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Epidemiology and impact of chronic disease multimorbidity in India: a systematic review and meta-analysis

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Abstract

Objectives: This is the first systematic review and meta-analysis of the prevalence of multimorbidity, its risk factors including socioeconomic factors, and the consequences of multimorbidity on health systems and broader society in India.

Methods: A systematic review of both published and grey literature from five databases (Medline, Embase, EBSCO, Scopus, and ProQuest) was conducted including original studies documenting prevalence or patient outcomes associated with multimorbidity among adults in India. We excluded studies that did not explicitly mention multimorbidity. Three independent reviewers did primary screening based on titles and abstracts followed by full-text review for potential eligibility. The risk of bias was independently assessed by two reviewers following the Appraisal Tool for Cross-Sectional Studies. We presented both qualitative and quantitative (through meta-analysis) summaries of the evidence. The protocol for this study was prospectively registered with PROSPERO (CRD42021257281).

Results: The review identified 5442 articles out of which 35 articles were finally included in this study. Twenty-three studies were based on the primary data while 12 used secondary data. Eleven studies were conducted in hospital/primary care setting while 24 were community-based. The pooled prevalence of multimorbidity based on (n=19) studies included for meta-analysis was 20% (95% CI: 19% to 20%). The most frequent outcomes were increased healthcare utilization, reduced health-related quality of life, physical and mental functioning.

Conclusion: We identified a wide variance in the magnitude of multimorbidity across age groups and regions with most of the studies from eastern India. Nation-wide studies, studies on vulnerable populations and interventions are warranted.

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Introduction

Multimorbidity, the co-occurrence of two or more chronic conditions in an individual is becoming a norm in low-and middle-income countries (LMICs).[1] This can be attributed to the rise in the ageing population along with an increase in non-communicable diseases (NCDs) vis-a-vis prevailing infectious diseases.[2] Multimorbidity encompasses all long term conditions (LTCs) including NCDs of chronic nature such as hypertension, diabetes or an infectious disease of longer duration such as filariasis or a mental health condition such as depression. This often leads to an increase in healthcare utilization, expenditure along with poorer patient outcomes.[3] Further, it also deteriorates the health-related quality of life (HRQoL).[4]

In LMICs such as India, multimorbidity is on the rise; evident by a recent study that estimated a 55% prevalence among adults attending public healthcare facilities.[5] However, the evidence on multimorbidity burden is scattered across various studies done in either small samples or particular regions, but no study to date has synthesized the national estimates. Although, the high prevalence indicates an additional burden on the already swamped healthcare system, the national estimate of multimorbidity burden could help in evidence based guidance to plan changes to the structure and delivery of primary care. Primary care is the first and foremost point of contact between multimorbid individuals and the healthcare systems.[6] It is thus imperative to strengthen primary care along with healthcare advancements to mitigate multimorbidity and its challenges such as polypharmacy, and unplanned emergency healthcare use. This also lays a financial burden on families making them vulnerable to impoverishment.[7] Additionally, multimorbid patients face convoluted care pathways as they navigate to multiple care providers and specialists for each of the condition.[8] Moreover, the existing guidelines focus on single disease-based management which makes it challenging for the healthcare providers to manage multiple long-term conditions.[8] Hence, multimorbidity and primary care research needs to be prioritized, for both resource and planning, and to identify effective interventions.

With emerging epidemiological trends of chronic conditions and transitioning demography, generating evidence on the burden of multimorbidity is new in Indian context.[9] Although, multimorbidity has become a norm, still multimorbidity and primary care research has not gained pace in the country.[9] A systematic review conducted in 2015, estimated 4.5% to 83% prevalence of multimorbidity in South Asia.[10] Given the increasing prevalence, there is a pressing need to assess the burden and outcomes of multimorbidity in India. Moreover, India has the second-largest population in the world which in itself reflects the need for special attention. Recent programs such as Ayushman Bharat and the establishment of Ayushman Arogya Mandir formerly Health and Wellness Centres along with integrating AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha, Sowa Rigpa, Homoeopathy) system in the mainstream medical facilities shows India's commitment to Universal Health Coverage (UHC) which could be given direction with a shred of cumulative evidence.[11] Nonetheless, various LMICs face similar situation in managing multimorbidity despite its rising prevalence. Additionally, the social determinants of multimorbidity remain alike for most of the LMICs and hence, identifying these determinants through the present review would generate relevant evidence for a wider population. These determinants can help in making the healthcare system aware and resilient towards the chronic care needs of local people. Therefore, this systematic review aimed to estimate the prevalence of multimorbidity, identify its risk factors including social determinants or consequences of multimorbidity in India.

Methods

Protocol and standards

This systematic review was prospectively registered with the International Prospective Register of Systematic Reviews (Registration ID: CRD42021257281).[12] It was performed and reported following Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines (Supplementary Table S1).[13]

Eligibility criteria

Original studies documenting prevalence, determinants or patient outcomes associated with multimorbidity; studies with participants aged ≥18 years; conducted either in a primary care/outpatient or community based setting from India were included. Studies in which multimorbidity was not explicitly defined; or included an index condition i.e. comorbidity were excluded. Additionally, systematic reviews, commentaries, editorials, newsletters and qualitative studies were also excluded.

Information sources and search strategy

We searched both medical literature databases and grey literature to make our search exhaustive. A comprehensive search was conducted using electronic databases Medline through PubMed and Embase along with EBSCO host and ProQuest. Google Scholar search engine was also used to retrieve articles. The reference list of included studies was hand-searched as an additional source of information.

The basic search syntax comprised of two concepts: multimorbidity and prevalence. We used PubMed to build the basic search strategy, although the individual search strategy for each database was developed separately. In PubMed, medical subject headings (MeSH) term for "multimorbidity" was entered in 2018.[14] However, for other databases the terms specific to database such as Emtree for Embase along with various other keywords were used to make the search strategy comprehensive. Thereafter, search strategy was refined to include data from India only. The detailed search strategy used for each database is provided in Supplementary Table S2. We included articles published up until August 2021.

Study selection, data extraction and synthesis

The studies retrieved from various databases were merged and screened for duplicates. Primary screening based on the titles and abstracts (following inclusion and exclusion criteria) was done by three reviewers (RV, AS and MB) independently. The articles were categorized as relevant, irrelevant or unsure; if any article was marked as irrelevant by all three of the reviewers it was eliminated. In the next stage, full texts of all included articles from primary screening were reviewed by three independent reviewers for potential eligibility (RV, AS and MB). This round strictly followed inclusion and exclusion criteria based on which studies were finally included. Any dissent was resolved by forming a consensus with the help of another reviewer (SP).

Data from relevant studies were extracted using a preformed and piloted data extraction sheet and entered by three independent reviewers (RV, AS and MB). This data was assessed by another reviewer (SP) to check for disparities. Differences in the data extraction were resolved by the entire team in consensus. Additionally, if the data was not clear, we contacted the respective authors for further clarity. We extracted the following information from the included studies: author, journal title, year of publication, study design, study setting, age, sex, sample size, prevalence, patterns and patient outcomes of multimorbidity. Additionally, we also collated data on definition of multimorbidity used, tool used for measuring multimorbidity, self-reported or objectively assessed, total number and list of long term conditions included.

Risk of bias in individual studies

The risk of bias was independently assessed by two reviewers (RV, AS) following the Appraisal tool for Cross-Sectional Studies (AXIS) that addresses cross-sectional study reporting and overall quality.[15] The AXIS tool comprehensively assesses studies based on twenty questions from the introduction (one question), methods (ten questions), results (five questions), discussion (two questions) and others (two questions). The AXIS tool covers the following key domains: study design, sample size, sampling method, and methods. Any potential differences between the reviewers were resolved by the third reviewer (SP). Each of the criteria was evaluated on its presence ("Yes" =1) or absence ("No"/ "Do not know"=0). The percentage of items presented as 'yes' was then calculated. Each question was scored with a possible score of one, with scores of each question summed to provide an overall score of twenty. The AXIS repartition: 0–50% has high risk of bias, 51–80% has medium risk of bias and 81–100% has low risk of bias.

Summary measures

The findings were summarized as qualitative and quantitative summary of the evidence. We qualitatively described the characteristics of the included studies whereas pooled prevalence estimates represented the quantitative summary. We used STATA version 17.0 (STATA Corp., Texas) for data analysis. We used 'metan' command to calculate the pooled prevalence based on random-effect model. The I^2 statistic was used to assess the variability between studies; this statistic can take values between 0% and 100%, with high values indicative of strong heterogeneity. We anticipated a high heterogeneity due to the nature of selected studies such as nationally representative samples vs. primary studies with relatively smaller sample size; and age group variations in the study i.e. 18 years and above or older adults like ≥45 years or ≥60 years. Hence, we planned sub group analysis based on the nature of data i.e. primary data or secondary data and age group considered i.e. ≥18 years or ≥45 years.

Patient and public involvement

We did not involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Results

We retrieved 5442 articles from the electronic databases after excluding 584 duplicates. A total of 35 articles[5,16-49]

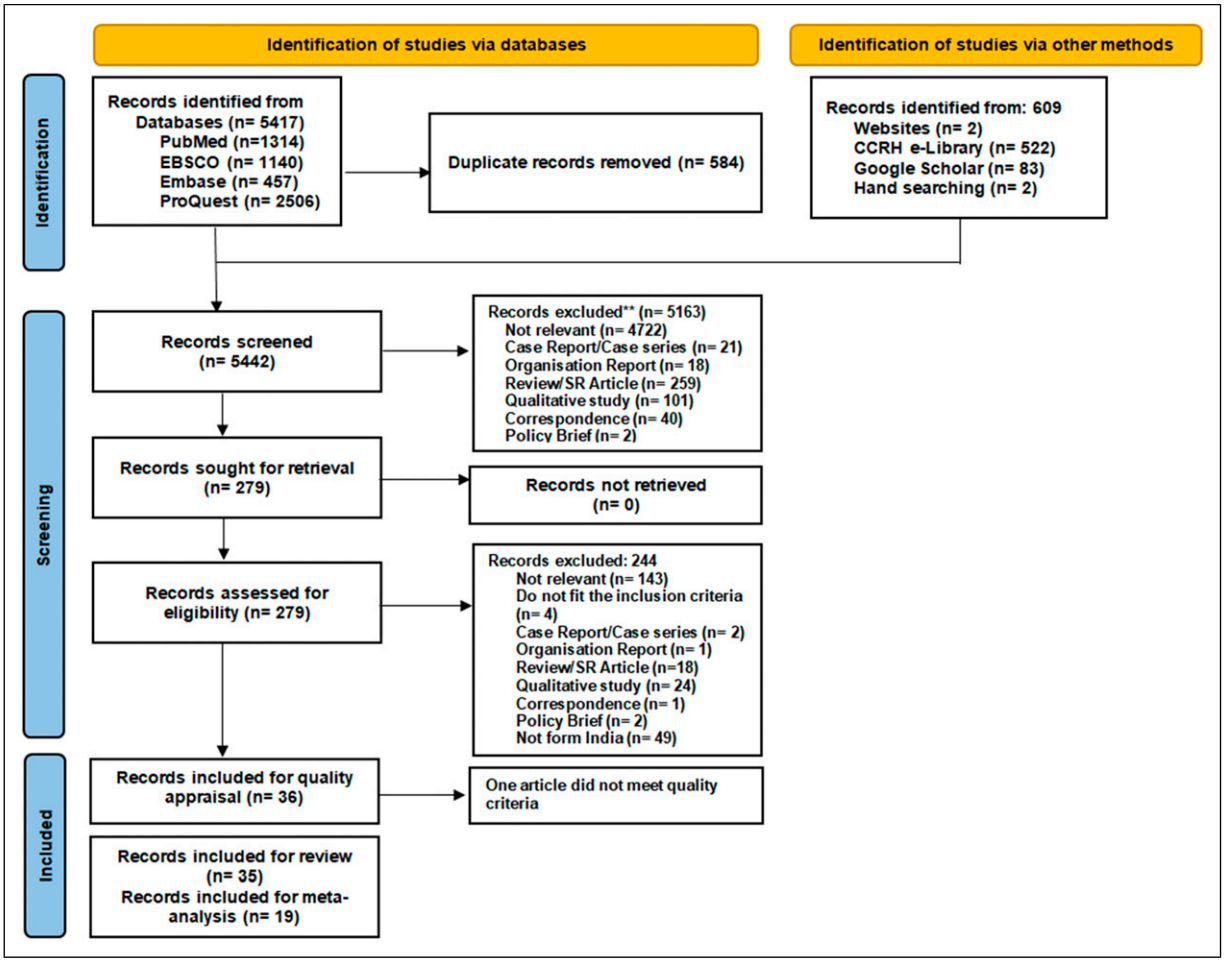

Figure 1. PRISMA flow diagram representing selection of studies included in systematic review.

met the inclusion criteria after primary as well as full-text screening, and quality appraisal (Figure 1).

General characteristics of selected studies

We observed 60.5% (n=23) of the included studies were based on primary data[5,17,19,20,22,25-29,32-35,37,39-43,45-48] whereas 39.5% were from secondary data analysis of nationally representative samples such as Longitudinal Ageing Study in India (LASI) wave-0 (n=1),[18] Study on Global Ageing and Adult Health (SAGE) wave-0[15] (n=1), SAGE wave-1[16,21,24,36,44] (n=5), LASI wave-1[32,35] (n=2), Building Knowledge Base on Population Aging in India (BKPAI)[38] (n=1), India Human Development Survey (IHDS-II)[31] (n=1) and -United Nations Population Fund (UNFDPA)[23] (n=1). Fifteen studies were from Odisha[5,17,19,25,26,28,32-34,39,40,42,45,47,48]; 12 studies[16,18,21,23,24,30,31,36,38,44,46,49] represented pan India and eight studies were from other states of India.[20,22,27,29,35,37,41,43] Eleven studies[5,19,25,26,28,32,33,34,39,43,47] were conducted in hospital/primary care (study conducted among patients attending hospitals/primary care) setting while 24 were from the community based set up (data collected by visiting household through face to face interviews)[16-18,20-24,27,29-31,35-38,40-42,44-46,48,49-49] (Table 1). All the studies defined the term multimorbidity. The number of conditions considered to assess multimorbidity ranged from 4 to 24 conditions with a median of 12 conditions (Supplementary Table S3). Hypertension and type-2 diabetes were uniformly included in all studies to assess multimorbidity. Two reports did not define the number of conditions included.[33,41] All the studies used self-reported questionnaires for the assessment of multimorbidity. The number of chronic conditions considered in the primary studies ranged from 9 to 24 (mean 17.1) whereas it ranged from 4 to 20 (mean 9.7) in studies published from secondary data.

Assessment of risk of bias

A total of 36 studies qualified for the quality check. We excluded one study which explored management of

Table 1. Characteristics of the included studies.

Sl. No	Author, year	State	Region	Study Design	Study Period	Sample size	No. of conditions included	Age in years	% Female	Setting	Prevalence of Multimorbidity	Type of data	Assessment tool used
1.	Pati S et al, 2014[16]	Assam, Karnataka, Maharashtra, Rajasthan, Uttar Pradesh and West Bengal	NR	Cross-sectional	2007-2010	10973	9	18-49; ≥50	61.34	Community (Rural , urban)	977 (8.90%)	Secondary (SAGE-Wave-1)	Self-developed
2.	Banjare P et al, 2014[17]	Odisha	East India	Cross-sectional	2011-2012	310	20	≥60	52.33	Community (Rural)	177 (57%)	Primary	Self-developed
3.	Arokiasamy P et al, 2015[18]	Karnataka, Kerala, Punjab, Rajasthan	NR	Cross-sectional	2010	1683	7	≥45	56.03	Community (Rural , urban)	151 (8.97%)	Secondary (LASI Wave 0)	Self-rated Health, Activity of Daily Living
4.	Pati S et al.,2015[19]	Odisha	East India	Cross-sectional	2013 - 2014	1649	22	18-60	44.14	Primary care (Rural , urban)	467 (28.32%)	Primary	Multimorbidity Assessment Protocol
5.	Vadreru L, 2015[20]	West Bengal	East India	Cross-sectional	2009	815	6	≥40	48.71	Community (Rural , urban)	NA	Primary	Self-developed
6.	Arokiasamy P, 2015[21]	Assam, Karnataka, Maharashtra, Rajasthan, Uttar Pradesh and West Bengal	NR	Cross-sectional	2007-2010	11230	8	≥18	49.10	Community (Rural , urban)	2471 (22%)	Secondary (SAGE-Wave-1)	Self-developed
7.	Gupta A et al, 2016[22]	Punjab	North India	Cross-sectional	2014	534	13	≥60	54.30	Community (Urban)	352 (65.91%)	Primary	Self-developed
8.	Mini GK, et al 2016[23]	Kerala, Tamil Nadu, South Punjab, Himachal Pradesh, Maharashtra, Odisha, West Bengal	NR	Cross-sectional	2011	9852	12	≥60	53.00	Community (Rural , urban)	3024 (30.7%)	Secondary (UNFDPA)	Self-developed
9.	Agrawal S et al, 2016[24]	Assam, Karnataka, Maharashtra, Rajasthan, Uttar Pradesh and West Bengal	NR	Cross-sectional	2007-2010	12198	9	≥18	61.32	Community (Rural , urban)	2927 (23.99%)	Secondary (SAGE Wave-1)	Self-developed
10.	Pati S et al, 2016[25]	Odisha	East	Cross-sectional	2014	103	18	≥18	44.66	Primary care (Rural , urban, semi-urban, Tribal)	24 (23.3%)	Primary	MAQ-PC
11.	Pati S et al, 2017[26]	Odisha	East	Cross-sectional	2013	197	11	NA	34.01	Hospital (Urban)	94 (47.7%)	Primary	Self-developed
12.	Audinarayana N. et al, 2017[27]	Tamil Nadu	South	Cross-sectional	2009-2011	778	12	≥60	53.21	Community (Urban)	475 (61.05%)	Primary	Self-developed
13.	Pati S et al.,2017[28]	Odisha	East	Cross-sectional	2013-2014	1649	21	≥18	44.14	Primary care (Rural , urban)	467 (28.32%)	Primary	MAQ-PC
14.	Jain K et al, 2018[29]	Rajasthan	North	Cross-sectional	2012-2013	400	20	≥50	38.25	Community (Urban)	124 (31%)	Primary	Self-developed
15.	Zhou C, et al, 2018[30]	Assam, Karnataka, Maharashtra, Rajasthan, Uttar Pradesh and West Bengal	NR	Cross-sectional	2002-2004	9199	9	18-70	48.62	Community	3155 (34.3%)	Secondary (WHS/ SAGE Wave 0)	Self-developed
16.	Muksor A et al, 2018[31]	All states/UTs	NR	Cross-sectional	2011-2013	1, 10,434	13	19-59	NA	Community (Rural , urban)	Rural: 651/72334 (0.9%) Urban: 609/ 38100 (1.6%)	Secondary (IHDS-II)	Self- developed
17.	Swain S et al, 2019[32]	Odisha	East	Cross-sectional	2017	342	21	≥40	44.44	Primary care	215 (63%)	Primary	Semi-structured and Edmonton frailty score tool
18.	Palo SK et al, 2019[33]	Odisha	East	Cross-sectional	2015	183	NA	NA	34.97	Primary care (Rural)	98 (53.5%)	Primary	Self-developed
19.	Pati S et al., 2019[34]	Odisha	East	Cross-sectional	2013-2014	1649	21	≥18	44.14	Primary care (Rural, Urban)	467 (28.32%)	Primary	MAQ-PC
20.	Verma V t al, 2019[35]	Uttar Pradesh	North India	Cross-sectional	2014-2015	400	9	≥60	46.25	Community (Rural, Urban)	212 (53%)	Primary	Self-developed
21.	Vancampfort D et al, 2019[36]	Assam, Karnataka, Maharashtra, Rajasthan, Uttar Pradesh and West Bengal	NR	Cross-sectional	2007-2010	34129	11	≥50	52.09	Community (Rural, Urban)	14812 (43.4%)	Secondary (SAGE Wave-1)	Self-developed
22.	Rohini C et al, 2020[37]	Kerala	South	Cross-sectional	2020	410	11	NA	59.75	Community (Rural)	186 (45.36%)	Primary	Self-developed
23.	Sathya T et al, 2020[38]	Himachal Pradesh, Kerala, Maharashtra, Odisha, Punjab, Tamil Nadu and West Bengal	NR	Cross-sectional	2011	9852	20	≥60	5192	Community (Rural, Urban)	1823 (18.5%)	Secondary (BKPAI)	Self-rated health and Activity of daily living
24.	Pati S et al,2020[39]	Odisha	East	Cross-sectional	2013-2014	1649	21	≥18	44.14	Primary care (Rural, Urban)	467 (28.32%)	Primary	MAQ-PC

(continued)

Table 1. (continued)

Sl. No	Author, year	State	Region	Study Design	Study Period	Sample size	No. of conditions included	Age in years	% Female	Setting	Prevalence of Multimorbidity	Type of data	Assessment tool used
25.	Kshatri JS et al.,2020[40]	Odisha	East	Cross-sectional	2019-2020	725	18	≥60	47.86	Community (Rural)	354 (48.8%)	Primary	MAQ-PC
26.	Panda M et al, 2020[41]	Delhi	North	Cross-sectional	2018-2019	300	18	≥60	NA	Community (Slum)	NA	Primary	EDMONSTON Frail Scale
27.	Kshatri JS et al., 2020[42]	Odisha	East	Cross-sectional	2019-2020	725	NA	60-106	47.86	Community (Rural)	354 (48.8%)	Primary	MAQ-PC, Frailty index for elderly, Instrumental activities of daily living
28.	Vargese S et al,2020[43]	Kerala	South	Cross-sectional	2017	525	12	18 to 70	53.14	Primary care (Rural)	85 (16.2%)	Primary	Self-developed
29.	Bayes Marin I, 2020[44]	Assam, Karnataka, Maharashtra, Rajasthan, Uttar Pradesh and West Bengal	NR	Cross-sectional	2007-2010	6558	8	≥18	49.60	Community (Rural, Urban)	NA	Secondary (SAGE Wave -1)	Self-developed
30.	Pati S et al, 2021[45]	Odisha	East	Cross-sectional	2020	600	23	NA	51.00	Community (Rural, Urban)	237 (39.5%)	Primary	MAQ-COVID-19
31.	Srivastava S et al, 2021[46]	All states except Sikkim	NR	Cross-sectional	2017-2018	31464	9	≥60	52.01	Community (Rural, Urban)	7551 (24%)	Secondary (LASI Wave-1)	Self -developed
32.	Pati S, et al., 2021[47]	Odisha	East	Cross-sectional	2019	500	24	≥60	47.80	Hospital (Rural, Urban)	250 (50%)	Primary	MAQ-PsyC
33.	Kshatri JS, 2021[48]	Odisha	East	Cross-sectional	2019-2020	725	21	≥18	47.86	Community (Rural)	354 (48.8%)	Primary	MAQ-PC
34.	Pati S et al, 2021[5]	Odisha	East	Cross-sectional	2015	1870	18	≥18	37.00	Primary care (Rural, Urban)	1028 (54.97%)	Primary	MAQ-PC
35.	Ansari S, 2021[49]	All states	NR	Cross-sectional	2017-2018	31464	10	≥45	53.00	Community (Rural, Urban)	7403 (23.53%)	Secondary (LASI Wave-1)	Centre for Epidemiological Studies Depression Scale

NR: Nationally representative, UT: Union Territory, IHDS- India Human Development Survey, WHS-World Health Survey, SAGE-Study on Global Ageing and Adult Health, LASI-Longitudinal Ageing Study in India, UNFDPA-United Nations Population Fund, BKPAI- Building Knowledge Base on Population Aging in India, NSS -National Sample Survey, MAQ-PC: Multimorbidity Assessment Questionnaire for Primary Care, NA: Not Available.

geriatric multimorbidity in old age home residents in India[50] as it scored only four points (20%). The quality appraisal of the remaining 35 included articles revealed that 15 studies scored 81-100% and were categorized as having low risk of bias,[17,18,20,28,29,32,33,37,39,41-43,46-48] whereas 20 studies scored 51-80% and were grouped as having medium risk of bias[5,16,19,21-27,30,31,34-36,38,40,44-45,49] (Supplementary Table S4).

Prevalence

The prevalence of multimorbidity was reported in 32 of the included studies and this ranged from 1.16% to 65.9% (Table 1). Three studies did not report the prevalence of multimorbidity.[20,41,44] The prevalence from twelve studies with a nationally representative sample ranged from 8.9% to 63.3% while the prevalence of multimorbidity from primary studies ranged from 16.2% to 65.9%.[5,17,19,20,22,25-29,32-35,37,39-43,45-48] The estimate of multimorbidity for Odisha (state with maximum studies, n=15)[5,17,19,25,26,28,32-34,39,40,42,45,47,48] ranged from 23.3% to 63.06% whereas for other states the prevalence ranged from 16.2 % to 65.9%.[20,22,27,29,35,37,41,43] Based on the age, among ten studies with a population of ≥60 years, the prevalence ranged from 30.7% to 65.9%. Similarly, the prevalence reported for studies that considered population aged ≥18 years (n=13) and ≥45 years (n=5) ranged from 1.16% to 55% and 9% to 63.06% respectively.

We included 19 studies for meta-analysis which gave a pooled prevalence of multimorbidity to be 20% (Figure 2). Separate meta-analysis was also conducted for studies reporting multimorbidity based on primary data which yielded the pooled prevalence of 43% (Supplementary Figure 1) while studies based on secondary data showed

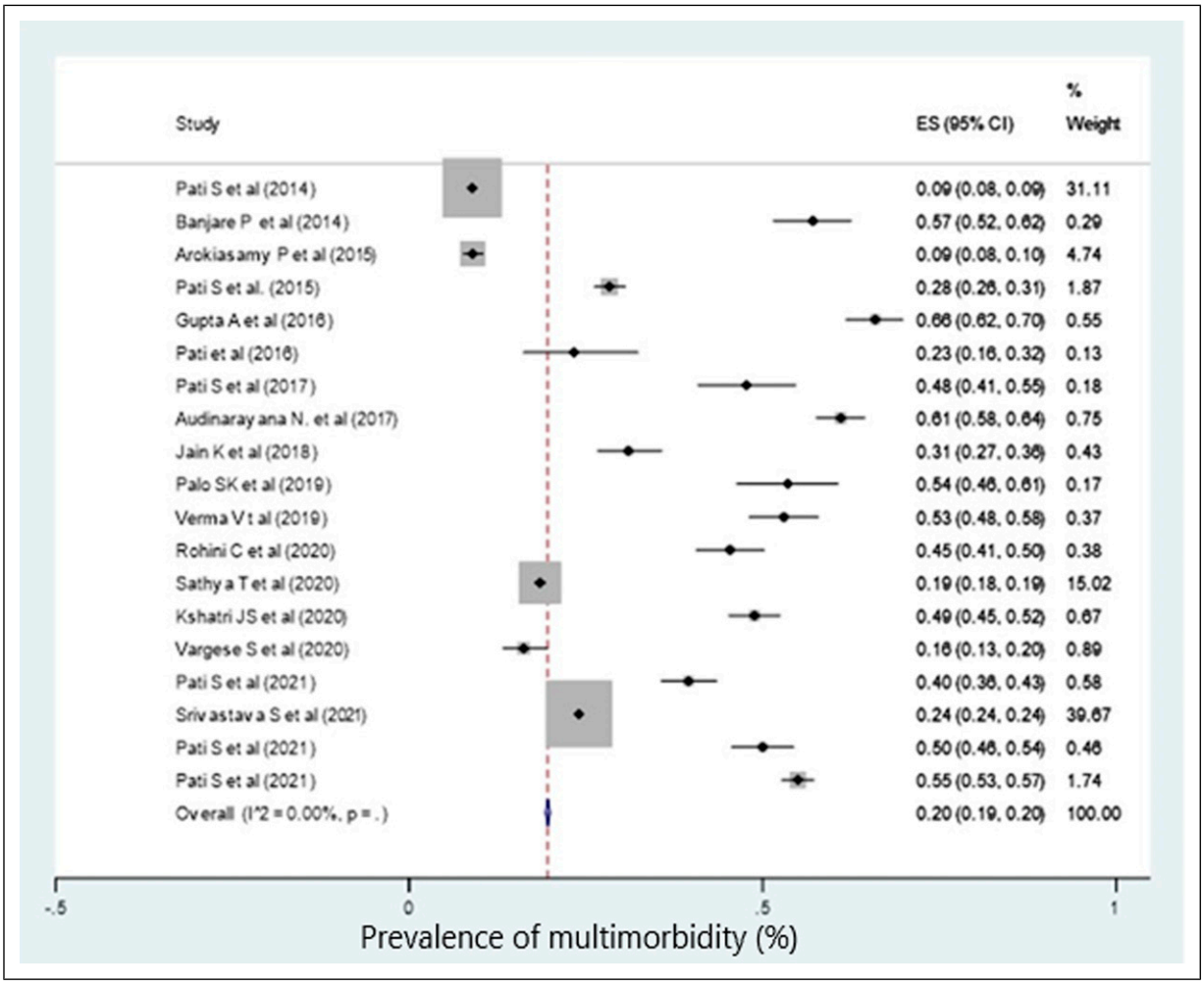

Figure 2. Pooled prevalence of multimorbidity in India.

Table 2. List of studies excluded from meta-analysis along with their reasons for exclusion.

S. No	Author, Year	Reason for Exclusion
1	Vadreru L et al., 2015 [20]	Data not available
2	Arokiasamy P et al., 2015 [21]	Data from SAGE wave-1 used, another study based on same data with larger sample included
3	Mini GK et al., 2016 [23]	Data from United Nations Population Fund used, another study based on same data included
4	Agrawal S et al., 2016 [24]	Data from SAGE wave-1 used, another study based on same data included
5	Pati S et al., 2017 [28]	Data same as Pati S et al, 2015 [19] (Included)
6	Zhou C et al., 2018 [30]	Data from SAGE wave-1 used, another study based on same data included
7	Muksor A et al., 2018 [31]	Data is not clear as data is segregated based on urban and rural.
8	Swain S et al., 2019 [32]	Definition of multimorbidity not uniform as other studies (Multimorbidity defined as ≥3 conditions)
9	Pati S et al., 2019 [34]	Data same as Pati S et al, 2015 [19] (Included)
10	Vancampfort D et al, 2019 [36]	Data from SAGE wave-1 used; another study based on same data included
11	Pati S et al., 2020 [39]	Data same as Pati S et al, 2015 [19] (Included)
12	Panda M et al., 2020 [41]	Data not available
13	Kshatri JS et al., 2020b [42]	Data same as Kshatri JS et al, 2020a [40] (Included)
14	Bayes MI et al., 2020 [44]	Data not available
15	Kshatri JS et al., 2021 [48]	Data same as Kshatri JS et al, 2020a [40] (Included)

the pooled prevalence to be 4% (Supplementary Figure 2). We also conducted a separate meta-analysis on the basis of age group selected i.e. studies reporting multimorbidity among participants aged ≥18 years that showed the pooled prevalence of 14% (Supplementary Figure 3) while studies among respondents aged ≥45years showed the pooled prevalence of 23% (Supplementary Figure 4). The list of studies excluded from meta-analysis along with their reasons for exclusion is presented in Table 2.

Pattern

Nine studies[17,23,26,28,33,37,40,44,47] gave information about the pattern of multimorbidity (Table 3). The commonly occurring disease clusters were the occurrence of two diseases or dyads (n=7)[23,26,28,33,37,40,47] followed by triads (n=4).[17,28,37,40] The commonly identified dyads were arthritis and hypertension,diabetes and hypertension, hypertension and overweight, tuberculosis and ulcer disease. In one study[28] patterns across gender were described; male- acid peptic disease + arthritis (7.95%); female- acid peptic disease + hypertension (10.58%). Additionally, it also presented patterns based on age; younger age group i.e. 18 to 29 years were acid peptic disease with arthritis/ chronic backache/ tuberculosis /chronic lung disease, while older age groups (≥40 years) had more frequent combinations of hypertension + arthritis/ chronic lung disease/ vision difficulty, and arthritis + chronic backache. Bayes Marin[44] described the patterns based on classes as cardio-metabolic or respiratory-mental-articular. Cardio-metabolic was reported to be high 6.1% (5.3 to 6.8) in India (diabetes, hypertension, myocardial infarction, angina/stroke). The triad of acid peptic disease + arthritis + chronic backache was common in men in all age groups whereas women reported combinations of hypertension + chronic backache + arthritis.[28]

Risk factors

Risk factors for multimorbidity were explored in 23 studies[5,16,17,18,19,20,22,23,24,27,29,33,35,37,39,40,41,43,46,47] that included age[16,17,19,23,27,29,33,37,39,43,47]; socioeconomic status [19,22,23,29,39]; sex [19,27,35,39]; body mass index (BMI)[24,46]; living arrangements (e.g. a traditional joint family system)[27,41]; and tobacco[17] and alcohol use[23] (Table 4). Significant positive associations were found for increasing age[16,17,19,23,27,29,33,37,39]; female sex[19,27,35,39]; higher educational attainment[18,19,23,39]; affluence[19,22,23,29,39]; obesity[24,46]; and tobacco[17] and alcohol use.[23]

Outcome/consequences

Fourteen studies[5,18-20,23,30,32,34,36,38,39,42,45,48] reported different health-related consequences associated with multimorbidity (Table 5). The most frequently reported consequences that interplay with multimorbidity was increased healthcare utilization (n=6)[19,23,30,32,34,39]; reduced health-related quality of life (n=2)[5,34]; reduced physical functioning/activities of daily living (ADL) (n=1)[18]; mental functioning (n=2)[5,34]; poor self-rated health (n=2)[18,20]; dissatisfaction about health care system (n=1)[30]; elderly abuse or mistreatment (n=2)[38,48]; and weak handgrip strength/frailty (n=3)[32,36,42]. The visit of multimorbid patients to a private clinic was 1.4 times higher than to public health setups.[19] The mean number of hospital visits per patient per year was 1.62 (95% CI, 1.31 to 1.93) and 2.81 (95% CI, 2.34 to 3.28) among patients with single chronic conditions and

Table 3. Patterns of multimorbidity.

Author, Year[Reference]	Pattern reported	Pattern description	*n/N (%) or (%)*
Banjare P et al, 2014[17]	Triad	Arthritis, Chronic Obstructive Pulmonary Disease (COPD), High Blood Pressure	8/164 (0.5)
Mini GK, et al 2016[23]	Dyad	Arthritis and High Blood Pressure	7.5
		Arthritis and Cataract	5.3
		Diabetes and High Blood Pressure	4.7
Pati S et al, 2017[26]	Dyad	Tuberculosis and Ulcer disease	3/197 (1.5)
Pati S et al., 2017[28]	Dyad, and Triad	Dyad	
		• Younger age group (18 to 29 years)	
		Acid Peptic Disease with Arthritis/ Chronic Backache/Tuberculosis/ Chronic Lung Disease.	**NA**
		• Older age group (≥40 years)	
		Hypertension with Arthritis/Chronic Lung Disease/Visual Difficulty; and Arthritis with Chronic Backache	**NA**
		• Male	
		Acid Peptic Disease with Arthritis	7.95
		• Female	
		Acid Peptic Disease with Hypertension	10.58
		Triad	
		• Male	
		• Acid peptic disease, Arthritis and Chronic Backache	3.64
		• Female	
		Acid Peptic Disease, Arthritis and Chronic Backache	4.12
Palo SK et al, 2019[33]	Dyad	Diabetes and Hypertension	14.1
Rohini C et al, 2020[37]	Dyad, and Triad	**Dyad**	
		Diabetes and Hypertension	127/410 (30.9)
		Triad	
		Diabetes, Hypertension and Ischemic Heart Disease	23/410 (5.6)
Kshatri JS et al.,2020[40]	Dyad, Triad, and Tetrad	**Dyad**	
		Combination of any two conditions	25
		Triad	
		Combination of any three conditions	15.2
		Tetrad and above	
		Combination of any four and above conditions	8.7
Bayes Marin I, 2020[44]	Cardio-metabolic	Cardio-metabolic (Diabetes, Hypertension, Myocardial Infarction, Angina/Stroke)	6.1
Pati S et al, 2021[47]	Dyad	Hypertension and Diabetes	14

*as per the availability of information; Dyad: combination of frequently occurring two condition; Triad: combination of frequently occurring three conditions; Tetrad: combination of frequently occurring four conditions; NA: Not Available.

multimorbidity respectively.[19] The mean number of medicines used increased from 0.56 (95% CI, 0.50 to 0.62) among patients with single chronic conditions to 1.17 (95% CI, 1.04 to 1.29) among patients with multimorbidity.[19] The mean hospital per visit per year in patients with multimorbidity was nine; this is two times the rate of hospitalization among those having one chronic condition.[23]

Discussion

Summary of evidence

This systematic review provides comprehensive evidence on the burden of multimorbidity in India. The prevalence of multimorbidity was observed to vary from 1.16% to 65.9%. Nonetheless, the retrieved studies were heterogeneous in the characteristics while the prevalence was quite similar between the different subgroups i.e., nationally representative samples and samples from different provinces in India. The prevalence was high among participants aged 60 years and above (range 30.7% to 65.9%). The studies which were planned a-priori focused on more number of chronic conditions (median 18) whereas the median conditions considered in studies based on secondary data was 9 while the overall median number of diseases considered was 12.

Comparison with existing literature

There is considerable heterogeneity among the measures used to assess multimorbidity in terms of number of diseases considered. In this review, the median numbers of diseases identified were 12 which is lower than the median number [Median: 17 (IQR: 11-23)] of conditions reported by a systematic review of 566 studies on multimorbidity.[51] Additionally, there was a variance in the median number of conditions considered in primary and secondary studies. A probable reason for the wide variance between the two is that the latter does not intend to assess multimorbidity rather the data is extrapolated to do so due to a lack of nationwide data pertaining to multimorbidity. Hence, there is an urgent need towards building a consensus on the number of diseases or groups to be included to assess multimorbidity which would help in improving inter-regional comparisons.[52] Moreover, LMICs such as India should plan to conduct nation-wide surveys on multimorbidity to elicit its real burden.[53] Here, the findings of a systematic review of systematic reviews is worth considering that recommended meaure selection (eg., using a cut-off of two or more conditions) be used for tools validated for the outcome of interest, and where there is no validated measures, or where multiple outcomes or populations are being considered, disease count should be used as an alternative.[54] Additionally, debates around the consideration of definition for complex multimorbidity is also worth considering where a study suggests that complex multimorbidity must consider complexity of conditions rather than simple count of diseases across body systems.[55]

We observed that the population aged 60 years and above had a higher prevalence (range 30.7% to 65.9%) of multimorbidity which is in contrast with the findings reported from China[56] which showed a very wide range (6.4% to 76.5%), though the latter was based on a narrative review. However, the pooled prevalence of multiple chronic illnesses reported in Caribbean and Latin American countries[57] was 47% which is higher than the pooled prevalence reported in our review. An Australian study[58] reported 52% prevalence which is also higher than the prevalence of multimorbidity in India. The presence of clusters of conditions or complexity (the number of domains present) increased with age. Similar findings were also observed from another study in Australia[59] where 83.2% of the surveyed participants aged 75 years or older had multimorbidity; with 58.2% having morbidity in three or more domains, and 33.4% in four or more. As the ageing population increases, multimorbidity will continue as a major health problem in the years to come[60] which needs urgent action.

In this review, we observed an increase in the health care cost and utilization which is consistent with the findings of Bori et al[61] in UK. Only twelve studies reported patterns/clusters/disease combinations but it indicated a shift in the conceptualization of multimorbidity from purely disease count to specific disease combinations/clusters. Additionally, we also noted the focus on specific age groups to be a trend in this review. These findings are consistent with the report of Bori et al.[61] Nonetheless, it is worth mentioning that these findings were not elicited by an earlier systematic review conducted among South Asian population[10] as the term multimorbidity was not defined in the MeSH (Medical Subject Headings of PubMed) terminology at that time.

Multimorbidity assessment largely depends on considering the simple count of diseases, however future studies should explore the most common combinations and frequently occurring clusters of diseases that could help in providing insights for the complex care needs of patients with multimorbidity. The health research as well as practice has conventionally focused on single-disease framework rather than multiple conditions. Therefore, a complementary strategy is needed, supporting general physicians to provide personalized patient centered, comprehensive continuity of care, especially in socioeconomically deprived areas.[62] Additionally, future studies eliciting the burden of multimorbidity among vulnerable populations such as urban poor, and tribal are warranted. Social determinants of health are equally relevant for chronic conditions and studies report that socio-economic marginalization increases the risk of multimorbidity.[63,64] Furthermore, the difficulties for these individuals are exacerbated by the 'inverse care law' which states that the rising demand for healthcare access leads to fewer consultations, decreased patient enablement and increased physician stress.[65] Hence, these factors highlight the importance of estimating the burden of chronic conditions and identifying their care seeking pathway so as to make the existing programmes more equitable and design future policies based on the evidence. Nonetheless, few studies have been published covering these vulnerable groups which were beyond the date of last search of this review.[66-74]

We also observed that studies were mostly conducted among patients attending out-patient department of primary care though no studies document the prevalence of multimorbidity among in-patients (IPD). A major gap exists in enumerating the care seeking pathway of these multimorbid individuals which may support in further taking steps towards primary care strengthening. We observed Multimorbidity Assessment Questionnaire for Primary Care (MAQ-PC) was the only validated tool which was designed to explicitly assess multimorbidity in India.[25] With a lack of gold standard, this tool has been developed following an iterative process that can be used for undertaking multimorbidity studies in future.

We observed affluence to be associated with multimorbidity which is consistent with the findings of a systematic review on multimorbidity in LMICS that observed an increased risk of NCD multimorbidity [Pooled OR from 10 studies: 1.35 (95% CI: 1.02 to 1.80)] among well-off individuals.[75] A possible explanation to this could be that affluent group has a higher capacity to pay for healthcare services which lead to better diagnosis and hence, self-report of multimorbidity. However, these findings differ from that of high-income countries where deprivation is associated with multimorbidity as suggested by a systematic review.[76] Additionally, most studies reported that the

Table 4. Risk factors/determinants/correlates for multimorbidity reported in studies.

Variable	Risk factors[Reference]	Comparator/ Reference for calculation of OR/IRR/RRR
Age	**Age in years**[16] 30–39: AOR 4.11; 95% CI: 2.18 to 7.74 40–49: AOR 7.87; 95% CI: 4.25 to 14.59 50–59: AOR 16.15; 95% CI: 8.83 to 29.54 60–69: AOR 23.56; 95% CI: 13.08 to 42.44 >70: AOR 39.15; 95% CI: 20.72 to 73.98	18-29
	Age in years[17] 65–70: AOR 2.33; 95% CI: 1.22 to 4.45 70–75: AOR 4.91; 95% CI: 2.18 to 11.05 ≥75: AOR 4.65; 95% CI: 1.87 to 11.52	60-65
	Age in years[19] 30-39: AOR 6.10; 95% CI: 3.19 to 11.65 40-49: AOR 8.49; 95% CI: 4.45 to 16.11 50-59: AOR 16.41; 95% CI: 8.55 to 31.48 60-69: AOR 16.14; 95% CI: 8:38 to 31.10 70-79: AOR 22.35; 95% CI: 11.15 to 44.71	18-29
	Age in years[23] ≥70: AOR 1.69; 95% CI: 1.52 to 1.8	60-70
	Age in years[27] ≥75: OR 1.76; β coefficient: 0.57	60-64
	Age in years[29] ≥60: IRR 1.38; 95% CI: 1.15 to 1.65	50-59
	Age in years[33] ≥60: years: AOR 4.96; 95% CI: 1.13 to 21.92	20-39
	Age in year[37] 40-49: AOR 10.7; 95% CI: 2.4 to 47.2 50-59: AOR 34.6; 95% CI: 7.9 to 149.4 60-69: AOR 70.1; 95% CI: 16.4 to 298.6	30-39
	Participants attending Public facility[39] **Age in years**[39] 30–39: AOR 6.70; 95% CI: 2.89 to 15.57 40–49: AOR 9.37; 95% CI: 4.05 to 21.64 50-59: AOR 16.73; 95% CI: 7.12 to 39.31 60-69: AOR 17.21; 95% CI: 7.35 to 40.28 ≥70: AOR 26.29; 95% CI: 10.52 to 65.66	18-29
	Participants attending Private facility[39] **Age in years**[39] 30–39: AOR 6.13; 95% CI: 2.06 to 18.21 40-49: AOR 8.73; 95% CI: 2.93 to 25.96 50-59: AOR 19.42; 95% CI: 6.52 to 57.80 60-69: AOR 16.48; 95% CI: 5.45 to 49.83 ≥70: AOR 20.73; 95% CI: 6.54 to 65.67	18-29
	Age in years[43] 30-39: AOR 2.81; 95% CI: 2.70 to 28.99 40–49: AOR 11.97; 95% CI: 1.43 to 99.22 50–59: AOR 19.42; 95% CI: 2.39 to 157.79 60–69: AOR 37.99; 95% CI: 4.68 to 308.42 ≥70: AOR 42.56; 95% CI: 5.15 to 352.42	18-29
	Age in years[47] 40-59: ARRR 2.9; 95% CI: 1.6 to 5.1 60+: ARRR 6.6; 95% CI: 3.3 to 13.1	18-39

(continued)

Table 4. (continued)

Variable	Risk factors[Reference]	Comparator/ Reference for calculation of OR/IRR/RRR
Sex	**Sex**[19] Female: AOR 1.61; 95% CI: 1.23 to 2.12 **Sex**[27] Female: OR 2.24; β coefficent: 0.81 **Sex**[35] **F**emale: 65.4%; p value: 0.0007 **Participants attending Public facility**[39] **Sex**[39] Female: AOR 1.6;95% CI: 1.11 to 2.27 **Participants attending Private facility**[39] **Sex**[39] Females: AOR 1.61; 95% CI:1.07 to 2.42	Male
Caste	**Caste**[29] SC/ST/OBC: IRR 0.74; 95% CI: 0.61 to 0.92 **Participants attending Public facility**[39] **Ethnicity**[39] Non-aboriginal: AOR 1.56;95% CI: 1.06 to 2.32	Other caste
Education	**Education**[18] Primary/middle: IRR 1.4; 95% CI: 1.02 to 1.91 High school: IRR 1.6; 95% CI: 1.07 to 2.4 **Education**[19] Primary: AOR 1.61; 95% CI: 1.17 to 2.22 Secondary and above: AOR 1.53; 95% CI: 1.03 to 2.25 **Education**[23] Formal schooling: AOR 1.16; 95% CI: 1.04 to 1.30 **Participants attending Private facility**[39] **Education**[39] Primary school completed: AOR 2.59; 95% CI: 1.59 to 4.23 Secondary schooling and above: AOR 1.99; 95% CI: 1.11 to 3.55	No schooling/education
Marital status	**Marital status**[22] Widow:79.2%; p value: 0.0001	Multimorbidity versus only one chronic condition
Employment	**Employment**[37] Unemployed: AOR 1.9; 95% CI: 1.03 to 3.6 **Occupation**[41] Engaged: β coefficient 1.8; AOR 5.9; p-value: 0.08	Daily wage or self employed Not engaged
SES	**SES**[19] APL: AOR 1.35; 95% CI: 1.03 to 1.78 **SES**[22] Upper middle: 70.7%; Middle: 74%; p=0.001 **SES**[23] Wealthiest: AOR 2.17; 95% CI: 1.81 to 2.59 **SES**[29] Middle: IRR 1.36; 95% CI: 1.07 to 1.73 Rich: IRR 1.37; 95% CI: 1.05 to 1.78 **Private facility**[39] **SES**[39] APL: AOR 1.35; 95% CI: 1.01 to 2.06	Below poverty line Multimorbidity versus only one condition Lowest Poor Below poverty line
Economic independence	**State of economic independence**[17] Fully dependent: AOR 5.21; 95% CI: 1.99 to 13.60 Partially dependent: AOR 3.02; 95% CI: 1.57 to 6.81	Not dependent

(continued)

Table 4. (continued)

Variable	Risk factors[Reference]	Comparator/ Reference for calculation of OR/IRR/RRR
Habit	**Habit**[17]	
	Chewing tobacco: AOR 2.82; 95% CI: 1.51 to 5.24	
	Life style habit[23]	
	Alcohol use**:** AOR 1.23; 95% CI: 1.01 to 1.5	Not chewing tobacco
	Habitual to any lifestyle habit[27]	No alcohol use
	Any lifestyle habit: OR 1.44; β coefficent: 0.37	Habitual
BMI and obesity	**BMI status Obesity**[24]	
	Obesity: AOR 2.33; 95% CI: 1.35 to 4.02	Normal BMI
	Overweight/obese[46]	Not over weight
	ObesityARRR:1.61; 95% CI: 1.48 to 1.74	
	Waist circumference[46]	Not high risk
	High risk waist circumference: ARRR:1.66; 95% CI: 1.52 to 1.80	
	Waist to hip ratio[46]	Not high risk
	High-risk wait-hip ratio: ARRR 1.45; 95% CI: 1.33 to 1.59	
Self-rated health	**Self-rated health**[20]	Multiple chronic condition versus no chronic condition
	Poor Self-rated health: AOR 2.61; 95% CI:1.44 to 4.72	
Family	**Family**[22]	
	Nuclear family: 56.7%; Joint families: 69.7%; p=0.003	Multimorbidity versus only one chronic condition
Family History	**Family history**[40]	No family history of diabetes
	Diabetes: AOR 1.67; 95% CI: 1.11 to 2.52	No family history of hypertension
	Hypertension: AOR 1.80; 95% CI: 1.29 to 2.50	
Living arrangement/ Housing/Living with Family	**Living arrangement**[27]	
	Living with married sons: OR 2.24; β coefficient: 0.81	Living alone
	Living with others: OR 2.10; β coefficient: 0.74	*95% CI is not given, β coefficient are significant at different p values*
	Living Alone[41]	Not alone
	Alone: β coefficient 3.5; AOR 34; p-value: 0.001	

APL: Above poverty line; ARRR: Adjusted Relative Risk Ratio; AOR: Adjusted Odds Ratio; BMI: Body Mass Index; SES: Socioeconomic status; IRR: Incidence risk ratio; SC: Scheduled Caste; ST: Scheduled Tribes; OBC: Other backward class; CI: Confidence Interval.

individuals with more years of schooling (either primary or secondary schooling) had a higher chance of having multimorbidity as compared to those with no formal education which is consistent with the findings of a systematic review that included studies from Southeast Asia.[72] A probable reason for this could be that with education, people tend to be more health conscious, and hence have better chances of diagnosis and self-report of chronic conditions.

Implications for research and practice

India is a federal union comprising of 28 states and 8 union territories, forming a total of 36 entities. The studies on multimorbidity within a state are very limited preventing the assessment of the actual burden in the country. The present evidence may be considered as a tip of the Iceberg. More studies specific to different zones of the country, state/province is required to assess the real burden of multimorbidity in India. India is a country of medical pluralism wherein apart from conventional medicine system, traditional and alternative system of medicine popularly known as Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy (AYUSH) are also instrumental in contributing to health care. AYUSH care utilization is higher among patients with chronic diseases and also for treating skin-related and musculo-skeletal ailments.[70] The current epidemiological transition has been a major driver impelling a radical rethink of the structure of health care, especially concerning the role, quality and capacity of primary health care. The development of new clinical care guidelines should be addressed to focus on multiple systems and not just only on one disease. Sensitization of frontline workers such as Accredited Social Health Activist (ASHA) and Community Health Officer (CHO) towards the needs of multimorbid individuals is required with a focus on family-level interventions for shared risk factors.[77] Capacity building of primary care staff to manage multimorbidity is also needed. Nonetheless, most LMICs face a similar healthcare challenge in combating multimorbidity where the determinants, patient outcomes as well as impact of multimorbidity on health system remain

Table 5. Summary of the relationship between multimorbidity and its patient outcomes (health outcomes, expenditure, and utilization).

Patient Outcomes	Multimorbidity specification	Estimate [95% CI]	Parameter estimate type	Ref.
Out-patient department (OPD) visit (n=2)	Number of chronic conditions (<3 vs ≥3)	1.09 [1.01 to 1.17] ↑	AOR*	32
	Multimorbidity vs. not	2.81 [2.34 to 3.28] vs. 1.62 [1.31 to 1.93]↑	Mean	34
Hospitalization (n=1)	Multimorbidity vs. not	9 vs. 3↑	Mean	23
	Multimorbidity vs. not	2.32 [1.82 to 2.95] ↑	AOR	23
Facility (n=1)	Private vs. Public	1.40 [1.08 to 1.81] ↑	AOR	19
Medicine taken(n=3)	Number of chronic conditions (<3 vs ≥3)	1.41 [1.27 to 1.56] ↑	AOR	39
	Multimorbidity vs. not	1.17 [1.04 to 1.29] vs. 0.56 [0.50 to 0.62]↑	Mean	19
	Private vs. Public	2.7 vs. 1.2↑	Mean	39
Health care expenditure/Out of pocket expenditure (OOPE) (n=1)	Physical conditions with Psychiatric conditions vs. only Psychiatric conditions	INR 12219 vs. INR 4414↑	Mean	45
Frailty (n=2)	Age <50 years vs. >50 years	4.45 [1.51 to 13.05] ↑	AOR	32
	Multimorbidity vs. not	1.93 [1.61 to 2.24] ↑	OR	42
Decision making in health care (n=1)	Men vs. Women	1.30 [1.12 to 1.91] vs. 1.02 [0.89 to 1.17] ↑	AOR	30
Dissatisfied about health care system (n=1)	Men vs. Women	1.40 [1.15 to 3.28] vs. 1.10 [1.07 to 1.29] ↑	AOR	30
Elderly abuse or mistreatment (n=2)	Two chronic conditions	3.02 [2.33 to 3.91] ↑	AOR	38
	three, and four or more chronic conditions	4.16 [3.02 to 5.74] ↑	AOR	38
	More chronic diseases	5.06 [3.50 to 7.31] ↑	AOR	38
	Multimorbidity vs. not	1.68 [1.11 to 2.57] ↑	AOR	48
Health-related quality of life (HRQoL) (n=2)	Multimorbidity vs. not	43.23 [42.62 to 43.84] vs. 43.69[43.35 to 44.03]↓	Mean	34
	Multimorbidity vs. not		Mean	5
Physical	Multimorbidity vs. not	41.07 vs. 42.48	Mean	34
Physical Mental	Multimorbidity vs. not	41.58 [40.74 to 42.43] vs. 44.52 [43.96 to 45.08]↓ 40.79 vs. 44.14 ↓	Mean	5
Activities of daily living (ADL) (n=1)	Multimorbidity vs. not	6.9 [4.8 to 10.3] ↑	Logit model, OR	18
Self-rated health (n=2)	Multimorbidity vs. not	15.1 [9.5 to 23.9] ↑	Logit model, OR	18
	Multimorbidity vs. not	2.6 [1.44 to 4.72] ↑	OR	20
Weak handgrip strength (n=1)	Two conditions	1.29 [1.11 to 1.50] ↑	OR	36
	Three conditions	1.41 [1.18 to 1.68] ↑	OR	36
	Four conditions	1.78 [1.46 to 2.18] ↑	OR	36
Higher care challenges (n=1)	Multimorbidity vs. not	1.48 [1.01 to 2.05] ↑	AOR	45

*OR: Odds ratio, AOR: Adjusted odds ratio. All reported outcomes are statistically significant.

alike. Hence, the findings of this study could also be extrapolated to countries with similar demographic and epidemiological transition along with similar health systems by targeting these determinants.

Strengths and limitations

We employed a comprehensive search strategy in various databases to find out exhaustive list of all available articles in the domain. Further, screening, data extraction and analysis were performed following prospectively registered protocol. Meta-analysis was done to synthesize the pooled prevalence which was a major strength of this study. However, heterogeneity and repetition in data led us to include only 19 articles in the meta-analysis. This review includes sample from both community and primary care set ups which is an additional strength. However, the fact that this study is restricted to India alone may be seen as a drawback. Nonetheless, India is the second-most populous nation in the world, hence it was imperative to perform this review for future policy decisions.

Conclusion

Multimorbidity has become a norm in India. The increasing burden of multimorbidity among older adults cannot be overlooked. Nation-wide primary studies to investigate the

real burden of multimorbidity are warranted. Additionally, studies pertaining to vulnerable groups such as urban poor and tribal along with interventions are also warranted. Uniform methods to assess multimorbidity are required.

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Author contributions

Concept and design: RV, AS and SP. Acquisition, analysis, or interpretation of data: RV, AS, MB, DN, RKM, RJ, ST, JTL and SP. Drafting of the manuscript: RV, AS, DN and SP. Critical revision of the manuscript for important intellectual content: MB, RKM, RJ, JTL and ST. Statistical analysis: RV and AS. Administrative and technical support: RJ, ST and SP. Supervision: SP. All authors have agreed on publishing the final version of manuscript.

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Ethical statement

Ethical approval

This review is based on the published literature, hence has no ethical concerns. We have not used individual patient data thus, eliminating privacy concerns.

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Data availability statement

All data underlying this research will be made available on reasonable request to the authors.

Supplemental Material

Supplemental material for this article is available online.

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