidity, prevalence, HICs, LMICs

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Introduction

As the world's populations are ageing rapidly, multimorbidity is becoming a major concern in public health. According to a recent report by the Academy of Medical Science,[1] in most high-income countries (HICs), multimorbidity is considered the norm, not the exception. Multimorbidity also appears to be increasingly prevalent in low- and middle-income countries (LMICs).[1] Patients experiencing multiple chronic conditions often have poorer health

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outcomes, such as declined physical and mental health functioning,[2] higher mortality rates[3] and frailty.[4] Their needs for medical care are also different. Instead of a highly specialised but isolated approach, as used for single disease treatment, multimorbidity patients need a complex and structured care plan.[1,5] This has serious impact on disease management, healthcare utilisation and costs.[6–8] To assess the impact of multimorbidity on public health and to project medical care needs for patients with multimorbidity, an accurate estimation of its prevalence is critical. Yet, the complex nature of multimorbidity poses great difficulties for research into this topic area. This is due partly to inconsistencies in the conceptualisation and definition of multimorbidity. For instance, despite being distinct clinical entities, multimorbidity and comorbidity are still used interchangeably. While the former is defined as the co-occurrence of two or more chronic diseases, the latter is perceived as 'the occurrence of medical conditions additional to an index disease'.[9] The ambiguity in the conceptualisation of multimorbidity leads to a lack of a consensus about its operationalisation. The number of diseases used as cut-off points, disease combination and measure of multimorbidity vary across studies.

Although multimorbidity prevalence and its variations have been examined and summarised in a number of systematic reviews,[10,11] these reviews usually only included studies in HICs. Only one review synthesised evidence on the prevalence and outcomes of multimorbidity in South Asia.[12] Nonetheless, there has not been a review that systematically assessed the variations of multimorbidity prevalence estimates at a global level. Our aims were therefore to (1) summarise the available evidence in the literature on the global prevalence of multimorbidity in the context of community settings, (2) carry out a meta-analysis of the prevalence estimates to provide a pooled estimate and (3) assess how multimorbidity was operationalised across the different studies to examine whether this factor could explain the heterogeneity of the prevalence estimates.

Methods

We conducted a systematic review and meta-analysis (registered on PROSPERO Ref no. CRD42018087435), which followed the PRISMA statement for systematic review and analysis[13] (Online Supplement 1).

Inclusion and exclusion criteria

Eligible studies were original, peer-reviewed articles (published either online or as hard copy, with available abstracts in English). Opinion pieces, conference presentations, books, letters, editorials, dissertations/theses or abstracts were not included. Studies with an index disease (e.g. multimorbidity among HIV-infected individuals) were also not eligible for inclusion, because they were deemed comorbidity studies. Only studies that clearly stated that their participants were community-based adults were considered. In other words, studies that recruited participants from communal establishments, such as hospitals, hospices, nursing homes or prisons, were ineligible. Those that used solely medical records from general practice as data source were also excluded to avoid selection bias. The study designs were restricted to cross-sectional and longitudinal studies. Where the design was longitudinal, only prevalence at baseline was included. Case-control and interventional studies (such as randomised controlled trials) were removed from consideration. There were no further restrictions regarding demographic characteristics of the population under study, for instance, age, sex, or socioeconomic status. Since the outcome of interest was the prevalence of multimorbidity, only studies that reported on this were selected.

Search strategy and study selection

We conducted an online literature search on Medline (Ovid interface), Embase (Ovid interface), PsycINFO (Ovid interface), Global Health (Ovid interface), Web of Science and Cochrane Library electronic databases, from inception up to May 2019. The term 'multimorbidity' and its various spellings (e.g. 'multi-morbidity', 'multimorbidities', 'multi-morbidities', 'multi morbidity', 'multi morbidities', 'multiple morbidities', 'multiple-morbidities') and 'prevalence' or 'epidemiology' were used (Online Supplement 2). We were interested in how multimorbidity was defined so deliberately excluded 'comorbidity' and other synonyms in our search strategy.

The titles and abstracts of all hits returned by the search were screened initially by the first reviewer (HN). The second reviewer (CD) tested a 10% random sample of all references to ensure that eligible studies were not missed out. Studies that satisfied all the eligibility criteria specified above were kept for full-text screening. The full-text screening was done independently by two reviewers (HN and GM). Where there were disagreements, HN and GM discussed to resolve them. AMP was consulted when agreement could not be reached. Disagreements were finally resolved by consensus.

Data extraction and quality assessment

We extracted all potentially eligible studies to EndNote (EndNote X8, Thomson Reuters). Duplicate articles were removed using EndNote X8 auto-deduplication function. Those that were not detected by this function were removed manually during the first screening.

A data extraction sheet was developed, pilot-tested on five randomly selected eligible studies and refined accordingly. We extracted the following information: year of study, study design, country of study, data source, sample size, mean age (men/women), definition of multimorbidity, measure of multimorbidity, prevalence of multimorbidity,

number of diseases, ascertainment of diseases and combination of diseases. In case this information could not be retrieved from the included studies, the corresponding authors of such studies were contacted. Six authors were contacted and three provided the requested information.

We adopted the age-related adjustment method developed by Fortin et al[11] to enable comparisons of age-specific prevalence across studies. If prevalence was reported for an age range, we calculated mean age between the lower and upper limits to present that range.[11] If prevalence was reported for an age range with an upper or lower limit only, we adjusted the age to 10 years above the lower limit and 10 years below the upper limit.[11] Exception of this rule was when the prevalence was reported for age groups such as 65+ or 75+, we used this prevalence without making any age adjustments.

To assess the risk of bias for individual studies, the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies was used. NOS uses eight items, categorised into three domains of potential bias, namely selection (representativeness of the sample, sample size, non-respondents, ascertainment of the exposure), comparability (the subjects in different outcome groups are comparable, based on the study design or analysis; and confounding factors are controlled) and outcome (assessment of outcome and statistical test).[14] A study can be given a maximum of one star for each item within the selection and outcome categories. A maximum of two stars can be given for comparability. Thresholds for converting the NOS to Agency for Healthcare Research and Quality standards (good, fair and poor)[15] are as follows:

- Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Poor quality: 0 or 1 star in selection domain OR 0 star in comparability domain OR 0 or 1 star in outcome/exposure domain.

Eligible studies after full-text screening were assessed (Online Supplement 3). Both good and poor quality studies were retained for sensitivity analysis at a later stage.

Data analysis

Overall and stratified analyses according to multimorbidity operational definitions (2+ and 3+ diseases cut-off points) and HIC–LMIC status were performed. HICs and LMICs were determined using the World Bank classification list of economies.[16] Where possible, prevalence of multimorbidity was also stratified by age and gender. Studies that reported multimorbidity prevalence, both standardised and non-standardised, using the 2+ chronic diseases cut-off point as definition, were included in the meta-analysis. To perform the meta-analysis, we used the metaprop command.[17] Multimorbidity prevalence was calculated as the quotient of the number of people with multimorbidity (numerator) and sample size (denominator). Where not available, the numerator was converted from the percentage of people with multimorbidity. Using absolute numbers to generate prevalence estimates enabled the calculation of standard error. Heterogeneity across studies was evaluated using I^2 statistic.[18] It was expected that the I^2 statistic would be high, due to the heterogeneous operationalisation of multimorbidity. Hence, a random-effects model was used. Finally, a sensitivity analysis was carried out to test the influence of a single study in meta-analysis estimation of the pooled prevalence. All quantitative synthesis of this review was done in STATA version 15.[19]

Results

Overview of studies

We identified 4360 studies from the initial search. After removing duplicates and records that were not original articles, there were 274 studies eligible for full-text screening. Two hundred four studies were further excluded after full-text screening, leaving 70 for final qualitative and quantitative synthesis. The PRISMA flow diagram in Figure 1 shows the exact process of studies selection.

Study quality and characteristics

Based on the NOS data quality assessment system, 63 studies were rated good quality (with a score of 6 or 7), 2 studies were rated fair quality (with a score of 5) and 5 studies were rated poor quality (with a score of 2 or 4). Those deemed poor quality were so because they omitted information about the representativeness of their data, sampling strategy or response rates (see Online Supplement 3). The total number of participants across 70 studies was 1,180,111 (men: 47.5%, women: 52.5%), with sample size ranging from 264 to 162,464. The mean age varied between 36 years and 75 years old. Thirty-seven studies were conducted in HICs (5 in Australia,[20–24] 4 in Canada,[25–28] 4 in Spain,[29–32] 3 in Germany,[33–35] 3 in Portugal,[36–38] 3 in the United Kingdom,[39–41] 3 in Hong Kong,[42–44] 2 in Singapore,[45,46] 2 in the United States[47,48] and 1 each in Cyprus,[49] Czech Republic,[29] Denmark,[50] Estonia,[29] Finland,[30] France,[51] Hungary,[29] Latvia,[29] Poland,[30] Ireland,[52] South Korea,[53] the Netherlands,[54] Sweden[55] and Switzerland[56]) and 35 in LMICs (9 in China,[30,57–64] 8 in India,[30,65–71] 10 in Brazil,[29,72–80] 3 in South Africa,[29,30,81] 2 in Ghana,[29,30] 2 in Pakistan,[29,71] 2 in Bangladesh,[29,82] 2 in Burkina Faso,[29,83] and 1 each in Bosnia and Herzegovina,[29] Colombia,[84] Dominican Republic,[29] Egypt,[85] Georgia,[29] Iran,[86] Kazakhstan,[29] Kenya,[29] Kosovo,[87] Laos,[29] Malaysia,[29] Mauritius,[29] Mexico,[30] Morocco,[29] Myanmar,[29] Namibia,[29] Nepal,[29] Paraguay,[29] the Philippines,[29] Russia,[30] Serbia,[88] Sri

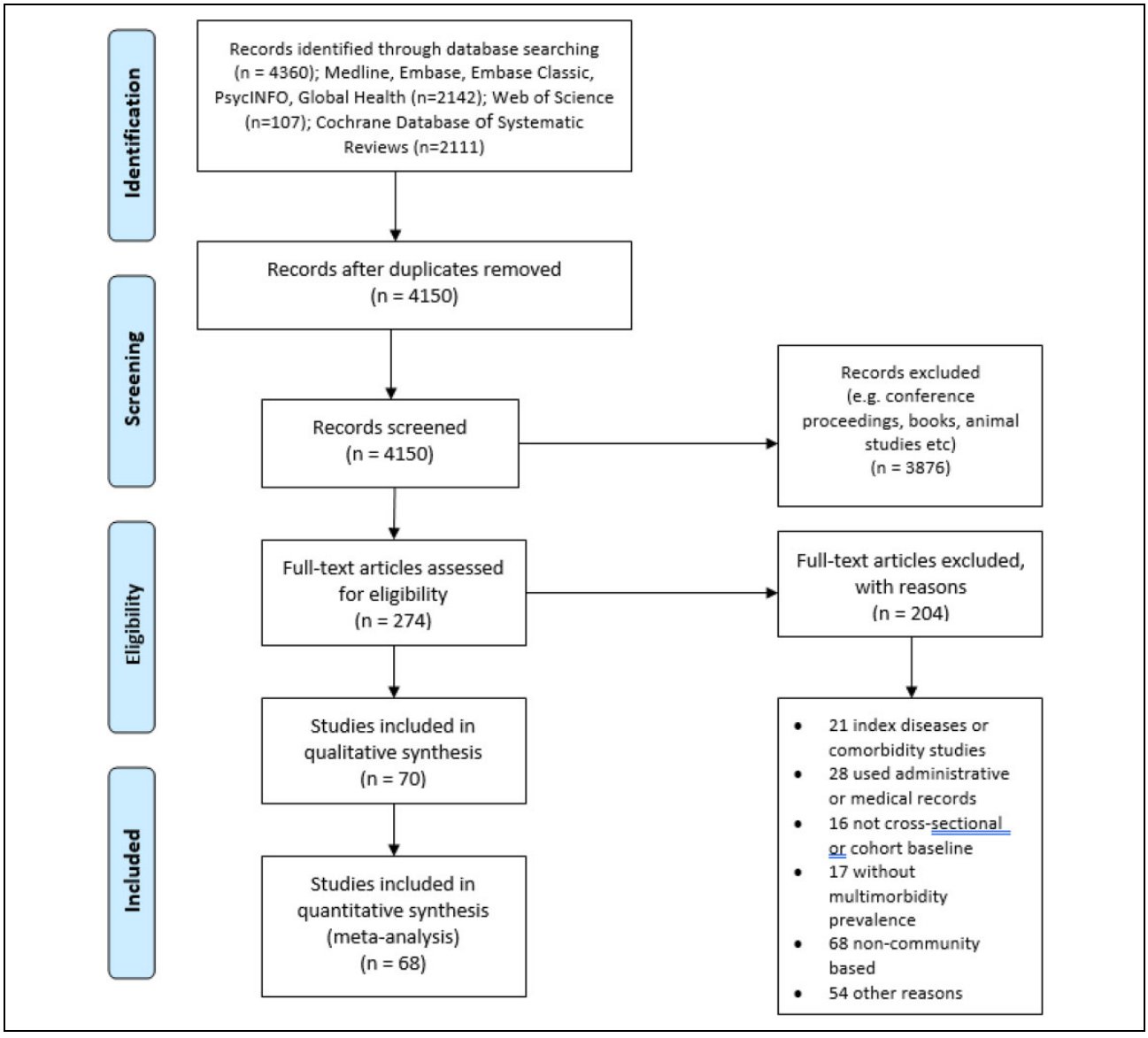

Figure 1. PRISMA flow diagram of studies selection.

Lanka,[29] Ukraine,[29] Uruguay[29] and Vietnam[89]) over a period of 25 years, from 1992 to 2017. Most of them (63 studies) were cross-sectional design, and seven[21,23,39,43,54,57,60] had a longitudinal design, from which we used data from the baseline assessment. Only 5 out of 70[22,47,75,76,80] studies focused solely on subgroups of either men or women. The number of diseases included in eligible studies ranged from 4 to 40 (with hypertension, diabetes, arthritis and stroke being four most frequent conditions). Disease count was the most common measure of multimorbidity, based on self-reported data. Details of studies' characteristics are provided in Table 1.

Prevalence of multimorbidity

Among 37 nationally representative studies in HICs, one conducted in Hong Kong reported the lowest prevalence (3.5%)[43] while another conducted in Russia reported the highest prevalence (70%).[30] Of those that were conducted in LMICs, one study which used data from a household survey in 26 villages in India reported the lowest multimorbidity prevalence (1%).[68] Another study with data derived from the Confucius Hometown Project in China, on the contrary, reported the highest prevalence estimate (90%).[64]

In addition to the common cut-off point of 2+ chronic diseases (2+MM) used in 68 studies, 20 studies also investigated the prevalence estimate when multimorbidity was defined as 'the co-occurrence of three or more chronic diseases'. As the number of diseases included in the definition increased, the prevalence decreased (Table 2). The biggest difference was observed in Khanam et al.'s study,[82] where the prevalence of 3+ morbidities (3+MM) was

Table 1. Characteristics of included studies.[a]

Study (country of study)	Data collection period	Data source	Sample size	Age	Gender (% men)	Prevalence (%) (95% CI)
Afshar 2015 (28 countries)	2003	WHO World Health Survey	125404	18+	48.5	7.8 (6.5–9.1)
Agborsangaya 2013 (Canada)	2012	Health Quality Council of Alberta (HQCA) 2012 Patient Experience Survey	4803	18+	44.2	36.1 (34.7–37.3)
Alaba 2013 (South Africa)	2008	South Africa National Income Dynamic Survey (SA-NIDS)	11638	18+	39.0	4.0 (3.6–4.4)
Alimohammadian 2018 (Iran)	2004–2008	Golestan Cohort Study (GCS)	49946	40–75	42.4	19.4 (19.1–19.8)
Amaral 2018 (Brazil)	2010	Population-based study	264	60–102	39.0	66.3 (60.4–71.7)
Araujo 2018 (Brazil)	2015	Population-based study	4001	60+	47.2	29.0 (27.6–30.5)
Banjare 2014 (India)	2011–2012	Cross-sectional survey	310	60+	49.4	56.8 (51.2–62.2)
Buttery 2016 (Germany)	1997–1999	German National Health Interview and Examination Survey 1998 (GNHIES98)	2884	50–79	47.6	M: 36.1 (33.6–38.7) F: 40.5 (38.1–43.0)
Camargo-Casas 2018 (Colombia)	2012	The SABE-B study	2000	60+	36.6	40.4 (38.3–42.6)
Chen 2018 (China)	2011	China Health and Retirement Longitudinal Study (CHARLS)	3737	45+	51.9	45.5 (41.4–49.7)
Cheung 2018 (Hong Kong)	2016–2017	Jockey Club Community eHealth Care project	2618	60+	47.5	41.8 (39.9–43.7)
de Carvalho 2017 (Brazil)	2013	National Health Survey	60202	18+	N/A	23.6 (22.9–24.3)
de Souza Santos Machado 2012 (Brazil)	2005	Population-based study	377	40–65	Women only	39.3 (34.5–44.3)
de Souza Santos Machado 2013 (Brazil)	2011	Population-based study	622	50+	Women only	58.2 (54.3–62.0)
Dhawalni 2016 (England)	2002–2003	English Longitudinal Study of Ageing (ELSA)	11212	50+	46.4	31.7 (30.9–32.6)
El Lawindi 2019 (Egypt)	2016–2017	Community-based study	2317	18–85	54.9	19.6 (18.0–21.3)
Fuchs 2012 (Germany)	2008–2009	German Health Update (GEDA)	21262	18–100	48.5	M: 36.3 (35.4–37.2) F: 43.9 (43.0–44.8)
Garin 2016 (9 countries)	2008–2012	WHO study on Global AGEing and Adult Health (SAGE) and the Collaborative Research on Ageing in Europe (COURAGE) survey	41909	50+	46.5	62.7 (55.2–70.1)
Ge 2018 (Singapore)	2015–2016	The Population Health Index Survey	1940	21+	44.3	36.9 (34.7–39.0)
Gu 2017 (China)	2013	Cluster random sampling survey	2452	60–93	51.5	49.4 (47.4–51.4)
Hameed 2015 (India)	2013	Community-based study	375	60+	57.9	79.4 (75.1–83.3)
Hien 2014 (Burkina Farso)	2012	Cluster random sampling survey	389	60+	55.3	65.0 (59.9–69.4)
Humphreys 2018 (UK)	2007–2008	The Hertfordshire Cohort study	2299	64–68	51.0	43.4 (41.4–45.5)
Islam 2014 (Australia)	2009	Stratified random sampling survey	4574	50+	N/A	52.0 (50.5–53.4)
Jankovic 2018 (Serbia)	2013	2013 Serbian National Health Survey	13765	20+	46.0	30.2 (29.4–30.9)
Jerliu 2013 (Kosovo)	2011	Nationwide cross-sectional study	1890	65+	50.2	51.1 (48.8–53.3)
Johnston 2019 (UK)	2001	The Aberdeen Children of the 1950s (ACONF)	7184	50+	47.7	5.4 (4.9–6.0)

(continued)

Table 1. (continued)

Study (country of study)	Data collection period	Data source	Sample size	Age	Gender (% men)	Prevalence (%) (95% CI)
Khanam 2011 (Bangladesh)	2003–2004	Poverty and Health in Ageing study	452	60–92	45.1	53.7 (49.2–58.3)
Kiliari 2014 (Cyprus)	2008	Nationally based survey	465	N/A	43.2	28.5 (24.7–32.9)
Kirchberger 2012 (Germany)	2008–2009	KORA-AGE study	4127	65–94	48.8	58.6 (50.7–60.2)
Kshipra 2018 (India)	2012–2013	Cross-sectional study	400	50+	N/A	31.0 (26.7–35.7)
Kumar 2015 (India)	2012–2013	Household survey	55091	N/A	52.3	0.7 (0.6–0.7)
Lai 2019 (Hong Kong)	1999	Thematic Household Survey (THS)	17229	35+	49.5	3.5 (3.2–3.8)
Laires 2019 (Portugal)	2014	The Portuguese National Health Interview Survey (Inquerito Nacional de Saude, INS)	15196	25–79	44.0	43.9 (43.1–44.7)
Lalitha 2016 (India)	2009	Household survey	815	40+	51.3	44.1 (40.6–47.5)
Lang 2015 (US)	2012–2013	EuroQol 5 dimensions (EQ-5D) study	3058	40–64	Women only	30.6 (29.0–32.3)
Larsen 2017 (Denmark)	2013	Danish National Health Survey	162283	16+	49.0	39.7 (39.4–39.9)
Le Cossec 2016 (France)	2008	Disability Healthcare Household Section Survey (HSM – Enquete Handicap Sante - Menages)	11089	55+	45.1	M: 18.7 (17.6–19.9) F: 15.2 (14.3–16.1)
Li 2019 (China)	2017	Community-based survey	4833	60+	45.5	16.1 (15.1–17.1)
Loprinzi 2015 (US)	2005–2006	2005–2006 National Health and Nutrition Examination Survey (NHANES)	2048	20+	50.9	58.4 (55.3–61.5)
Loza 2009 (Spain)	1999–2000	EPISER study	2192	N/A	N/A	30.0 (25.0–34.0)
Lujic 2017 (Australia)	2005–2009	45 and up study	90352	45+	44.3	37.4 (37.1–37.7)
Maregoni 2016 (Sweden)	2001–2004	Swedish National Study on Ageing and Care in Kungsholmen (SNAC-K)	3155	60+	35.7	52.4 (50.6–54.2)
Mini 2017 (India)	2011	UNFPA funded national survey	9852	60+	47.0	30.7 (29.8–31.6)
Ninh 2015 (Vietnam)	2010	Population-based study	2400	60+	34.8	41.6 (39.5–43.8)
Noguchi 2016 (Australia)	2005–2007	Concord Health and Ageing in Men Project (CHAMP)	1705	70–99	100.0	69.3 (67.1–71.5)
Nunes 2016 (Brazil)	2012	Population-based cross-sectional study	2927	20+	41.1	29.1 (27.1–31.1)
Nunes 2019 (Brazil)	2015–2016	The Brazilian Longitudinal Study of Ageing (ELSI-Brazil)	9412	50+	46.0	67.8 (65.6–69.9)
Nunes 2015 (Brazil)	2008	Population-based survey	1593	60+	37.2	81.3 (79.3–83.3)
Pache 2015 (Switzerland)	2003–2006	Cohorte Lausannoise (CoLaus) study	3714	35–75	47.0	34.8 (33.3–36.4)
Park 2018 (Korea)	2013–2014	The sixth Korean National Health and Nutritional Examination Survey (KNHANES)	5996	50+	46.6	26.8 (25.7–27.9)
Picco 2016 (Singapore)	2012–2013	Well-being of the Singapore Elderly (WiSE) study	2565	50+	N/A	55.4 (53.4–57.3)
Ramond-Roquin 2016 (Canada)	2010	PRECISE study	1710	18+	48.3	63.8 (61.5–6.1)
Roberts 2015 (Canada)	2011–2012	Canadian Community Health Survey (CCHS)	105416	25–75	40.5	12.9 (12.6–13.2)
Rodrigues 2018 (Portugal)	2013–2015	EpiDoc 2 study	2393	65+	44.2	67.9 (66.0–9.7)

(continued)

Table 1. (continued)

Study (country of study)	Data collection period	Data source	Sample size	Age	Gender (% men)	Prevalence (%) (95% CI)
Romana 2019 (Portugal)	2015	Inquerito Nacional de Saude com Exame Fisico (INSEF)	4911	25–74	47.5	38.4 (37.0–39.8)
Ruel 2014 (Australia)	2000–2002	North West Adelaide longitudinal Health Study (NWAHS)	1854	20+	44.1	32.0 (30.0–4.0)
Ruel 2014 (China)	2002	Jiangsu longitudinal Nutrition Study (JIN)	1020	18+	48.0	14.0 (12.0–16.3)
Ryan 2018 (Ireland)	2010	The Irish Longitudinal Study on Ageing (TILDA)	4823	50+	N/A	53.7 (52.3–55.1)
Sakib 2019 (Canada)	2015	The Canadian Longitudinal Study of Ageing (CLSA)	29841	45–64	49.4	39.6 (38.4–40.7)
Singh 2019 (India and Pakistan)	2010–2011	The Cardiometabolic Risk Reduction in South Asia Surveillance Study (CARRS Surveillance Study)	16287	20+	47.3	9.4 (8.7–10.1)
Su 2016 (China)	2013	Multistage cluster study	2058	80+	42.1	49.2 (47.0–51.3)
Timmermans 2019 (the Netherlands)	1992–1993	The Longitudinal Ageing Study Amsterdam (LASA)	2199	64–84	44.9	43.6 (41.6–45.7)
Valadares 2015 (Brazil)	2012–2013	Cross-sectional study	736	45–60	Women only	53.0 (49.4–56.6)
Violan 2013 (Spain)	2006	Health Survey for Catalonia database 2006	15926	15+	49.5	59.6 (58.8–60.4)
Wang 2014 (China)	2011	Cross-sectional community household survey	162464	All	51.4	11.1 (10.6–11.6)
Wang 2017 (Australia)	2007	2007 Australian National Survey of Mental Health and Wellbeing	8841	16–85	49.7	28.7 (27.8–9.7)
Wang 2015 (China)	2010–2011	Confucious Hometown Aging Project (CHAP)	1480	60+	40.6	90.5 (88.9–91.9)
Wang 2015 (China)	2012	Jilin Provincial chronic Disease Survey	21435	18–79	N/A	24.7 (24.1–25.4)
Wong 2008 (Hong Kong, China)	N/A	Cross-sectional study	3394	65+	56.0	68.0 (66.4–9.5)

M: male; F: female; CI: confidence interval.

[a]Multimorbidity was defined as the presence of two or more chronic diseases in the same individual; 95% CI as reported in original studies was presented in Table 1. Where this was not available, we used the 95% CI generated by STATA for the meta-analysis. For studies that investigated multimorbidity prevalence in several countries, the prevalence presented in Table 1 was the pooled country prevalence estimates.

reported to be 19.5%, which represented a decrease of 34.3 percentage points compared to the prevalence of 2+ morbidities (53.8%). On average, the weighted difference between the prevalence of 2+MM and 3+MM was 12.9 percentage points.

Among 25 studies that explored gender variations, the majority (21 studies) reported a higher prevalence in women than in men. Alaba and Chola,[81] in particular, found that multimorbidity was almost double in females (74% in females vs. 26% in males). The reverse trend was observed in only four studies.[51,65,67,68] Nevertheless, when men were reported to have higher multimorbidity prevalence, the differences in prevalence estimates between the two sexes were relatively small (Online Supplement 4). Figure 2 shows that the prevalence of multimorbidity invariably increased for both men and women as they aged. There was an upward trend, where multimorbidity prevalence was positively associated with age. Of nine studies that reported age–sex specific prevalence, Kirchberger et al.[35] found that the highest prevalence was in the 85+ group (men: 76.3%; women: 88.1%). Although this association was supported by 24 other studies that investigated age-specific prevalence, three studies observed a lower prevalence estimate among the oldest old (80–85 age group). Kiliari et al,[49] in particular, found that after the age of 85, the prevalence of multimorbidity in Cyprus decreased to 33.3% (from 80% in the previous age bracket). The highest prevalence estimate was reported for the 75+ age group in Spain (92.9%).[32] The largest variation, with prevalence of multimorbidity ranging from 16.3% to 87.5%, was around the age of 70.

Table 2. Prevalence of multimorbidity by two or more diseases and three or more diseases cut-off points.

Study	2+ MM (%)	3+ MM (%)	Difference	Sample size
Araujo (2018)	29.0	15.2	13.8	4001
Banjare and Pradhan (2016)	56.8	30.0	26.8	310
Dhawalni (2016)	31.7	11.7	20.0	11212
Garin (2014)	9.7	5.4	4.3	4583
Humphreys (2018)	47.6	21.6	26.0	2299
Khanam (2011)	53.8	19.5	34.3	452
Lang (2015)	17.9	12.7	5.2	3058
Lujic (2017)	37.4	8.7	28.7	90352
Nunes (2016)	29.1	14.3	14.8	2927
Nunes (2019)	67.8	47.1	20.7	9412
Nunes (2015)	81.3	64.0	17.3	1593
Ramond-Roquin (2016)	63.8	48.9	14.9	1710
Roberts (2015)	12.9	3.9	9.0	105416
Ruel (2014)	32.0	9.0	23.0	1854
Su (2016)	49.2	18.5	30.7	2058
Wang (2014)	11.1	6.1	5.0	162464
Wang (2015)	90.5	76.5	14.0	1480
Wang (2015)	24.8	12.0	12.8	21430
Wang (2017)	26.0	10.1	15.9	8820
Wong (2008)	68.0	42.4	25.6	3394
Average difference			18.4	
Weighted average difference			12.9	

2+MM: two or more disease cut-off point; 3+MM: three or more disease cut-off point.

Meta-analysis

Data combined from 106 prevalence estimates (from 68 studies) showed that the overall random-effect pooled prevalence of multimorbidity was 33.1% (95% CI): 30.0–36.3%). There was a considerable difference in the pooled prevalence estimates between HICs (44 estimates) and LMICs (62 estimates). Specifically, the pooled prevalence of multimorbidity among HICs was 37.9% (95% CI: 32.5–43.4%), while the pooled prevalence estimate among LMICs was 29.7% (26.4–33.0%; Figures 3(a) and (b), Online Supplement 5).

However, when standardised prevalence was removed (34 estimates), LMICs' prevalence was found to be higher than that of HICs. This difference, nonetheless, was marginal, with HICs prevalence being 41.3% (95% CI: 35.2–47.4%) and LMICs 43.5% (95% CI: 38.4–48.6%). The overall pooled estimate of non-standardised prevalence rose to 42.4% (95% CI: 38.1–46.6%; Online Supplement 6). Heterogeneity across studies, both before and after adjusting for standardisation, was very high ($I^2 > 99\%$). A sensitivity analysis showed that none of the studies included in our review skewed the overall pooled estimates.

Discussion

This systematic review provides an up-to-date and comprehensive analysis of multimorbidity prevalence at a global level. It shows that prevalence estimates varied substantially according to age, gender and operational definitions of multimorbidity. This was due to wide variations in sample size, characteristics and how prevalence was reported across studies. Nevertheless, the main findings from our review were consistent with those in previous studies and systematic reviews.[10,90] Specifically, our data suggested that multimorbidity increases with age. While the prevalence estimates varied between and within age groups, most studies in our sample indicated that a large proportion (more than 50% in many cases) of individuals over the age of 65 had multimorbidity. Where prevalence estimates by gender were reported, females appeared to have higher multimorbidity prevalence rates than males. This is indicative of an association between sex and multimorbidity (evidence of which was provided in multiple studies[74,86]). Although there was no uniformity in disease combinations and cut-off points, it followed that the higher the cut-off point, the lower the prevalence. This finding supported an observation by Harrison et al.,[91] where it was found that from 44% (when multimorbidity was defined as 2+ diseases), the prevalence reduced to 27% (for 3+ diseases), 15% (for 4+ diseases), 7% (for 5+ diseases) and only 3% (for 6+ diseases). The highest prevalence estimates in our sample were reported in studies that used the 2+MM definition. Harrison et al.[91] also ascertained that the combination of diseases may make multimorbidity prevalence differ significantly. In the existing literature, a range of different combinations have been proposed from a list of 16 chronic diseases[92] to a list of 291 diseases[93] and anything in between.[94] Ferrer et al.[92] argued that an open list of diagnoses should be used, since it gave the highest prevalence estimate. In our sample, the number of diseases

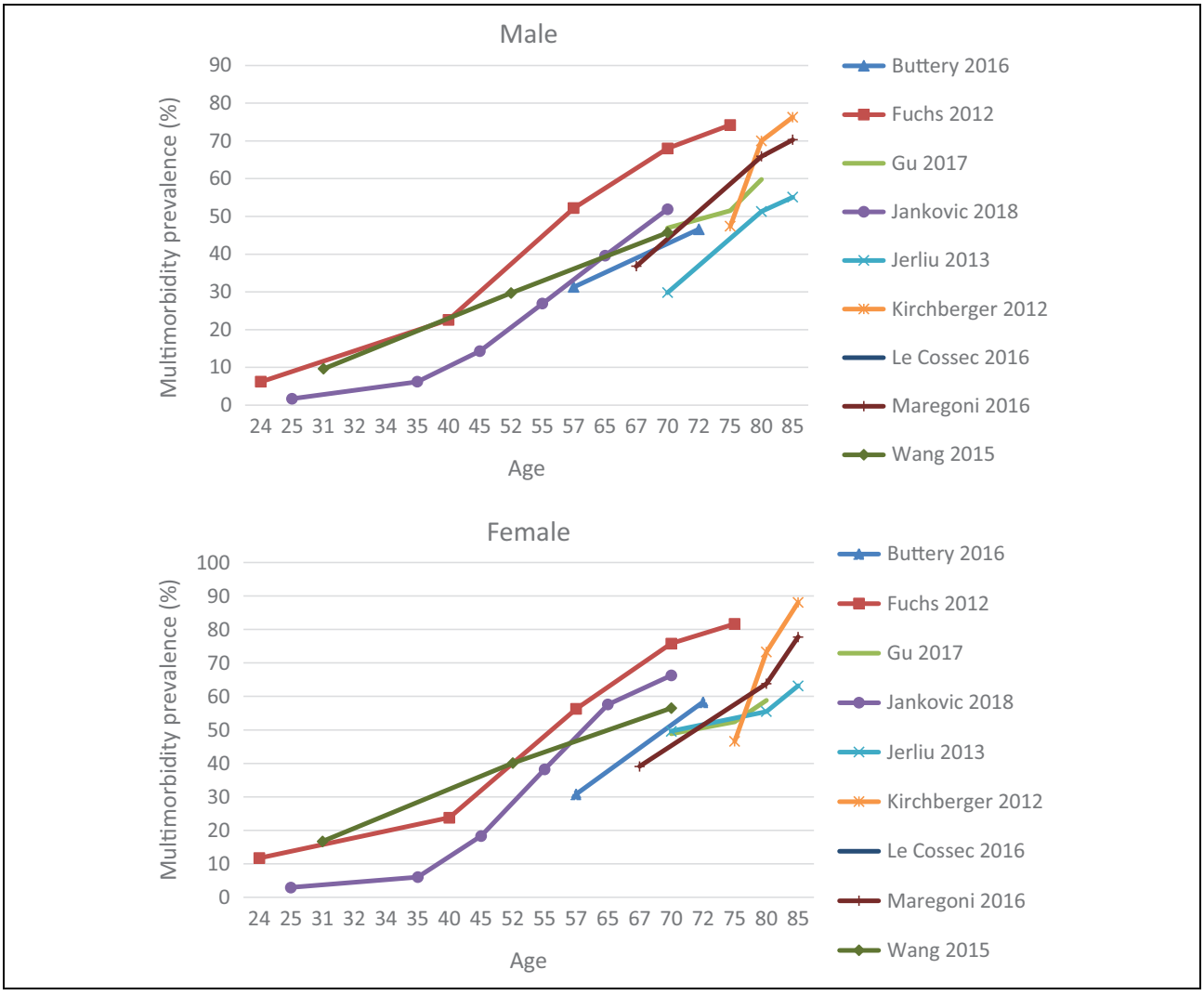

Figure 2. Age- and sex-specific prevalence of multimorbidity.

ranged from 4 to 40, but a similar trend (i.e. the higher the disease number, the higher the prevalence) was not found. The prevalence of multimorbidity estimated using a list of 40 diseases was, in fact, lower than the prevalence estimated using a list of six diseases. The concern perhaps should be shifted to the fact that there were no specific criteria for disease inclusion in these studies. They were often determined by the authors' experience and expertise rather than a standardised list. Most commonly, conditions included were those with the highest prevalence or clinical relevance.[12]

Our quantitative synthesis of the data generated a pooled prevalence estimate of 33.1% (95% CI: 30.0–36.3%), which must be interpreted with some caveats. When both age–sex standardised and non-standardised prevalence estimates were included, stratified analysis suggested that there were differences between HICs and LMICs multimorbidity prevalence. Specifically, multimorbidity prevalence was higher in HICs than LMICs. However, when only non-standardised prevalence estimates were taken into consideration, the prevalence of multimorbidity was shown to be marginally higher in LMICs than in HICs. This reverse trend could be due to the fact that of the 34 standardised prevalence estimates removed, 27 of them were from LMICs. The inclusion of these 27 standardised estimates might have deflated the original pooled prevalence estimated for LMICs. Nonetheless, it was not yet clear whether the geographical variation in multimorbidity prevalence was genuine (i.e. multimorbidity prevalence was higher in HICs than LMICs) or whether it simply reflected the differences in diagnostic and data management systems between HICs and LMICs. Xu et al.[95] suggested that the difference between HICs and LMICs prevalence estimates might also be due to the comparatively limited knowledge on multimorbidity from LMICs compared with HICs, which, consequently, led to fewer publications on multimorbidity prevalence in LMICs.[95]

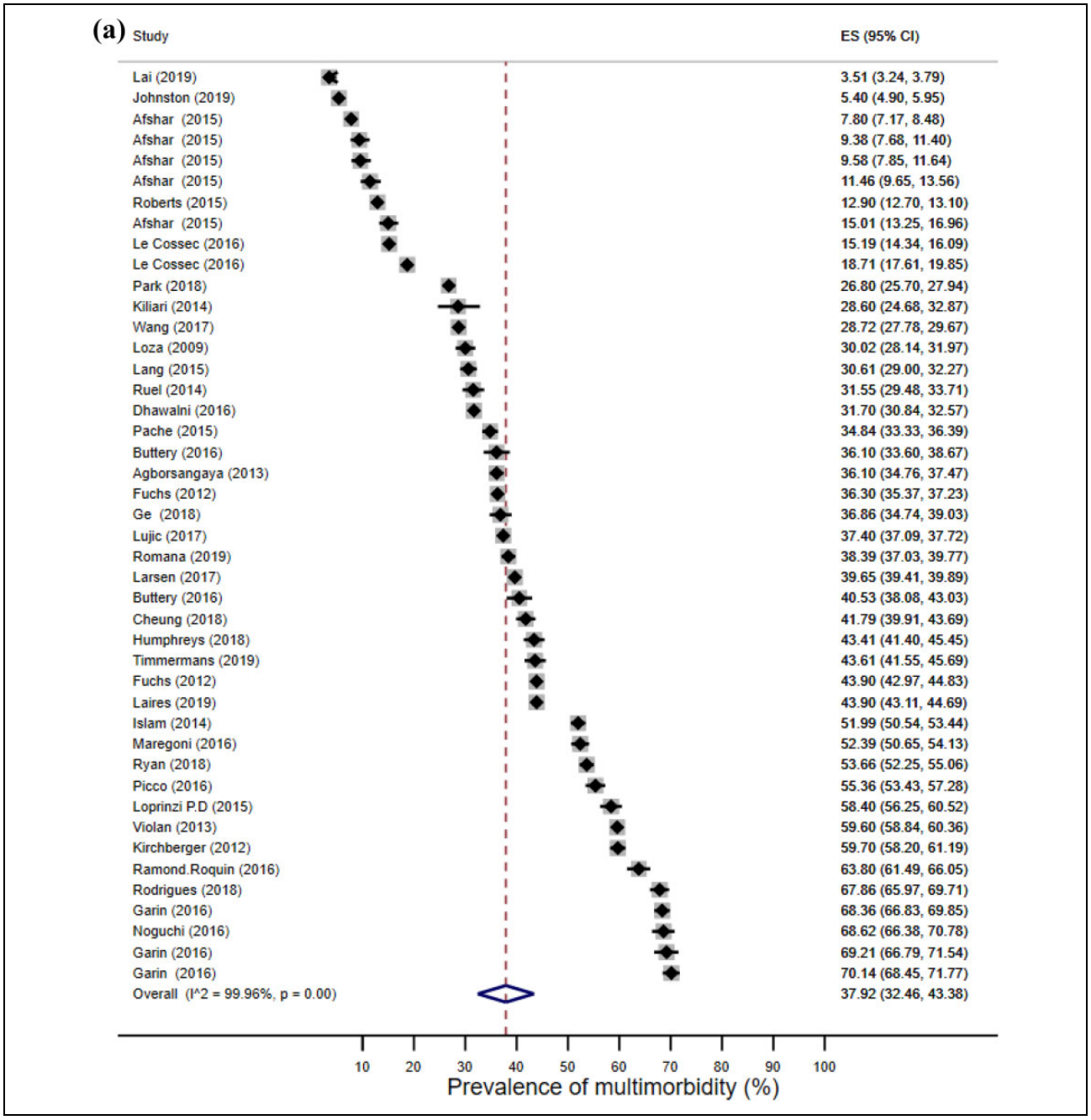

Figure 3. (a) Forest plot showing multimorbidity prevalence in HICs. (b) Forest plot showing multimorbidity prevalence in LMICs. HIC: high-income country; LMIC: low-income country.

The reduction in heterogeneity level as a result of stratified analysis was not considerable (all I^2 statistics were greater than 99%). In this review, attempts have been made to ensure consistency of prevalence estimates by including in the meta-analysis only studies that used 2+MM definition, disease count measure and self-reported data in community settings.

Implications of findings

Inconsistencies in the prevalence of multimorbidity may lead to an over-/underestimation of healthcare costs, hospital admissions, resources distribution and general disease burden. This, subsequently, hinders the effects of health interventions. The need for a uniform method to estimate multimorbidity prevalence, therefore, becomes more and more urgent. Future research on multimorbidity is urged to follow a standardised protocol, using a consistent disease classification system, disease cut-off point and measure of multimorbidity. Since the age structures of HICs and LMICs are different, both crude and standardised prevalence should be reported. Results from prevalence studies should also be stratified by gender and age. Age

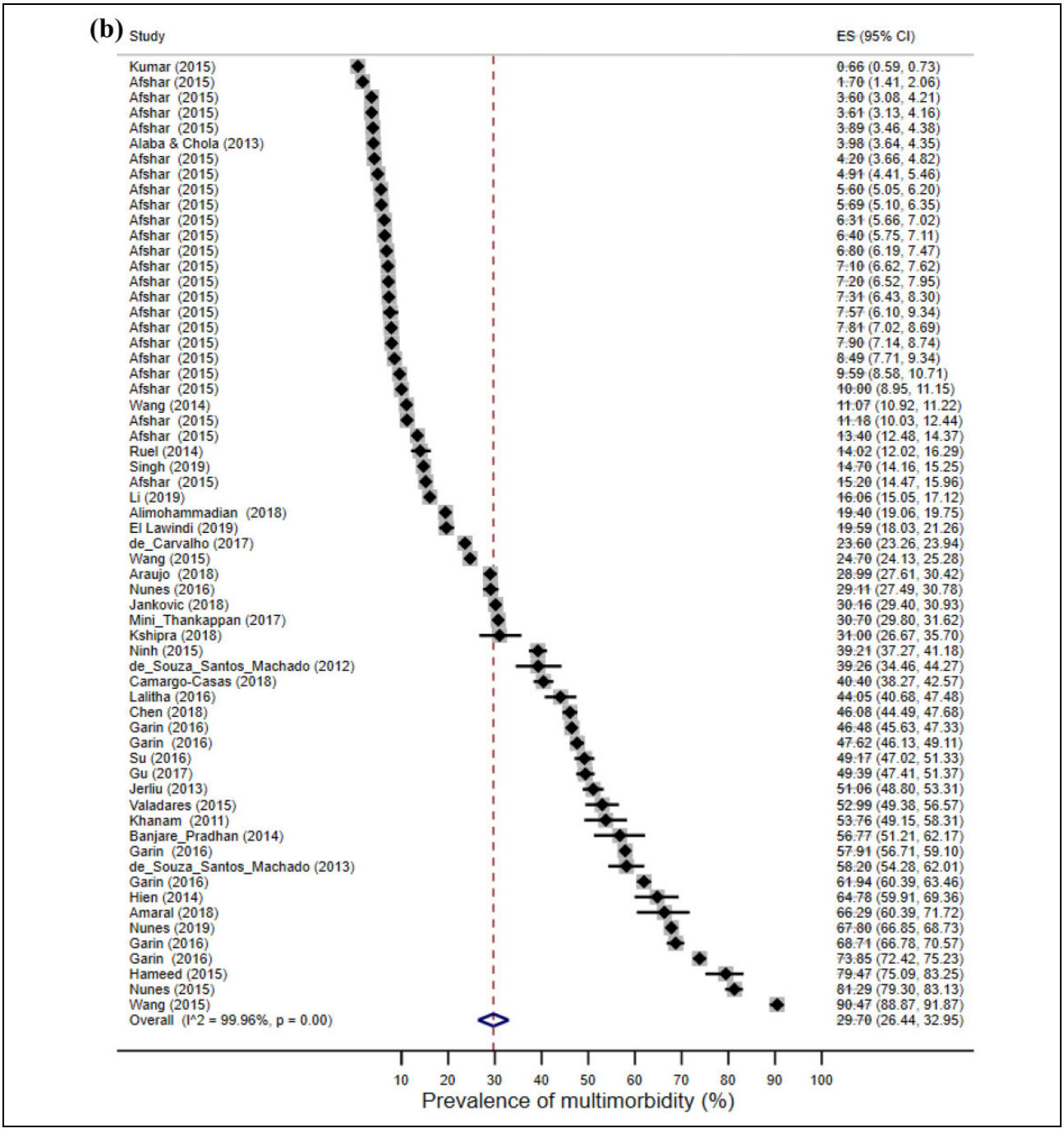

Figure 3. (Continued).

groups, where possible, should be categorised using standardised intervals.

Strengths and limitations

The strengths of this review lie in the fact that our study selection and screening processes were vigorous. Our search strategy and inclusion criteria were comprehensive, which, subsequently led to our review being the largest systematic review on multimorbidity prevalence to date. Results after the initial screening were double-checked by a second reviewer, and the full-text screening that followed was carried out independently. Our data extraction and quality assessment were also cross-checked and very few disagreements arose. The studies included in the analysis were mainly of high quality, all community-based and covered both HICs and LMICs. This enabled the findings to be extrapolated to the global population.

This review, however, was not without limitations. Notwithstanding effort made to ensure eligible studies were

included, there were still possibilities that potentially eligible articles (especially those not in English) were missed out. This might contain studies that focused on two or more chronic conditions without using the term multimorbidity in their titles or abstracts. Most of the studies in our sample reported multimorbidity prevalence based on self-reported data (though some also used medical examinations such as blood test). Results of such studies were therefore prone to response bias (due to misunderstanding of survey questions or recall timeframe). The majority of studies in this review were cross-sectional, which only allowed estimation of multimorbidity at a certain point in time. In addition, the measures of multimorbidity used in these studies were mostly disease count, with only one exception of the functional comorbidity index (FCI) in one study.[56] Disease count and FCI were only 2 of nearly 20 different measures available to date. Fortin et al.[96] reported a much higher prevalence of multimorbidity when using the Cumulative Illness Rating Scale, compared with the prevalence measured by disease count in other studies.[96] A simple count of chronic diseases, despite being the most common method to estimate multimorbidity prevalence, may sometimes be considered too crude a measure.[97] That being said, in a cross-sectional, population-based study conducted in Switzerland by Pache et al.,[56] the prevalence of multimorbidity measured by disease count was found to be higher than that measured by the FCI.[56] The lack of consistency in measuring and reporting the prevalence of multimorbidity in the included studies was a factor that needs to be taken into account when interpreting findings from our analyses. However, as discussed above, given that there is no consensus about multimorbidity, heterogeneity across studies is inevitable.

Finally, for our meta-analysis, we used absolute numbers (i.e. the number of people reporting multimorbidity and sample sizes) to generate multimorbidity prevalence estimates. However, this strategy did not take into account the weights that were applied to the prevalence estimates in some studies. Our results, therefore, need to be interpreted with this caveat in mind.

Conclusion

Investigating multimorbidity prevalence is of great importance in the study of ageing. This systematic review of 70 studies reveals that a large proportion of the global population, especially those above the age of 65, are affected by multiple chronic diseases. The prevalence estimates of multimorbidity differ among studies. The need for a consistent operationalisation of multimorbidity is evident. It will enable more accurate estimations of disease burden and, consequently, more effective disease management and resources distribution.

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Supplemental material

Supplemental material for this article is available online.

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