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SYSTEMATIC REVIEW

A Systematic Review of Cost-of-Illness Studies of Multimorbidity

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Abstract

Objectives The economic burden of multimorbidity is considerable. This review analyzed the methods of cost-of-illness (COI) studies and summarized the economic outcomes of multimorbidity.

Methods A systematic review (2000–2016) was performed, which was registered with Prospero, reported according to PRISMA, and used a quality checklist adapted for COI studies. The inclusion criteria were peer-reviewed COI studies on multimorbidity, whereas the exclusion criterion was studies focusing on an index disease. Extracted data included the definition, measure, and prevalence of multimorbidity; the number of included health conditions; the age of study population; the variables used in the COI methodology; the percentage of multimorbidity vs. total costs; and the average costs per capita.

Results Among the 26 included articles, 14 defined multimorbidity as a simple count of 2 or more conditions. Methodologies used to derive the costs were markedly different. Given different healthcare systems, OOP payments of multimorbidity varied across countries. In the 17 and 12 studies with cut-offs of ≥2 and ≥3 conditions, respectively, the ratios of multimorbidity to non-multimorbidity costs ranged from 2–16 to 2–10. Among the ten studies that provided cost breakdowns, studies with and without a societal perspective attributed the largest percentage of multimorbidity costs to social care and inpatient care/medicine, respectively.

Conclusion Multimorbidity was associated with considerable economic burden. Synthesising the cost of multimorbidity was challenging due to multiple definitions of multimorbidity and heterogeneity in COI methods. Count method was most popular to define multimorbidity. There is consistent evidence that multimorbidity was associated with higher costs.

Key points for decision makers

Despite substantial methodological variations between COI studies, there is consistent evidence of considerable economic burden associated with multimorbidity.

Yet pooling the costs from different studies is impossible given different environments, such as healthcare systems, period of observation and perspectives.

Social care is the most important cost drivers in multimorbidity COI studies with societal perspective while inpatient care/medicine in studies without societal perspective.

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1 Background

The term multimorbidity refers to the presence of multiple concurrent chronic health conditions in one individual without an index disease [1]. Regardless of the specific definition of multimorbidity adopted, it is common [2], particularly in the elderly with prevalence estimates of 65–98% for those aged >65 years [3–5]. Additionally, a growing body of evidence has indicated an increasing prevalence of multimorbidity [6]. In the Netherlands, Uijen and van de Lisdonk found that the prevalence of people with two or more chronic health conditions increased from 12.3% to 20.5% in primary care from 1985 to 2005 [7]. In the United States, Ward found that the prevalence of multimorbidity increased from 21.8% in 2001 to 25.5% in 2012 using the data from a national household survey [8, 9].

Multimorbidity is one of the most problematic "chronic health conditions" [10] because of the escalating prevalence and its far-reaching health consequences. Multimorbidity can have a drastic and lifetime impact, as it is unlikely to be cured. Additionally, compared to single health conditions, multimorbidity has been related to poorer health-related quality of life [11, 12], higher health service utilization [13], and negative occupational consequences [14], such as productivity loss due to presenteeism (e.g., 'continuing to work while sick') and absenteeism. Moreover, healthcare resource consumption is expected to increase not only because of the accumulation of chronic health conditions but also because of interactions and synergies among health conditions present within an individual [15]. Given the concurrent changes in epidemiology, the use of resources and morbidity-related costs of multimorbid conditions are likely to undergo enormous changes as well, especially since uniform definition and measure of multimorbidity have been lacking.

Some researchers have begun to summarize the associations of multimorbidity and costs. Lehnert et al. reviewed the literature in 2011 which was restricted to studies of older adults only [16]. Sambamoorthi et al. conducted a narrative expert review which does not meet the criteria for a systematic review, i.e. did not report use of systematic review methodology, did not describe a study protocol and therefore was not registered on Prospero, did not include a standardised assessment of study quality, and did not follow guidelines for reporting systematic reviews (e.g. PRISMA) [17]. Our review meets all of these criteria and we believe it presents an important and distinct contribution to this field. Another advantage of this review was providing the breakdown of costs. The aim of this study was two-fold: we first compiled a general description of COI methods, and we subsequently systematically reviewed studies on the costs of multimorbidity, analyzing the different methods used, summarizing their findings on the economic impact of multimorbidity and evaluating the quality of the included COI studies.

2 Methods

A literature search was performed in the following electronic databases: PROSPERO, Cochrane Library (including the HTA database, DARE and Cochrane database of systematic reviews), health economic evaluations databases [including the NHS economic evaluation database (NHS EED) and health economic evaluations database (HEED)], National Institute for Health and Care Excellence (NICE) Evidence Services, Google Scholar, Scopus, and PubMed. The search strategy combined key words related to multimorbidity, comorbidity and multiple chronic health conditions. The search was restricted to papers written in English and published since 2000 up to October 2016. The inclusion criteria were peer-reviewed COI studies (including cross-sectional, cohort and modeling studies); the exclusion criterion was studies focusing on an index disease. The main difference between comorbidity and multimorbidity was whether an index disease was specified or not. Calculating the costs without distinguishing those two situations may lead to an underestimation of the burden of multimorbidity. As in "comorbidity", allied treatments of the dominant disease might also apply to the triggered secondary diseases, while in "multimorbidity", each disease receives relatively independent treatments. Therefore, we included "comorbidity" in the search terms primarily because of the interchangeable use of the terms "comorbidity" and "multimorbidity" in the literature. Then, during the article screening stage, studies were excluded if they focused on "an index disease". Figure 1 illustrates the literature search and selection process and presents the reasons for study exclusion. As an example, the search strategy for PubMed is shown below.

(((multimorbidity[Title/Abstract]) OR (multi-morbidity[Title/Abstract]) OR (comorbidity[MeSH Terms]) OR (co-morbidity[Title/Abstract]) OR ((multiple[Title/Abstract]) AND (chronic[Title/Abstract] OR long-term[Title/Abstract] OR "long term"[Title/Abstract]) AND (illnesses[Title/Abstract] OR diseases[Title/Abstract] OR conditions[Title/Abstract]))) AND ((forecasting[MeSH Terms]) OR (health expenditures[MeSH Terms]) OR (spending[Title/Abstract]) OR (costs and cost analysis[MeSH Terms]) OR (cost-of-illness[Title/Abstract]) OR (cost of illness[Title/Abstract])) AND English[Language] AND ("2000"[Date–Publication]: "3000"[Date–Publication])) NOT (letter[Publication Type] OR news[Publication

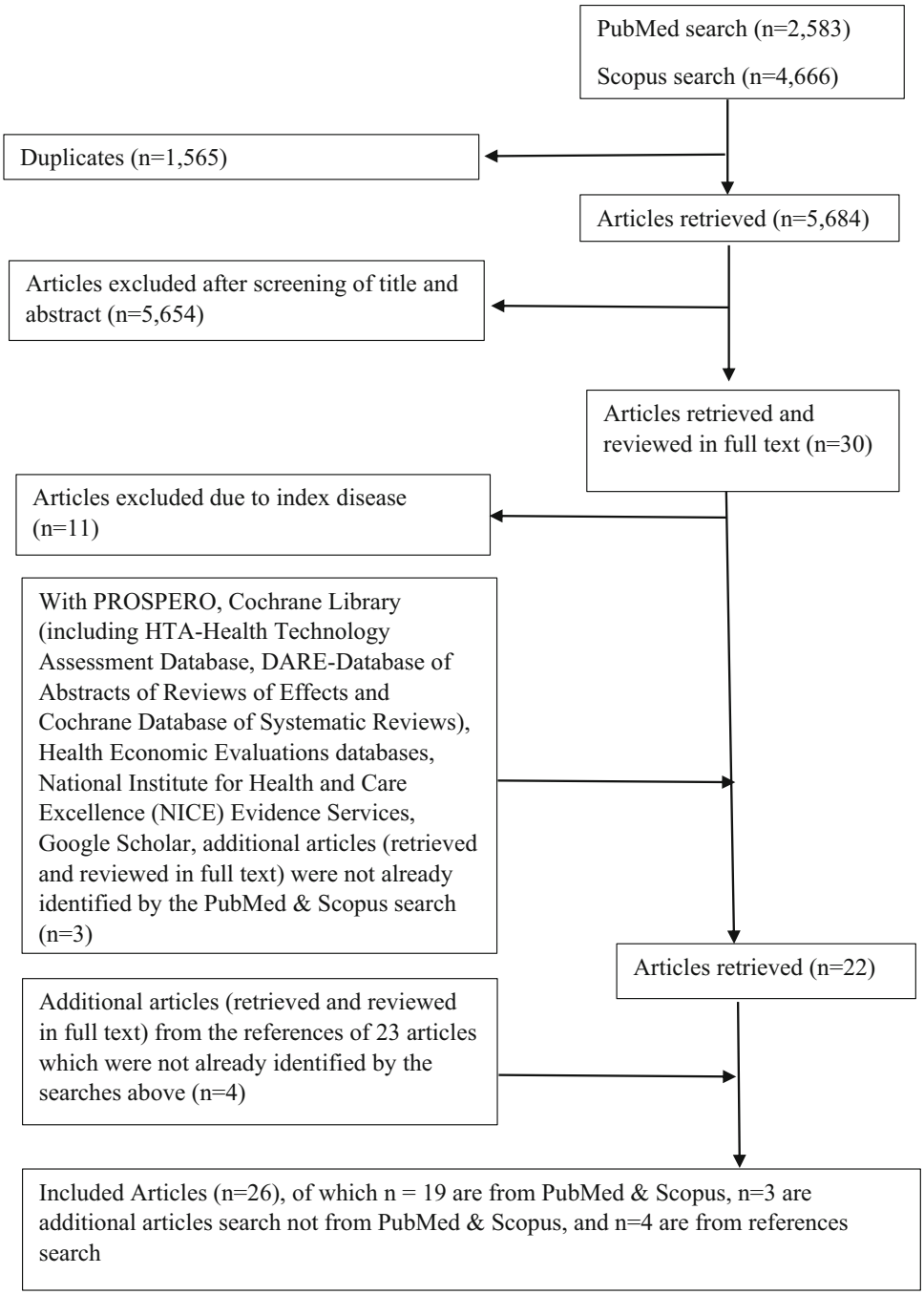

Fig. 1 Flowchart illustrating the search process

Type] OR editorial[Publication Type] OR "newspaper article"[Publication Type] OR comment[Publication Type]).

All titles and abstracts were screened by two independent reviewers (LLW and LS), after which the full texts of all potentially eligible papers were obtained and screened by the same two reviewers. For any disagreement, the abstract was set aside for further evaluation. After a consensus was reached on the final sample of papers, the primary reviewer (LLW) screened the reference lists of the included papers for additional papers that fulfilled the inclusion criteria. This review was reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [19].

Formal international guidelines for quality analyses of COI studies are lacking; therefore, relevant information was extracted referring to the British Medical Journal Checklist [20] for economic submissions and was adapted for COI studies by Molinier et al. [21]. Equal weight was assigned to each item of the checklist, and the final score

was the sum of the ten individual items. The two reviewers assessed each study separately. If there was disagreement between two reviewers at this stage, the paper was discussed with reference to the aforementioned COI study checklist until agreement was reached.

This systematic review summarized the results referring to the items of COI methods, which have been described elsewhere [18, 20, 21]. The items included the definition of multimorbidity, the epidemiological approach, the perspective of the study and the type of costs assessed, resource consumption and unit costs, and sensitivity analyses (dimensions shown in Tables 1, 2).

Investigating subgroup heterogeneity in COI estimates represents an area for future research [22]. Therefore, the included studies had to be stratified and presented by different components of costs, with clear explanations of the groups. To make the costs comparable, cost estimates were all converted to USD ($), according to the 2016 exchange rate for each study and each currency, with adjustments over time based on the consumer price index (CPI) for the original currency. Costs were reported as average annual costs (per-capita costs) unless stated otherwise, because the total costs reported in the different studies varied depending on the included sample sizes. The results were synthesized descriptively.

3 Results

A total of 7249 studies were identified from the PubMed and Scopus literature search. After the titles, abstracts and full text were screened, 19 studies remained. Then, we incorporated three studies from other databases that were not identified from PubMed and Scopus. With these 22 studies, we screened the references and identified four studies that had not been identified in our literature search. Finally, twenty-six studies met our criteria (shown in Tables 1, 2, 3). The years of valuation ranged from 1996 to 2013. Thirteen studies were conducted in the United States [3, 23–34], seven in Europe [13, 35–40], two in Australia [41], one each from Canada [42], Singapore [43] and Taiwan [44], and two in middle- or low-income regions [40, 45]. Overall, twenty studies used a prevalence approach [3, 13, 23–28, 30–32, 35, 37–41, 43, 45, 46], seven used an incidence approach [27, 29, 33, 34, 36, 42, 44], and only one used an economic model to estimate the lifetime costs of multimorbidity [36]. The studies analyzed samples ranging in size from 1252 to 292 million [28]. Twenty-five studies specified the age range of the sample [26]. Twenty-one studies calculated estimates in a population 65 years and older [3, 13, 23–25, 27, 28, 30–32, 35–41, 43–46], eight studies included people under 18 years old [23–25, 28, 30, 36, 38, 44], and three studies were conducted in children only [33, 34, 42]. The average annual cost of multimorbidity per capita ranged from $49 [40] to $252,313 [33], showing significant variation by study. Additionally, out-of-pocket (OOP) expenditures ranged from $49 [40] to $6,858 [27], which was lower than public insurance costs. Children with three or more life-threatening complex chronic conditions in their last year of life had the highest costs ($252,313) [33].

3.1 Identifying Multimorbidity

In total, fourteen studies provided the same, clear definition of multimorbidity, i.e., the ≥2 simple count method [13, 23, 29–32, 35, 37–41, 43, 45]. Twelve studies estimated the costs by number, including five "organ system" and seven "health condition or symptom" studies, although they did not refer to the term "multimorbidity". For other definitions of multimorbidity, COI information was very limited. Only four studies accounted for the severity of health conditions when measuring multimorbidity; two of them used the cumulative illness rating scale (CIRS) [35, 37]; the clinical risk groups (CRG) model [36] and Rx-defined morbidity groups (Rx-MG) [44] were each used only once. The number of health conditions included when identifying multimorbidity ranged from 4 [32] to 259 [23, 26, 29].

3.2 Epidemiological Approach

Six studies followed an incidence-based approach [27, 29, 33, 34, 36, 42, 44], and twenty studies calculated prevalence-based healthcare costs [3, 13, 23–28, 30–32, 35, 37–41, 43, 45, 46]. Lifetime costs were estimated in only one study [36], and unfortunately, specific multimorbidity-related costs were unavailable.

3.3 Perspective of the Analysis and Costs Assessed

Three perspectives were included: eighteen studies were from the payer's perspective [3, 23–31, 34, 36, 39–41, 44–46], six were from healthcare providers' perspective [13, 32, 33, 35, 38, 42], and two used the societal perspective [37, 43]. However, both of the studies from the societal perspective defined costs as including only healthcare and social care costs. Twelve studies included both medical and non-medical expenditures when quantifying direct costs [3, 23, 24, 27, 28, 31, 32, 37, 40, 41, 43, 46].

3.4 Estimating Resource Consumption

Three approaches can be used to estimate resource consumption: bottom-up, top-down and econometric [18].

Table 1 Methodology of included cost-of-illness studies in multimorbidity

Study	Country	Perspective	Epidemiological approach	Study design	Year of valuation	Currency
Hwang et al. [23]	USA	Payer (OOP)	Prevalence	Cross-sectional	1996	USD
Garis et al. [24]	USA	Payer (public insurance)	Prevalence	Cross-sectional	1995	USD
Wolff et al. [3]	USA	Payer (public insurance)	Prevalence	Cross-sectional	1999	USD
Anderson et al. [25]	USA	Payer (public insurance)	Prevalence	Cross-sectional	1998	USD
Thorpe et al. [26]	USA	Payer (public insurance)	Prevalence	Cross-sectional	1987	USD
Thorpe et al. [26]	USA	Payer (public insurance)	Prevalence	Cross-sectional	1997	USD
Thorpe et al. [26]	USA	Payer (public insurance)	Prevalence	Cross-sectional	2002	USD
Schoenberg et al. [27]	USA	Payer (OOP)	Prevalence/ incidence	Cross-sectional	1998	USD
Schoenberg et al. [27]	USA	Payer (OOP)	Prevalence/ incidence	Cross-sectional	2002	USD
Paez et al. [28]	USA	Payer (OOP)	Prevalence	Cross-sectional	2005	USD
Glynn et al. [13]	West of Ireland (national representative)	Health care providers	Prevalence	Cross-sectional	2009	EUR
Naessens et al. [29]	USA	Payer	Incidence	Cohort (4 years follow-up)	2007	USD
Nagl et al. [35]	Germany	Health care providers	Prevalence	Cross-sectional	2010	EUR
Carreras et al. [36]	The county of Baix Empordà in Catalonia (Spain)	Payer (public insurance)	Incidence	Cohort (lifetime)	2007	EUR
Kuo et al. [44]	Taiwan	Payer (public insurance)	Incidence	Cohort (6 years follow-up)	2010	USD
Lochner et al. [30]	USA	Payer (public insurance)	Prevalence	Cross-sectional	2011	USD
Machlin et al. [31]	USA	Payer (public insurance)	Prevalence	Cross-sectional	2009	USD
McRae et al. [41]	Australia	Payer (public insurance)	Prevalence	Cross-sectional	2009	AUD
Heider et al. [37]	Germany	Payer (OOP)	Prevalence	Cross-sectional	2009	EUR
Orueta et al. [38]	Basque country (region in Spain/ France)	Societal	Prevalence	Cross-sectional	2011	EUR
Pati et al. [45]	India	Health care providers	Prevalence	Cross-sectional	2007	INR
Bahler et al. [39]	Switzerland	Payer	Prevalence	Cross-sectional	2013	Swiss francs
Lee et al. [40]	China	Payer (OOP)	Prevalence	Cross-sectional	2010	CNY
Lee et al. [40]	Ghana	Payer (OOP)	Prevalence	Cross-sectional	2010	GHC
Lee et al. [40]	Mexico	Payer (OOP)	Prevalence	Cross-sectional	2010	INR
Lee et al. [40]	Russia	Payer (OOP)	Prevalence	Cross-sectional	2010	MXN
Lee et al. [40]	South Africa	Payer (OOP)	Prevalence	Cross-sectional	2010	RUB
Lee et al. [40]	India	Payer (OOP)	Prevalence	Cross-sectional	2010	ZAR
Meraya et al. [32]	USA	Health care providers & payer	Prevalence	Cross-sectional	2011	USD
Picco et al. [43]	Singapore	Societal	Prevalence	Cross-sectional	2013	SGD

Table 1 continued

Study	Country	Perspective	Epidemiological approach	Study design	Year of valuation	Currency
Carpenter et al. [46]	Australia	Payer (OOP)	Prevalence	Cross-sectional	2009	USD
Cohen et al. [42]	Canada	Health care providers	Incidence	Cohort (2 years follow-up)	2005-2007	CAD
Ananth et al. [33]	USA	Health care providers	Incidence	Cohort (4 years follow-up)	2012	USD
Zhong et al. [34]	USA	Payer (public insurance)	Incidence	Cohort (4 years follow-up)	2004	USD

OOP Out-of-pocket, *USA* United States of America, *USD* United States dollar, *EUR* Euro, *AUD* Australian dollar, *INR* Indian rupee, *CNY*, Chinese yuan, *GHC* Ghana cedi, *MXN* Mexican peso, *RUB* Russian rouble, *ZAR* South African rand, *SGD* Singapore dollar, *CAD* Canadian dollar

While the top-down approach typically requires cost data as well as relative risks to calculate population-attributable fractions, the bottom-up approach often requires data from multiple sources, and the econometric approach often requires only a single dataset [18]. Sixteen studies gathered data on resource consumption from different departments (bottom-up approach) [3, 13, 25, 26, 29–38, 42, 44]. One used a combined bottom-up and top-down approach [35]. Ten studies extracted costs from the single database, called an econometric approach [23, 24, 27, 28, 39–41, 43, 45, 46]. The follow-up periods included lifetime follow-up in a study that adopted an incidence-based approach [36], six years in one study [44], four years in three studies [29, 33, 34] and two years in one study [42].

3.5 Valuation of Unit Costs

3.5.1 Sources of Cost Estimations

Most American studies calculated costs from Medicare payments and the medical expenditure panel survey (MEPS), which provided national, continuous and comparable estimates over time. An Irish study used data from primary care consultations and outpatient and inpatient visits extracted from family practices [13]. One study quantified indirect costs [43]. Four studies did not provide the unit costs [25, 36, 38], and one study reported the unit incremental cost only [37].

3.5.2 Discounting Costs

Studies with time horizon less than one or two years did not normally discount costs. In all included studies in this review, costs were not discounted, even in the longitudinal studies with more than a two-year follow-up.

3.6 Sensitivity Analysis

None of the studies analyzed or discussed the variables that had a significant impact on cost estimates.

3.7 Presentation of Results

The results were clearly presented in most studies and were mainly well explained and consistently reported in relation to the methods adopted. Three studies did not differentiate costs. Based on the key methodological points, a checklist of questions was used with full explanations given for clarity (Table 3). For thirteen studies, the answer to seven of ten questions was "yes", and all the studies were scored "no" on question 9 "Were the major assumptions tested in a sensitivity analysis?" Questions 3 "Were direct/indirect costs sufficiently disaggregated?" and 7 "Were unit costs appropriately valued?" received fewer "yes" answers than the other questions. In one American study [24], the costs were sufficiently disaggregated only for single conditions, and the costs of multimorbidity were presented only as additional or supplementary information.

4 Discussion

We systematically reviewed 26 COI studies on multimorbidity without restricting the studies to any specific definition of multimorbidity, and this broad inclusion contributed to a comprehensive understanding of multimorbidity and its economic burden. The costs of multimorbidity ranged from $49 [40] to $252,313 [33] annual per capita and increased according to the level of multimorbidity within each study. We found a relative paucity of data on the costs of multimorbidity, but the available data still provided valuable information for us to better

Table 2 The definition, measure, costs of multimorbidity

Study	Definition of MM	Measure of MM	Number of included conditions	Age range (y.o.)	Prevalence of MM (%)	%(MM) of total costs	Direct costs		Indirect costs	Average costs of MM ($)*		MM/non-MM	
							Direct medical costs	Direct non-medical costs		MM2+	MM3+	MM2+	MM3+
Hwang et al. [23]	MM2+	Count	259	0–80+	17.0	38.1	Yes	No	No	1387	1733.0	3	3
Garis et al. [24]	NS	Count	9	0+	NA	NA	Yes	Yes	No	7938	NA	NA	NA
Wolff et al. [3]	NS	ACG	3493	65+	65 (MM2+)/43 (MM3+)	95.3	Yes	Yes	No	10,627	14,276.0	11	10
Anderson et al. [25]	NS	Count	NS	0+	NA	NA	Yes	No	No	NA	NA	NA	NA
Thorpe et al. [26]	NS	Count	259	NS	76.4	92.2	Yes	No	No	13,330	14,989.8	6	3
Thorpe et al. [26]	NS	Count	259	NS	80.5	95.1	Yes	No	No	10,950	12,158.8	5	4
Thorpe et al. [26]	NS	Count	259	NS	86.2	97.2	Yes	No	No	11,666	12,864.0	6	5
Schoenberg et al. [27]	NS	Count	8	65+	58.1	70.6	Yes	Yes	No	3858	4109.0	2	2
Schoenberg et al. [27]	NS	Count	8	65+	70.4	78.6	Yes	Yes	No	6856	7687.6	2	2
Paez et al. [28]	NS	Count	NS	0+	24 (MM2+)/13 (MM3+)	48.5	Yes	Yes	No	1844	2306.0	16	4
Glynn et al. [13]	MM2+	Count	147	50+	66.2	82.5	Yes	No	No	2211	2602.0	2	2
Naessens et al. [29]	MM2+	Count	259	18–64	54.3	82.5	Yes	No	No	13,285	16,245.0	4	4
Nagl et al. [35]	MM2+	CIRS	33	65+	86.4	94.8	Yes	No	No	3778	4422.0	2	2
Carreras et al. [36]	NS	CRG model	All 857,385 ICD codes (815,227 diagnostics and 42,158 procedures)	0+	17.8	NA	Yes	No	No	NA	NA	NA	NA
Kuo et al. [44]	NS	Counting the number of Rx-MG	55	0–71	80	NA	Yes	No	No	1045	NA	4	NA
Lochner et al. [30]	MM2+	Count	15	0+	67.3	92.6	Yes	No	No	13,949	NA	6	NA

Table 2 continued

Study	Definition of MM	Measure of MM	Number of included conditions	Age range (y.o.)	Prevalence of MM (%)	%(MM) of total costs	Direct costs		Indirect costs	Average costs of MM ($)*		MM/non-MM	
							Direct medical costs	Direct non-medical costs		MM2+	MM3+	MM2+	MM3+
Machlin et al. [31]	MM2+	Count	20	18+	25.0	60.3	Yes	Yes	No	11,934	NA	4	NA
McRae et al. [41]	MM2+	Count	6	50+	55.8	81.0	Yes	Yes	No	1781	2014	2	2
Heider et al. [37]	MM2+	CIRS-G	14	57–84	NA	74.0	Yes	Yes	No	NA	NA	NA	NA
Orueta et al. [38]	MM2+	ACG	52	0+	23.6	63.6	Yes	No	No	NA	NA	NA	NA
Pati et al. [45]	MM2+	Count	NS	18+	1.3–30.6	NA	Yes	No	No	240	NA	NA	NA
Bahler et al. [39]	MM2+	Count	22	65+	76.6	94.7	Yes	No	No	8233	NA	5	NA
Lee et al. [40]	MM2+	Count	9	18+	1.4% in 18–29 years old to 40.0% in those aged 70+ years	NA	Yes	Yes	No	655	NA	NA	NA
Lee et al. [40]	MM2+	Count	9	18+		NA	Yes	Yes	No	92	NA	NA	NA
Lee et al. [40]	MM2+	Count	9	18+		NA	Yes	Yes	No	165	NA	NA	NA
Lee et al. [40]	MM2+	Count	9	18+		NA	Yes	Yes	No	151	NA	NA	NA
Lee et al. [40]	MM2+	Count	9	18+		NA	Yes	Yes	No	49	NA	NA	NA
Lee et al. [40]	MM2+	Count	9	18+		NA	Yes	Yes	No	60	NA	NA	NA
Meraya et al. [32]	MM2+	Count	4	21+	100.0	NA	Yes	Yes	No	12,317	16,454	NA	NA
Picco et al. [43]	MM2+	Count	10	60+	51.5	80.7	Yes	Yes	No	11,167	NA	2	NA
Carpenter et al. [46]	NS	Count	11	50+	71.1	3.4	Yes	Yes	No	4447	3415	3	2
Cohen et al. [42]	NS	Count	9 organ systems	0–16	6.7	NA	Yes	No	No	36,434	NA	NA	NA
Ananth et al. [33]	NS	Count	9 organ systems	0–17	66.1	88.59	Yes	No	No	252,313	360,046	4	4

Table 2 continued

Study	Definition of MM	Measure of MM	Number of included conditions	Age range (y.o.)	Prevalence of MM (%)	%(MM) of total costs	Direct costs		Indirect costs	Average costs of MM ($)*		MM/non-MM	
							Direct medical costs	Direct non-medical costs		MM2+	MM3+	MM2+	MM3+
Zhong et al. [34]	NS	Count	20	1–19	17	44.84	Yes	No	No	8551	15,797	4	6

*All costs are in $ (1 EUR = 1.0886 USD;1 AUD = 0.762966 USD;1 INR = 0.014948 USD;1 CHF = 1.005635 USD;1 CNY = 0.143719 USD;1 MXN = 0.049118 USD;1 RUB = 0.016234 USD;1 ZAR = 0.071561 USD;1 SGD = 0.717926 USD; December 18, 2016)

ACG Adjusted clinical groups, *Rx-MG* Rx-defined morbidity groups, *CRG* clinical risk groups, *CIRS* cumulative illness rating scale, *CIRS-G* cumulative illness rating scale for geriatrics, *ICD* the international classification of diseases, *MM* multimorbidity, *MM2+* two-cutoff count method of multimorbidity, *MM3+* three-cutoff count method of multimorbidity, *y.o.* years old, *NS* not specific, *NA* not available

elucidate the current magnitude of the economic burden of multimorbidity. Methods were highly heterogeneous producing a wide range of COI estimates. Even at the lower bounds, these costs were substantial.

4.1 Costly Multimorbidity

The proportion of costs due to multimorbidity in relation to the total costs ranged from 3.4 to 97.8%. Most ($n = 18$) estimates were 60% and above. One study with an extraordinarily low estimate (3.4%) [46], which seemed inconsistent with the other studies, only evaluated three-month cases of out-of-pocket (OOP) expenditures in Australia. Two factors could explain this finding. First, the respondents had a 17% higher average income than the Australian general population [46] and thus underrepresented lower socioeconomic groups (including the indigenous population), who are most likely to experience higher cost burdens. Second, the conditions included in the study were all chronic, which required ongoing treatment [47], and the short duration of the study may not have reflected all incurred costs.

The highest costs of multimorbidity per person occurred in the last year of life among children with life-threatening conditions ($252,313) [33]. The costs in all three studies with young respondents ranged from $8551 [34] to $252,313 [33] and did not include direct non-medical or indirect costs. Although the childhood prevalence estimates of chronic health conditions ranged from 0.22 to 44% [48], which was much lower than the 12.9–95.1% prevalence of multimorbidity in the broader age groups [49], multimorbid children and their families still faced substantial financial pressure. Moreover, the included studies indicated a persistence of high costs in the following years.

4.2 Heterogeneity of Multimorbidity COI Studies

Three relevant perspectives of the costs of multimorbidity were included. The societal perspective, including care costs, was used in two studies, but they did not account for the costs of productivity loss due to multimorbidity [50], including presenteeism, absenteeism, premature retirement and death, which are responsible for a substantial proportion of the financial burden [51]. Information about productivity loss, premature retirement and death could be derived from the working population. Only one Australian study in this review was conducted among working-age adults and included those who were not in the workforce [29]. Unemployed populations are more likely to have more chronic conditions than employed groups [50]. However, that study did not estimate productivity loss, which could have been addressed with the available data.

Table 3 Answers to the methodological questions by study

Questions/answers	All studies	Hwang et al. [23]	Garis et al. [24]	Wolff et al. [3]	Anderson et al. [25]	Thorpe et al. [26]	Schoenberg et al. [27]	Paez et al. [28]	Glynn et al. [13]	Naessens et al. [29]	Nagl et al. [35]	Carreras et al. [36]	Kuo et al. [44]	Lochner et al. [30]	Machlin et al. [31]
1 Was a clear definition of the illness given?		1	p	p	0	p	p	0	1	1	1	p	p	1	1
2 Were epidemiological sources carefully described?		1	1	1	P	0	1	1	1	0	1	p	1	1	1
3 Were direct/indirect costs sufficiently disaggregated?		1	0	0	0	0	0	1	1	0	1	0	0	0	0
4 Were activity data sources carefully described?		1	1	1	1	1	1	1	1	0	p	p	1	1	p
5 Were activity data appropriately assessed?		1	1	1	0	p	1	1	1	p	1	1	1	1	p
6 Were the sources of all cost values analytically described?		1	0	0	0	1	1	1	1	0	1	1	1	p	0
7 Were unit costs appropriately valued?		1	1	1	1	1	1	1	1	1	1	p	1	1	1
8 Were the methods adopted carefully explained?		p	1	1	p	p	1	1	1	0	1	1	1	p	p
9 Were the major assumptions tested in a sensitivity analysis?		0	0	0	0	0	0	0	0	0	0	0	0	0	0
10 Was the presentation of study results consistent with the methodology of the study?		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total score by study															
Yes (1)	165	8	6	6	3	4	7	8	9	3	8	4	7	6	4
No (0)	58	1	3	3	5	3	2	2	1	6	1	2	2	2	3
Partially (p)	37	1	1	1	2	3	1	0	0	1	1	4	1	2	3

Table 3 continued

Questions/answers	All studies	McRae et al. [41]	Heider et al. [37]	Orueta et al. [38]	Pati et al. [45]	Bahler et al. [39]	Lee et al. [40]	Meraya et al. [32]	Picco et al. [43]	Carpenter et al. [46]	Cohen et al. [42]	Ananth et al. [33]	Zhong et al. [34]
1 Was a clear definition of the illness given?		1	1	1	p	1	1	1	1	p	p	p	p
2 Were epidemiological sources carefully described?		1	1	1	1	1	p	1	1	1	1	1	1
3 Were direct/indirect costs sufficiently disaggregated?		0	p	1	1	1	1	0	1	1	0	0	0
4 Were activity data sources carefully described?		1	1	1	1	1	1	p	p	1	1	1	p
5 Were activity data appropriately assessed?		1	1	1	1	1	1	1	1	1	1	1	p
6 Were the sources of all cost values analytically described?		1	p	1	p	1	1	0	1	1	p	1	1
7 Were unit costs appropriately valued?		1	1	1	0	0	0	0	1	1	1	1	1
8 Were the methods adopted carefully explained?		1	1	p	1	1	p	1	1	1	1	1	1
9 Were the major assumptions tested in a sensitivity analysis?		0	0	0	0	0	0	0	0	0	0	0	0
10 Was the presentation of study results consistent with the methodology of the study?		1	1	1	1	1	1	1	1	1	1	1	1
Total score by study													
Yes (1)	165	8	7	8	6	8	6	5	8	8	6	7	5
No (0)	58	2	1	1	2	2	2	4	1	1	2	2	2
Partially (p)	37	0	2	1	2	0	2	1	1	1	2	1	3

Total score by study is the sum of answers. *P* Partially

Six studies adopted a cohort study design, with follow-up periods ranging from two to six years. The remaining twenty studies used cross-sectional data, which reflect only the time of data collection and are limited in their ability to draw valid conclusions about associations or possible causality [52]. Compared to other reviews of COI studies on a specific single disease, this review on multimorbidity included fewer cohort studies [53]. Data collection over a long period of time is difficult and time- and cost-intensive; however, modeling designs could compensate for these challenges [54]. In this review, only Carreras et al. simulated individual costs until death using a stationary Markov chain under the assumption that transition probabilities were constant [36]. This approach was not consistent with the nature of chronic conditions, in which health states change dynamically, and modeling of chronic conditions should consider this difference [54]. However, the lifetime multimorbidity costs could be reasonably predicted in this regional study.

Several studies did not fully describe their methods and were thus difficult to assess. This ambiguity might be due to a general lack of economic awareness in the medical journals that support economic studies. A community-based cohort ensures a more representative patient population, but the diagnosis of this cohort may rely on self-reported data, which are certainly less precise. The studies analyzed here confirm that multimorbidity is costly and suggest that the costs of multimorbidity account for a large share of the total costs (Table 2).

Given different healthcare systems, OOP payments varied across countries, but OOP expenditure of multimorbidity is always greater than that of non-multimorbidity. For example, in China, the patients with multimorbidity have higher OOP expenditure than those without multimorbidity, even among those with health insurance [40]. Findings from economic studies in different countries or regions cannot be easily generalized due to monetary issues; for example, different currencies have different purchasing power for the same product [56].

4.3 Definitions of Multimorbidity

It is well known that there is no singular definition of multimorbidity, and the two cut-off count method is generally the most broadly accepted definition used. In this review, we found that all the COI studies that provided a definition of multimorbidity adopted only this method. Most of the studies that did not specifically define multimorbidity also presented costs by the number of multimorbid conditions. Using the same definition increased the comparability within the available COI studies.

The number of included health conditions used to identify multimorbidity ranged from 4, which were highly prevalent, disabling or expensive conditions in an American community [32], to 259, which included all conditions in clinical classification systems [29]. The costs did not increase as more conditions were included. The wide variation in severity within specific conditions [55] could produce different costs. For example, children with life-threatening conditions had the highest healthcare expenditure in this review [33].

Using the two cut-off count method to define multimorbidity, the ratios of the costs of multimorbidity to non-multimorbidity ranged from 2 to 16, while the ratios ranged from 2 to 10 using the three cut-off count method. Nevertheless, interpreting these quantitative results is problematic because of the different approaches used. Domestic characteristics within each country or region, such as clinical practice settings and healthcare systems, also affect resource consumption and unit costs. For example, medication costs can vary among studies because of the use of tariffs in solidarity systems, which are not comparable to free prices in private systems.

The different methodologies used to identify multimorbidity led to the wide range in expenditures reported above. The number and diversity of available studies on multimorbidity provide an insufficient scientific basis for further explorations on multimorbidity. Therefore, it is vital to improve the methodological quality of multimorbidity COI research to gain a better understanding of this common and important phenomenon. Moreover, further research is needed to clarify the costs of multimorbidity from the societal perspective.

4.4 Limitations and Strengths

The results of this review are limited by the nature of the studies identified. The main limitation of this review is its inability to include all relevant studies. Costs were estimated in 16 countries or regions from 1996 to 2013. The large number of abstracts derived from the databases improved the sensitivity of our search strategy. The absence of a MeSH term for multimorbidity is a clear limitation. However, adding multimorbidity-related terms from previous studies to our search strategy helped circumvent this limitation. We included papers published in English only, which restricted our sample to some extent. The OOP can vary widely between countries because of different health insurance systems and types of diseases, therefore, we have only reported the range of OOP payment in different countries. Based on the fact that multimorbidity is not prevalent in the young population, the pediatric multimorbidity studies were rare, therefore, the costs of multimorbidity could not be distinguished by age and the finding of pediatric studies in this review was limited.

Moreover, the practicality of COI studies themselves in aiding policy decision-making has been debated [57, 58], and their inability to prioritize resources has been criticized as well [59, 60]. COI studies, which aim to identify and measure all costs of health condition serve a different purpose than other health economic evaluations (e.g., cost–benefit, cost-effectiveness, and cost-utility analyses), which aim to assess both costs and outcomes of the adopted intervention/policy [61–63]. However, COI studies can provide useful information as long as they adhere to standardized and acceptable methodologies [64, 65]. Furthermore, the results of COI studies have been used by organizations such as the World Bank and the World Health Organization to estimate public, private and total national health expenditures globally [66]. Different stakeholders can utilize COI studies for different purposes [67]. For example, governments can estimate the financial impact of a disease on public budgets for resource allocation purposes, whereas pharmaceutical corporations can identify diseases with high management costs and direct research and development investments accordingly. However, caution is warranted when using COI studies; for optimal resource allocation, they should be used in combination with other thorough economic evaluations [68].

Despite these limitations, this review provides an overview of the range of estimates reported in recent decades, and the collated evidence provides a greater understanding of the COI of multimorbidity than the results provided by individual studies. Moreover, this review adds systematic evidence about the methodologies used to analyze multimorbidity costs and provides insight into the reasons for the disparate results among studies. Although multimorbidity complicates the findings of COI studies, this review can be useful for informing decisions about the prioritization of resources [69, 70], particularly when combined with other economic assessments.

5 Conclusion

Noting the substantial methodological variations between studies, multimorbidity was associated with a considerable economic burden. Although this review identified two studies estimating the costs from a societal perspective, there was a consistent theme throughout the included studies that those with multimorbidity had higher costs than those without multimorbidity. Future research should focus on improving the methods of estimating costs. A closer agreement of definition of multimorbidity is still required to allow consistent comparisons and enhance the interpretation of study findings among future studies.

Author Contributions Statement Lili Wang conceptualised the article, registered in PROSPERO, conducted the preliminary searches, screening of search results, data extraction, risk of bias (quality) assessment and data analysis, and wrote the manuscript. Lei Si advised on data analysis, conducted the second round screening of search results, data extraction and risk of bias (quality) assessment, and helped revise the manuscript. Fiona Cocker helped revise the manuscript. Andrew J Palmer assisted in conceptualising the study and revised the manuscript. Kristy Sanderson assisted in conceptualising the paper and revised the protocol and manuscript. All authors gave final approval of the version to be published.

Compliance with Ethical Standards

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