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Soley-Bori Marina, Ashworth Mark, Bisquera Alessandra, Dodhia Hiten, Lynch Rebecca, Wang Yanzhong, Fox-Rushby Julia

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Authors

Marina Soley-Bori , Mark Ashworth, Alessandra Bisquera, Hiten Dodhia, Rebecca Lynch, Yanzhong Wang, and Julia Fox-Rushby

Authors' affiliations

Marina Soley-Bori, PhD, Research Fellow in Health Economics, King's College London, School of Population Health Sciences, London, UK.

Mark Ashworth, DM, MRCP, FRCGP, Reader in Primary Care, King's College London, School of Population Health Sciences, London, UK.

Alessandra Bisquera, MSc, Research Fellow in Medical Statistics, King's College London, School of Population Health Sciences, London, UK.

Hiten Dodhia, MBChB, MSc, FFPH, Consultant in Public Health (Lambeth Council), Visiting Lecturer at King's College London; London, UK.

Rebecca Lynch, PhD, Research Fellow in Medical Anthropology, King's College London, School of Population Health Sciences, London, UK.

Yanzhong Wang, PhD, Reader in Medical Statistics, King's College London, School of Population Health Sciences, London, UK.

Julia Fox-Rushby, PhD, Professor of Health Economics, King's College London, School of Population Health Sciences, London, UK.

Corresponding author information

Marina Soley-Bori
King's College London, School of Population Health Sciences
Guy's Campus, Addison House, Workspace AH 3.04
London SE1 1UL
Marina.soley_bori@kcl.ac.uk

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ABSTRACT

Background: Managing multimorbidity is complex for both patients and healthcare systems. Multimorbid patients often use a variety of primary and secondary care services. Country-specific research exploring the utilisation and cost consequences of multimorbidity may inform future interventions and payment schemes in the UK.
Aim: To assess the relationship between multimorbidity, healthcare costs and utilisation. To determine how this relationship varies by disease combinations and health care components.
Design of study: Systematic literature review using Bidirectional Citation Search to Completion (BCSC). References and citations from initial articles were iteratively reviewed until no further sources were found.
Method: MEDLINE and grey literature were searched for UK studies since 2004. An iterative review of references and citations was completed. Authors from all papers selected were asked to check for completeness of UK evidence. A quality assessment tool was used to assess risk of bias (National Institute of Health National Heart, Lung, and Blood Institute tool). Data were extracted, findings synthesized, and study heterogeneity assessed; meta-analysis was conducted when possible.
Results: Seventeen studies were identified, 7 predicting healthcare costs and 10 utilisation. Multimorbidity is associated with increased total costs, hospital costs, care transition costs, primary care use, dental care use, emergency department use and hospitalisations. Several studies demonstrated the high cost of depression and of hospitalisation associated with multimorbidity.
Conclusion: In the UK, multimorbidity increases utilisation and costs of primary, secondary and dental care. Future research is needed on whether integrated care schemes offer efficiencies in health care provision for multimorbidity.

How this fits in

Multimorbidity, the presence of two or more conditions, is becoming the norm rather than the exception in primary care. Our review of 17 UK studies has drawn attention to both the high service utilisation and cost of providing health care to patients with multimorbidity, particularly when depression is one of the conditions. One unanswered question is whether models of 'integrated care' might mitigate the high cost of care.

1. INTRODUCTION

With improvements in public health and access to good quality care, people are living longer but frequently with multimorbidity. Multimorbidity—often defined as the coexistence of two or more conditions(1)—challenges quality improvement and cost-containment efforts. In 2015, 54% of England's over-65 population exhibited multimorbidity; this percentage is projected to increase to 68% by 2035(2). The current single disease-oriented model of care delivery struggles to address the needs of multimorbid patients, who often experience care fragmentation, difficulty in managing their treatments, and poor health outcomes(3–6). The Quality and Outcomes Framework (QOF), a quality improvement programme available to all GP practices in England since 2004, links payments to 77 indicators reflecting public health and clinical targets(7). However, as it takes no account of multimorbidity(8–10), GPs are not incentivised through this significant mechanism to focus on multimorbidity.

Besides quality of care shortfalls, multimorbidity may also result in higher healthcare utilisation and costs compared with single health conditions(11). Lehnert and colleagues systematically reviewed 35

studies of the relationship between multimorbidity, costs and utilisation. They showed that costs and utilisation (including physician visits, hospitalisations, and medication use) tend to increase with the number of conditions. Lehnert's review, conducted in 2010, did not find any UK studies on this topic. The relationship between multimorbidity and costs and utilisation, particularly its magnitude, may vary not only by person-specific and environmental factors (e.g. frailty, income deprivation, availability of social care services), but also across health systems (12,13).

This article summarizes findings on the relationship between multimorbidity, costs and utilisation in the UK, with additional focus on the definition of multimorbidity, analytic methods used, study limitations and research gaps. Implications for research and policy are also identified.

2. METHODS

This systematic search of literature followed the Bidirectional Citation Search to completion (BCSC) method. BCSC starts by selecting an initial set of relevant papers ('pearls'), based on expert knowledge or a systematic literature review, followed by a review of references and citations of the 'pearls' to gather further appropriate literature. After excluding irrelevant papers from the reference and citation search, this process is repeated until no further sources are found. BCSC mirrors snowballing of citation searches forward and backward, and iteratively repeats this process until no further studies are identified. Although rarely used as the primary method of systematic searching, BCSC may be an equally effective technique to comprehensively gather studies than a conventional systematic literature review (14,15).

To identify the initial list of pearls, the authors' initial knowledge of papers was supplemented by a Boolean logic search on Medline. The query (**Appendix 1**) combined terms used in the NICE multimorbidity guidelines(16), Medline UK filter(17), and two systematic literature reviews on multimorbidity(1,18). The NICE Evidence Search catalogue(19), SIGN (20), and the website of the International Research Community on Multimorbidity(21) were also used to identify additional publications and grey literature.

Two authors independently reviewed the first 100 titles and abstracts. The study inclusion and exclusion criteria (**Table 1**) were further refined after discussing discrepancies and a second double review of 100 sources was conducted. The first author screened the remaining articles. To target original research testing the relationship between multimorbidity and costs and utilisation, descriptive cost-of-illness, economic burden, or cost-effectiveness studies were excluded, along with literature reviews, meta-analyses, and study protocols. Results of the search and selection are reported in accordance with PRISMA guidelines(22) (**Figure 1**, *Panel a*). The final list of selected articles was shared with the corresponding author of each paper to check for comprehensiveness.

Data extraction and analysis focused on the study aims, definition of multimorbidity, justification of analytic framework and econometric techniques to estimate cost and utilisation models, findings, stated limitations, and research gaps. Risk of bias was assessed with the National Institute of Health's Heart, Lung, and Blood Institute quality assessment tools for observational cohort and cross-sectional studies(23). Following piloting of the data extraction form, two authors extracted data on a randomly selected 10% of papers to check for consistency, the first author extracted the remainder. The results were grouped by cost or utilisation study type, tabulated (**Table S1**), and reported narratively. Multimorbidity parameter estimates, which quantify its relationship with costs and utilisation, were gathered and systematically presented for analysis. The heterogeneity among studies was assessed with I^2 and data were pooled in a meta-analysis when possible.

3. RESULTS

This review identified 1,304 articles from the electronic searches, excluding duplicates. A total of 9 articles (initial "pearls") met our inclusion criteria after title, abstract, and full-text review (**Figure 1**, *Panel a*). By inspecting the references and citations of the initial pearls, 8 more papers were selected (**Figure 1**, *Panel b*), producing 17 papers for synthesis (3,13,24–38) (**Appendix 3**). Contact with study authors (65% response) produced no further papers.

3.1. Study aims and data

The relationship between multimorbidity and healthcare utilisation was explored in ten studies, while seven papers tackled multimorbidity and costs. Six studies covered the UK, nine focused on England and two on Scotland. Both cross-sectional and longitudinal study designs were used, with up to 8 years of participant follow up. The average sample size was 210,495 individuals (range 419(24) to 819,590(25)) among the utilisation studies and 109,746 individuals (range 39,381(26) to 282,887(27)) for the cost studies.

3.2. Definition of Multimorbidity

Large variability in the type of diseases considered to create the multimorbidity or condition count indicators was observed (Figure S1). All studies included conditions pertaining to the endocrine, and cardiovascular and circulatory systems. However, only a few (n=5) considered the reproductive system or infectious diseases. QOF conditions were used in 5 studies**.** The number of diseases included in the multimorbidity or disease count measures ranged from 4 to any (see **Appendix 4)**. For example, Charlton and colleagues only considered CHD, stroke, colorectal cancer, and diabetes(27), while Payne and colleagues included 40 conditions covering almost all body systems(28). Most studies did not provide an explicit definition of multimorbidity; six studies formally defined multimorbidity as two or more conditions. Two studies only considered long term conditions to build their multimorbidity measures, while six studies focused on chronic conditions.

3.3. Characteristics of the studies on multimorbidity and utilisation

Some focal points of multimorbidity and utilisation studies included the interplay among multimorbidity, deprivation and utilisation, the combination of mental and physical conditions, the effect of multimorbidity among individuals with a long-term condition, and the comparison of alternative multimorbidity measures (**Table S1**, Panel a).

Most studies (6 out of 10) explored the determinants of unscheduled care use, including emergency department visits and hospital visits. Three studies aimed to explain primary care utilisation, while one study explored dental care use. Seven studies applied a retrospective cohort study design, while cross-sectional (n=2) and prospective cohort study designs were used in the remaining papers. Six studies presented a justification for their analytic framework, including a study hypothesis (n=6) or a reasoning behind the utilisation model specification (n=3). Most utilisation models were calibrated using binary (use/non-use) logistic regression (n=7). Other multivariate regression techniques included OLS with a log-transformed dependent variable, GLM with a log-link and a negative binomial distribution, and a negative binomial regression. The most common predictors were age, gender, and deprivation. Other less common independent variables were education level, smoking status, distance to nearest hospital, and patient satisfaction. Three papers assessed the goodness of fit of the utilisation models (29–31).

Multimorbidity contributes to higher healthcare utilisation, except for prolonged hospital stay among the oldest patient group (90+ years) (**Table 2**). Patients with 4 or more conditions have almost 15 times the odds of experiencing an unplanned potentially preventable hospitalisation

(OR=14.38)(28). The combination of mental and physical conditions particularly increases the probability of unplanned hospital care, between 58% and a 100% (28,31,36). In primary care, multimorbidity—defined as 2 or more morbidities—more than doubles its expected use (OR=2.56) compared to 0-1 morbidities (3). Adding a multimorbidity measure to a primary care utilisation model already accounting for age, gender, deprivation, and GP practice fixed effects notably improves goodness of fit (R-squared increased from 0.22 to 0.37 with ACG categories or 0.42 with number of prescribed drugs)(30).

Review Manager 5 was used to calculate the overall effect of multimorbidity on healthcare utilisation. Results from the random effects model (**Appendix 6**) suggest that people with multimorbidity are expected to use health services 2.56 times more than people without multimorbidty (OR=2.56, 95% 1.88-3.47). An I^2 =99% indicates considerable heterogeneity among our studies, which highlights that the meta-analysis results should be considered with caution.

3.4. Characteristics of the studies on multimorbidity and costs

Exploration of multimorbidity and costs included the interplay between multimorbidity and deprivation, the cost impact of specific disease combinations, the relationship between age, time-to-death, and multimorbidity, and the comparison of alternative multimorbidity measures, among others (**Table S1**, panel b).

Four main types of costs were assessed: total, primary care, hospital, and care transition costs. **Table 3** shows that most studies (5 out of 7) included hospital costs. Among the three studies that explored total costs (27,32,38), Kasteridis and colleagues generate total costs based on not only primary care and hospital care, but also mental health, community care, social care, and continuing care(38).

In most studies, costs were computed by multiplying the quantity of services used by standard unit costs. The main unit cost sources included the Personal Social Services Research Unit (PSSRU), the General Practice Research Database (GPRD), NHS reference costs, and RESIP Gemscript Code Dictionary and the First Data Bank Europe (FDBE) for drug unit costs. The papers predicting hospital costs(26) and care transitions costs to hospitals(35) used Healthcare Resource Groups (HRGs).

Three papers used a longitudinal design, while cross-sectional and retrospective cohort study designs were used in three and one paper, respectively. Four studies presented a justification for their analytic framework, including a study hypothesis (n=4) or a reasoning behind the cost model specification (n=1).

Regarding the statistical techniques used to model costs, three papers chose a two-part model(27,32,38). In the first stage, the probability of incurring positive costs is modelled. In the second stage, costs are estimated using a GLM model with a log-link and Gamma distributed errors or OLS regression with logged costs, conditional on costs being positive. Three other papers directly calibrated cost models using OLS regression (with logged or unlogged costs)(13,26,29), and the remaining paper compared OLS and a GLM model with a long-link and a Poisson distribution(33). Besides clinical factors (e.g. indicators variables for certain medical conditions), cost models typically also adjusted for age, gender, and deprivation. Only one paper included a measure of functional status or age-related impairments(32). Four papers assessed the goodness of fit of the cost models(26,32,33,38).

Multimorbidity is positively associated with total costs, hospital costs, and care transition costs (**Table 3**). Based on the results of two studies, patients with 1 to 3 conditions have between 1.55 and

2.85 times the mean expected total cost of individuals without any morbidity (27,32). The relationship between multimorbidity and primary care costs, however, does depend on the specific disease pairs that patients exhibit and their age. In other words, not all disease combinations result in higher primary care costs than treating separate patients with each condition. Depression is the main cost-increasing comorbidity across all ages, while hypertension tends to be mostly cost-limiting(13). Goodness of fit analyses suggest that adding multimorbidity to the specification of total or primary care cost models results in large R-squared gains—R-square increased from 0.14 to 0.32 when Expanded Diagnosis Clusters (114 chronically related groupings of diagnoses) were added to an age, gender, and deprivation-only model(33).

Only 2/7 cost studies presented parameter estimates quantifying the relationship between multimorbidity and costs. Thus, a meta-analysis of cost studies was not feasible.

3.5. Risk of bias assessment

Eight studies were considered to have the least amount of bias with valid results (good quality) (13,25–28,30,32,33), while the remaining studies were susceptible to some biases but deemed insufficient to nullify their results (fair quality) (3,24,29,31,34–38). A sample size justification was rarely provided and the exposure (in this case, multimorbidity) was only assessed once in most cases. Only five studies measured the exposure before the outcome (in this case, utilisation or costs). Loss to follow-up only was reported in one out of the nine cohort studies (**Appendix 5**).

3.6. Limitations and research gaps

The main limitations discussed in the 17 studies cover issues on data, measurement of confounders, and multimorbidity indicators. First, Hazra et al. underscore the need to incorporate social care data into existing nationally representative datasets to create comprehensive total cost measures (32). Second, small area level social deprivation measures, which were included in most selected papers and are considered an important confounder, may cover extensive variability in socioeconomic status within a given small area and, therefore, suffer from measurement error(25,34). Salisbury et al. (29) and Payne et al. (28) discuss the importance of accounting for disease severity. This oft-disregarded confounder can be important, as some diagnosed conditions may be inactive or have no functional status implications. Third, Brilleman et al. caution against multimorbidity indicators based on QOF conditions because the primary focus is quality of care rather than chronicity (30). They also discuss the need to explore disease clusters of more than two conditions and to create new measures of multimorbidity calibrated on UK data(13,33).

Other research gaps identified include exploring more detailed outcomes such as reasons of hospitalisation, regular A&E use, or length of hospitalisation.

DISCUSSION

Summary

This literature review identified 17 studies exploring the costs and utilisation consequences of multimorbidity in the UK. Findings suggest that multimorbidity translates to increased costs and utilisation, including total costs, hospital costs, care transition costs, primary care use, dental care use, emergency department use, and hospitalisations. The most sizeable effect of multimorbidity is on unplanned, potentially preventable, hospitalisations, with up to 14.38 times increase in the odds for those with 4 + conditions. This effect is independent of age (28). Depression is a particularly

important cost and utilisation-increasing condition (13,27,28) and total primary care cost of multiple conditions are not purely additive, depending on specific disease combinations and age groups (13).

Strengths and Limitations

This study brings together UK literature on the statistical and econometric modelling of cost and health service utilisation associated with multimorbidity. As part of BCSC, the identification of the initial set of relevant papers included a systematic literature review to minimize bias in study choice. This was supported by a clear set of inclusion and exclusion criteria throughout the search methodology, from the systematic literature review to the citation and reference review of the initial pearls. However, our choice to maximize the generalisability of findings across disease conditions meant that papers focused on the effect of multimorbidity on a single disease patient population were excluded. A second limitation is that, even though studies from a single country were gathered, considerable heterogeneity across papers in their populations, conditions included in the multimorbidity measures, and statistical techniques was observed; the utilisation meta-analysis results should be considered with caution. Finally, the applicability of our results to other countries may be limited, but their country-specific focus aims to better inform UK healthcare policy.

Comparison with existing literature

The results of this UK-focused review concur with Lehnert's study, which was based on 35 non-UK international studies. Multimorbidity is positively associated with costs and utilisation, with a particularly large effect on hospital stays. However, a shift in the conceptualisation of multimorbidity from purely disease counts to specific disease combinations/clusters and the focus on specific age groups are trends noted in this review. This review, by using a less conventional search strategy, brings together 17 new UK-specific studies and comprehensively summarises the magnitude of the relationship between multimorbidity and utilisation and costs.

Implications for research and practice

Conceptual frameworks describing how multimorbidity affects healthcare costs and utilisation considering clinical, behavioral, and environmental factors—such as the one developed by Zulman and colleagues on comorbidity interrelatedness and quality of care(6)—should more often guide statistical and econometric modeling of these outcomes. The impact of disease severity, diagnosis sequence, and quality of care on costs of multimorbid patients remains mostly unexplored, as well as polypharmacy and risk of medication adverse events. Identifying the most common disease clusters has also been recognised by Whitty and colleagues as essential to advance towards a cluster-medicine model that successfully combines specialist and generalist care(39). Multimorbidity often worsens quality of life and disability, which are only partially captured by primary and secondary healthcare data. A comprehensive measurement of multimorbidity utilisation and costs requires integrating social care data into existing nationally representative datasets.

NHS England policy(40) supports expansion of integrated care schemes, particularly those with better coordinate community health, mental health and hospital services. This review, identifying depression as the main cost-increasing condition and highlighting the substantial contribution of multimorbidity to unplanned hospitalisations, provides evidence in support of this policy goal.

The impact of multimorbidity on health care costs and utilisation: a systematic review of the UK literature

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TABLES

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
▪ Original research ▪ UK study ▪ Focused on assessing the relationship between multimorbidity and costs/utilisation as stated in the title or the study goal in the abstract ▪ Published after 2004*	▪ Non-human research ▪ Descriptive cost-of-illness or economic burden studies, literature reviews or meta-analyses (unless meets inclusion criteria**), cost-effectiveness studies, or study protocols ▪ Study population is limited to a single condition, or a single condition with a procedure, risk factor, or complication of the single condition

* The 2004 threshold corresponds to the year when QOF was implemented and the NHS began the deployment of improved computerized applications for clinical records and diagnoses.** In this case, references were searched for additional primary studies.

Table 2. Summary of the relationship between multimorbidity, costs, and utilisation

Utilisation/Cost type	MM specification	Magnitude	Parameter estimate type	Reference
Primary care visits (n=3)				
	Number of QOF LTCs	**0.37** (0.36-0.38)	Marginal effect	(29)
	MM vs not	**2.56** (2.48-2.64)	Odds ratio	(3)
Dental visits (n=1)				
	MM vs not	**1.23** (1.08-1.38)	Odds ratio	(37)
A&E visits (n=2)				
	HADS score of 8 or more vs lower	**1.58** (1.04-2.41)	Odds ratio	(36)
	1 QOF LTC vs none	**1.12** (1.10-1.13)	Odds ratio	(25)
	2 QOF LTC vs none	**1.28** (1.25-1.31)	Odds ratio	(25)
	3 QOF LTC vs none	**1.65** (1.59-1.71)	Odds ratio	(25)
	≥4 QOF LTC vs none	**2.55** (2.44-2.66)	Odds ratio	(25)
Hospitalisations (n=4)				
All	1 LTC vs none	**1.77** (1.59-1.98)	Odds ratio	(34)
	2 LTC vs none	**2.41** (2.12-2.72)	Odds ratio	(34)
	3 LTC vs none	**3.53** (3.06-4.07)	Odds ratio	(34)
	≥4 QOF LTC vs none	**4.33** (3.63-5.17)	Odds ratio	(34)
	MM vs not	**2.58** (2.48-2.69)	Yearly rate ratio	(3)
Unplanned all	1 PC vs none	**1.70** (1.59-1.82)	Odds ratio	(28)
	2 PC vs none	**2.69** (2.50-2.89)	Odds ratio	(28)
	3 PC vs none	**3.47** (3.21-3.76)	Odds ratio	(28)
	≥4 PC vs none	**5.87** (5.45-6.32)	Odds ratio	(28)
Unplanned potentially preventable	1 PC vs none	**2.50** (2.07-3.03)	Odds ratio	(28)
	2 PC vs none	**4.93** (4.06-5.99)	Odds ratio	(28)
	3 PC vs none	**6.82** (5.55-8.37)	Odds ratio	(28)
	≥4 PC vs none	**14.38** (11.87-17.43)	Odds ratio	(28)
Prolonged length of stay	MM vs not (90+ population)	**0.61** (0.32-1.13)	Risk ratio	(24)
Total Costs (n=3)				
	1-3 LTC vs none	**1.62** (1.28-2.03)	Mean ratio	(32)
	4-6 LTC vs none	**2.53** (2.01-3.19)	Mean ratio	(32)
	7-9 LTC vs none	**3.82** (3.01-4.85)	Mean ratio	(32)
	1 LTC vs none	**1.99** (1.95-2.03)	Mean ratio	(27)
	2 LTC vs none	**2.53** (2.46-2.58)	Mean ratio	(27)
	3 LTC vs none	**2.86** (2.72-3.03)	Mean ratio	(27)
Care transition costs (n=1)	Comorbidity pairs vs index LTC	p<0.001	Increasing trend in association	(35)
Primary care costs (n=2)	Costs of 1 patient with 2 LTC vs 2 separate patients with each LTC	Increasing or decreasing costs when co-occurring	Estimated prevalence-adjusted cost	(33)
Hospital costs (n=1)	Individual LTC Time to Death (TTD) as a proxy for morbidity	p<0.01 for 90% of the estimated coefficients	Estimated coefficient	(26)

Notes: The number of articles is indicated in parenthesis next to the cost or utilisation type. See **Appendix 3** for the complete 17 study references. Mean ratios can be obtained by exponentiating the parameter estimates from a GLM model with the log-link, they have an interpretation similar to an odds ratio. For example, individuals with 7-9 conditions have 3.82 times the mean expected total costs of individuals without comorbidities. QOF=Quality and Outcomes Framework. MM=multimorbidity. HADS score=Hospital Anxiety and Depression Scale. LTC=long-term condition. PC=physical condition. Prolonged length of stay is defined as 7 or more days in the hospital. Care transitions are defined as healthcare changes from general practice to Accident and Emergency (A&E) or hospital care.

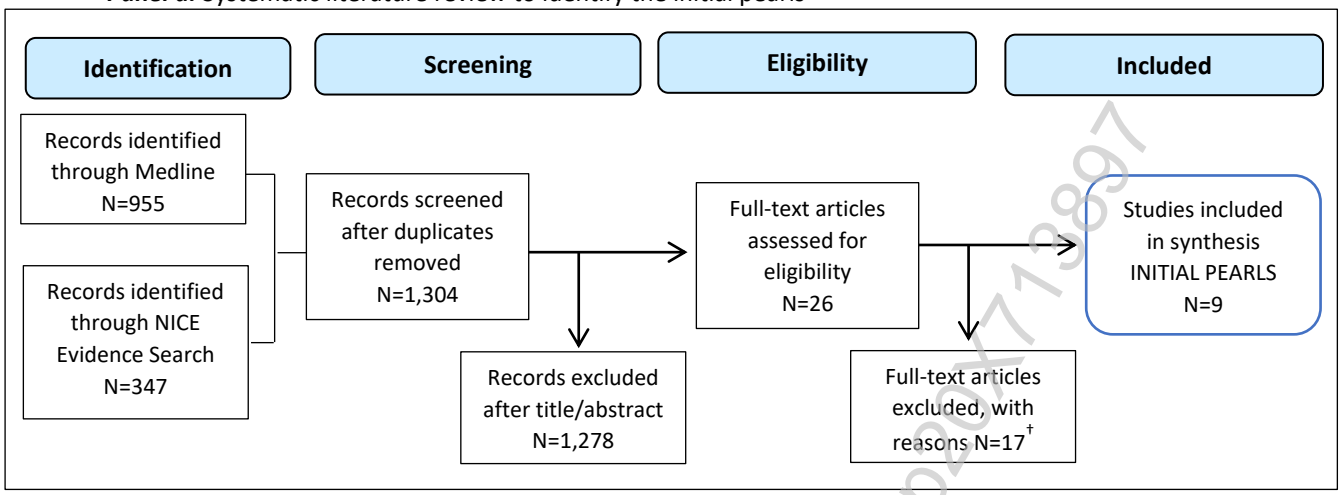
Table 3. Cost components by study

	Total cost			Primary care costs		Hospital costs	Care transition costs
	Hazra,2018(10)	Charlton, 2013 (4)	Kasteridis, 2014 (11)	Brilleman, 2014 (12)	Brilleman, 2013 (13)	Howdon, 2018 (3)	Kadam, 2013 (15)
Primary care							
Primary care episodes			●				
Clinic face-to-face visits	●	●		●	●		
Telephone contacts	●	●		●	●		
Out-of-hours encounters	●	●		●	●		
Investigations				●	●		
Medication	●	●	●	●	●		
Emergency consultations	●	●					
Home visits	●	●					
Hospital							
Acute inpatient			●				
Hospital admission	●	●				●	●
Outpatient visit	●	●				●	
Day case visit	●	●	●			●	
Accident and emergency visit	●	●	●			●	●
Mental health			●				
Community care			●				
Social care			●				
Continuing care			●				

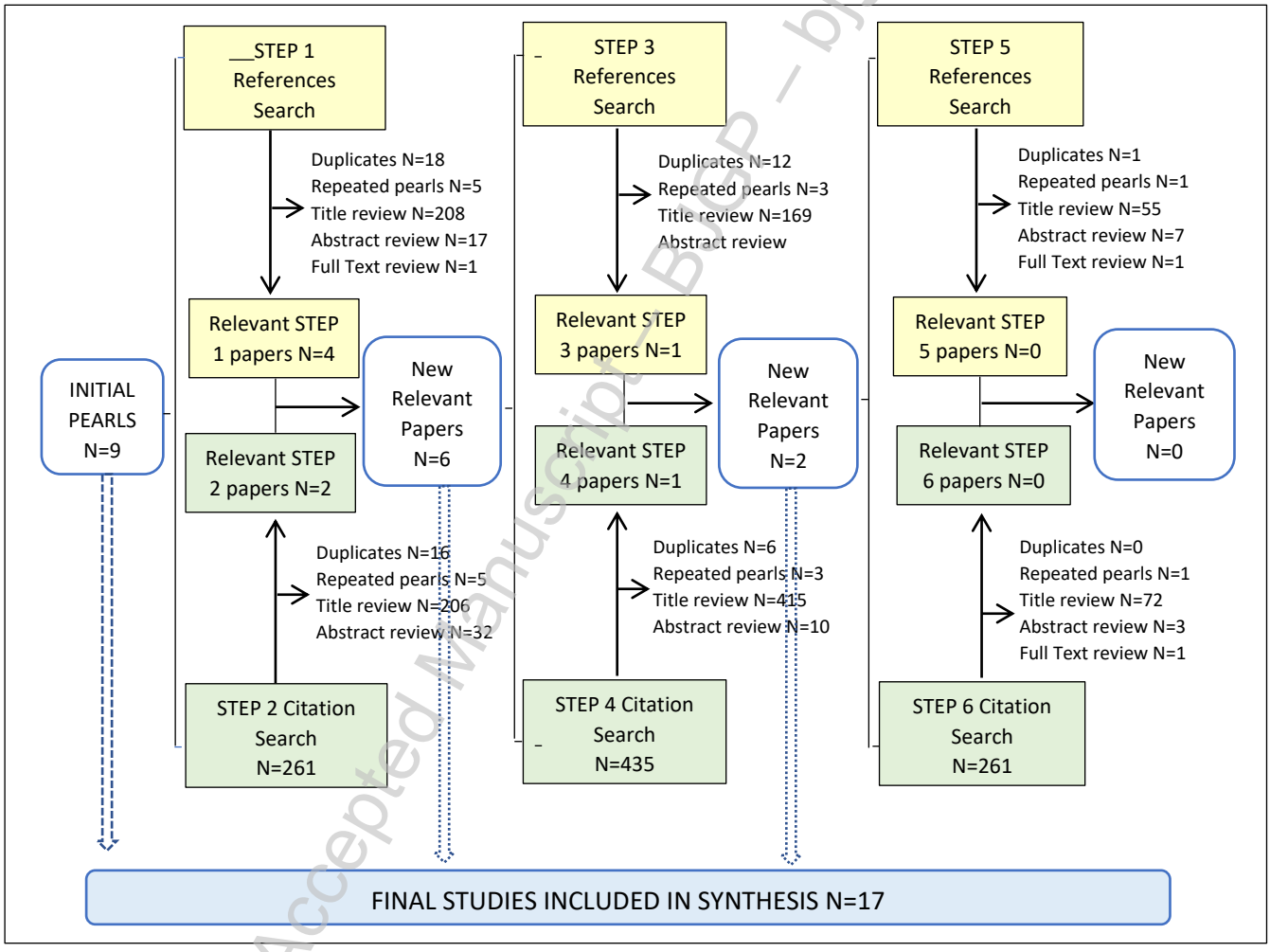
FIGURES

Figure 1. Flowchart illustrating the search process

Panel a. Systematic literature review to identify the initial pearls

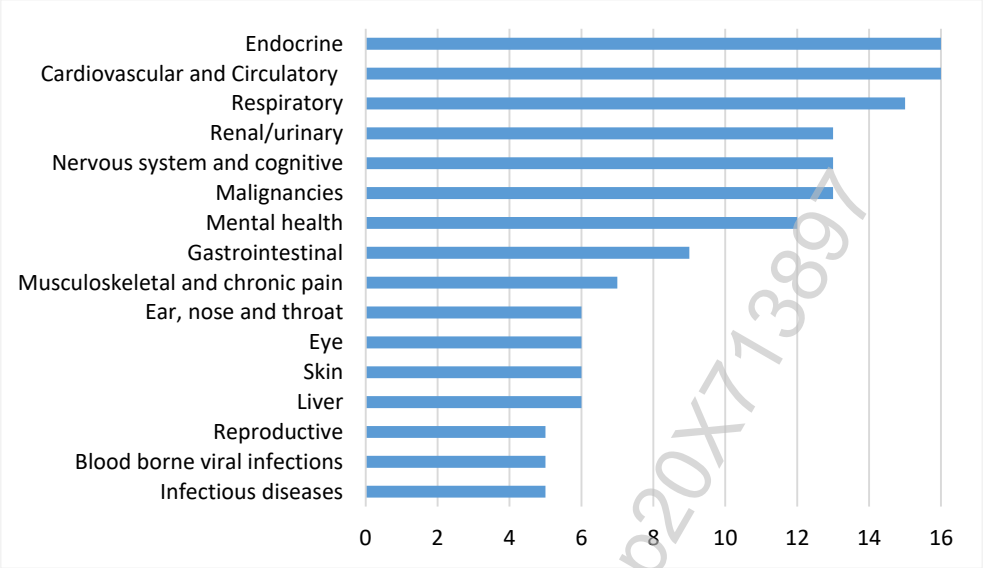


Panel b. Bidirectional citation exclusion process based on the initial pearls



Notes: † **Appendix 2** presents the list of these 17 excluded full-text articles with reasons.

Figure 2. Number of papers that included each body system in their multimorbidity measures



Note: Medical conditions were grouped into body systems to facilitate data display. See **Appendix 4** for more details. This graph excludes Kasteridis and colleagues' study as it did not detail the 49 conditions included in its multimorbidity measure.

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