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Multimorbidity in primary care:

a systematic review of prospective cohort studies

Abstract

Background
Primary care increasingly deals with patients with multimorbidity, but relevant evidence-based interventions are scarce. Knowledge about multimorbidity over time is required to inform the development of effective interventions.

Aim
This review identifies prospective cohort studies of multimorbidity in primary care to determine: their nature, scope and key findings; the methodologies used; and gaps in knowledge.

Design
Systematic review.

Method
Studies were identified by searching electronic databases, reviewing citations, and writing to authors. Searches were limited to adult populations with no restrictions on publication date or language. In total, 996 articles were identified and screened.

Results
Of the 996 articles, six detailing five completed prospective cohort studies were selected as appropriate. Three of the studies were undertaken in the US and two in The Netherlands; none was nationally representative. The main focus of the studies was: healthcare utilisation and/or costs (n = 3); patients' physical functioning (n = 1); and risk factors for developing multimorbidity (n = 1). The conditions that were included varied widely. The findings of these studies showed that multimorbidity increased healthcare costs (n = 2), inpatient admission (n = 1), death rates (n = 1), and service use (n = 3), and reduced physical functioning (n = 1). One study identified psychosocial risk factors for multimorbidity. No study used random sampling, sample sizes were relatively small (414–3745 patients at baseline), and study duration was relatively short (1–4 years). No study focused on prevalence, treatment use, patient safety, service models, cultural or socioeconomic factors, and patient experience, and no study collected qualitative data.

Conclusion
Few longitudinal studies based in primary care have investigated multimorbidity. Further large, long-term prospective studies are required to inform healthcare commissioning, planning, and delivery.

Keywords
chronic disease; multimorbidity; primary care; review.

INTRODUCTION

The dramatic rise in long-term conditions presents a significant challenge to healthcare systems worldwide.[1] Primary care is key to the management of patients with long-term conditions[2,3] but, in the main, takes a single-disease approach,[4] even though multimorbidity — the co-occurrence of two or more long-term conditions within an individual — is common.[5–8]

Despite the high prevalence of multimorbidity, the evidence base for interventions is extremely limited.[9,10] An important precursor to developing effective interventions is knowledge about multimorbidity over time in 'real-life' primary care settings. Prospective cohort studies are the most robust way to observe 'real-life' issues over time.[11] They have fewer potential sources of bias than retrospective and case–control studies, and yield true incidence and relative risk compared with randomised trial data that, due to strict eligibility for the trial, low recruitment levels, or large numbers of people refusing consent, often have restricted generalisability. As such, prospective cohort studies are the 'gold standard' for studying and describing the natural history and development of morbidity, as well as the development and implementation of prognostic models of care.[12]

Although reviews of the impact of multimorbidity have been undertaken,[13] there are no published reviews of cohort studies on multimorbidity in primary care. This article reports the findings of a systematic review of prospective cohort studies of multimorbidity in primary care. The aims were to determine:

- the nature, scope and key findings of the published studies;
- the methodologies used in the studies; and
- any gaps in knowledge.

METHOD

Inclusion and exclusion criteria

Multimorbidity was defined as an individual having two or more conditions, without a specific index condition being specified. Studies with a prospective, longitudinal design, whose main focus was multimorbidity in adults in primary care settings, were included. There were no restrictions on publication date or language of the full paper, but an abstract in English had to be available. As prospective cohort studies are the 'gold standard' for conducting such research, retrospective studies, cross-sectional study designs, evaluation studies, randomised controlled trials and intervention studies, studies that

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How this fits in

Multimorbidity is becoming the norm, rather than the exception, in primary care, but evidence-based interventions are scarce. As knowledge of the effects of multimorbidity over time is a necessary precursor to developing effective interventions, a systematic review of prospective cohort studies of multimorbidity in primary care was carried out. Out of 996 articles identified, only six articles from five completed studies were found that were relevant; although the studies identified provide useful information, they also demonstrate significant gaps in knowledge. To plan future healthcare services and treatment guidelines for those with multimorbidity, a better understanding of the personal experience, treatment, and health service use, as well as the psychological, physical, and social factors that influence multimorbidity over time, is needed.

recruited only children aged <18 years, and those whose main focus was neither multimorbidity nor primary care data and/or settings were excluded.

Search strategy

The following databases were searched; the corresponding start date is given in parentheses:

- PubMed (1960);
- Medline (1950);
- PsycINFO (1887);
- CINAHL (1982);
- the CSA Conference Papers Index (1982);
- the Index to Scientific and Technical Proceedings (via ISI Web of Science) (1990); and
- BioMedCentral (BMC) journal study protocols (2000).

In addition, hand searches of key journals (*Family Practice*, *BMC Health Services Research*, *BMC Public Health*, *Chronic Illness*, *Journal of Clinical Epidemiology*) were carried out for the 12 months preceding the start of this review. All searches were carried out by one researcher on 23 March 2010. Experts in the field of multimorbidity were also contacted to help identify relevant studies; they carried out hand searches of reference lists in included studies in an attempt to identify other relevant studies.

A mixture of Medical Subject Headings (MeSH) and key words were used to search PubMed and Medline; headings and key words for CINAHL; descriptors, key words and methodology terms for PsycINFO; and topics and keywords for ISI Web of Science. Other databases including the CSA Conference Papers Index and the BMC journals database rely on keyword searches. The exact search terms for selected databases are shown in Table 1. As comorbidity and multimorbidity are not consistently defined in the literature, articles using either term were searched for and included.

Multiple searches were performed via PubMed to identify relevant papers prior to, and after, the introduction of key MeSH terms. The term 'cohort studies' was only introduced as a MeSH term in 1989 and 'comorbidity' in 1990; to find articles prior to those dates the study used different search terms, such as the MeSH terms 'follow-up studies' or 'prospective studies' instead of 'cohort studies', and variations of the keywords 'comorbid' and 'multimorbid' in the title or abstract.

Data extraction and analysis

All citations (title and abstract) were screened by two different reviewers. If either reviewer could not confidently include or exclude the paper based on the abstract or citation, the full paper was obtained. In total, 27 papers were read in full. All authors contributed to the double screening exercise. If there was a disagreement about whether a paper should be included or excluded, it was read by one or more additional reviewers and an agreement was reached through discussion. A data extraction sheet was used independently by two reviewers and compared for consistency; again, any disagreements were resolved through discussion.

The study adhered to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement to ensure our review was of good quality.

RESULTS

Eight prospective cohort studies on multimorbidity in primary care settings that were described in nine papers were identified from a total of 996 articles. Three protocol papers[14–16] were excluded, leaving six papers, which related to five separate cohort studies (Figure 1).[17–22]

Nature and scope of studies

Study aims. Three studies[19,21,22] focused on healthcare utilisation and/or costs, but also included some patient outcomes (severity of disease,[22] new morbidity,[19] and mortality[22]).

Table 1. Search terms used in main databases

Database	Search terms
PubMed	1. MeSH Heading = ("Primary Health Care" OR "Physicians, Family" OR "Family Practice") AND "Cohort Studies" AND ("Comorbidity" OR Title/Abstract = comorbid* OR Title/Abstract = (co-morbid* OR multimorbid* OR multi-morbid*) NOT MeSH = ("Intervention Studies", "Clinical Trials as Topic", "Cross-Sectional Studies" "Retrospective Studies") NOT Publication Type = ("Clinical Trial") *[Search parameters: humans; all adults aged 19+; studies from 1989 to present when 'cohort studies' was introduced as a MeSH term]* 2. As above but instead of 'cohort studies': MeSH heading = ("Follow-Up Studies" OR "Prospective Studies" OR "Epidemiologic Methods") *[Search parameters: humans; all adults aged 19+; studies up to end 1988]*
CINAHL	Headings = Comorbidity OR Keyword = (multimorbid* or multi-morbid*) AND Headings = (Primary Health Care Or Physicians, Family Or Family Practice) AND Heading = Prospective Studies NOT 'trial' in title
PsycINFO	Descriptors = (general practitioners or family medicine or family physicians or primary health care) AND Descriptors = ((comorbidity) OR Keyword = ("multimorbid*" or "multi-morbid*" or "comorbid*" or "co-morbid*") AND Methodology = (Longitudinal study or followup study or prospective study) NOT Title = (Trial)
ISI Web of Science	Topic = (multi-morbid* OR comorbid* OR co-morbid* or multimorbid*) AND Topic = (Longitudinal stud* OR cohort stud* OR prospective stud* OR cohort stud*) AND Topic = (Primary Health Care OR Physician*, Family OR Family Practice* OR general practitioner* OR family medicine OR family physician*) NOT Title = (TRIAL) NOT Title = (HOSPITAL*) *[Search parameters: timespan = all year; databases = SCI-EXPANDED, SSCI, CPCI-S]*
CSA Conference Papers Index	[KEYWORDS] (Primary health care or family physicians or family practice) AND ("multi-morbid*" or "comorbid*" or "co-morbid*") AND (Longitudinal study or cohort study or prospective study) AND multimorbid* AND (general practitioners or family medicine or family physicians) AND (followup study or follow-up study)

CPI-S = Conference Proceedings Citation Index – Science. SCI-Expanded = Science Citation Index – Expanded. SSCI = Social Sciences Citation Index.

One study focused solely on patient outcomes (physical decline),[20] while another (written up in two papers[17,18]) looked at psychosocial risk factors. Full details are given in Table 2.

Theoretical or conceptual frameworks. Two papers explicitly described a theoretical or conceptual framework for the study.[18,20] Van den Akker *et al*'s 2006 paper[18] drew on a theory of general disease susceptibility; Bayliss *et al*'s analyses[20] were based on a conceptual interaction between long-term conditions and the 'psychosocial environment' that impacted on physical wellbeing. The aim was to aid clinical decision making and the management of physical decline by informing a generic chronic care model for patients with multimorbidities; implicitly, this relates to the cost to the healthcare system. The model implicit in Van den Akker *et al*'s 2001[17] paper focused on psychosocial, as well as disease, factors impacting on the development of multimorbidity.

In the remaining three studies, no conceptual model was stated or implied. The impetus for these studies appeared to be to investigate the relationship between multimorbidity and resource use.[19,21,22]

Study location. Three studies were conducted in the US[20–22] and two in The Netherlands[17,18] (Table 3). None of the cohorts were multicountry but they were restricted to a single region of The Netherlands,[17–19] three urban US cities,[20] and the geographical area served by a single US primary care practice.[21,22]

Key overall study findings

Two studies (three papers) reported risk factors for the course of multimorbidity, including the type of disease[20] and psychosocial characteristics.[17,18] Van den Akker *et al*[17,18] identified psychosocial risk factors — negative life events, an external health locus of control, and a social network of less than five people — for developing multimorbidity,[17] which may predominantly apply in conditions that do not have a known common pathophysiological origin.[18]

One study[20] found that certain combinations of chronic conditions — for example, chronic respiratory disease (CRD), congestive heart failure (CHF), and diabetes — presented a greater risk for physical decline than others, and some combinations — such as CRD and osteoarthritis — resulted in higher patient consultation rates.[19]

Three studies reported that patients with multimorbidities had higher healthcare utilisation[19,21,22] than those with only a single condition. Increasing multimorbidity predicted higher healthcare charges in an outpatient setting and an increased likelihood of inpatient admission or death.[21,22]

One study suggested that a simple count of prescribed medications might have the greatest predictive validity for healthcare utilisation and costs, and diagnosis-based measures might be best for predicting 1-year mortality; however all measures had poor to modest predictive validity.[23]

No study had health inequalities or socioeconomic status as its major focus. Perkins *et al*'s study[21] did compare the

Table 2. Study aims

	Van den Akker *et al*, 2001[17]	Van den Akker *et al*, 2006[18]	Schellevis *et al*, 1994[19]	Bayliss *et al*, 2004[20]	Perkins *et al*, 2004[21]	Parkerson *et al*, 1995[22]
Main study focus	Risk factors for developing multimorbidity	Risk factors for developing multimorbidity	Healthcare utilisation and impact of multimorbidity on individual (patient) outcomes	Impact of multimorbidity on individual (patient) outcomes	Healthcare utilisation and costs and impact of multimorbidity on individual (patient) outcomes	Healthcare utilisation and costs and impact of multimorbidity on individual (patient) outcomes
Study aims	To profile patients' vulnerability to multimorbidity in terms of the influence of coping style, life events, health locus of control, long-term difficulties, type of living arrangement, and social networks	To explore multimorbidity and its relation with psychosocial characteristics by categorising and comparing multimorbid diseases that have a common pathophysiological origin and those that do not	To examine consultation rates and incidence of 'intercurrent' morbidity (new illnesses including acute ones) in generalpractice in in cohorts of patients with five common chronic diseases	To assess the effect of certain comorbid conditions on physical wellbeing over time in a population of persons with chronic medical conditions; to compare these effects to that of hypertension alone	To compare the predictive validity of five commonly-used measures of multimorbidity among a large cohort of older adults who are vulnerable and cared for in a single primary care practice	To address the need for a primary care case-mix model to estimate the probability of follow-up severity of illness, utilisation of services, and cost of health care

impact of patients' income, sex, age, and ethnic origin on multimorbidity using five different measures of it; contradictory results were found, depending on the measure used.

Methodologies used

Study design and methods. Table 3 describes the methods used in the five studies. Studies varied widely in: their eligibility criteria for inclusion in the cohort; how multimorbidity was measured; which outcomes were assessed; the type of primary care setting/patient selection procedures used; and the type of data that were collected.

Selection of primary care settings and patients. None of the studies randomly selected primary care settings or GPs, then randomly selected patients. They recruited a volunteer sample of practices,[20] GPs who had taken part in a previous study,[19] practices registered on a database,[18,19] or used a convenience sample of patients.[21,22] The studies recruited between one and 15 practices. Between four and 42 GPs participated in three studies (four articles);[17–19,22] 225 GPs participated in another;[20] and one did not state how many GPs took part.[21] One study included all eligible patients from the study practices,[19] one study (written up in two articles) randomly sampled patients (the method of randomisation was not stated),[17,18] while the others used convenience samples.[20–22]

Four studies had a potentially biased sample due to: loss to followup;[20] patient non-response;[17,18] the study inclusion/exclusion criteria;[17] or the method of sampling patients.[17,18,20–22] Table 3 shows the characteristics of those patients excluded or lost due to non-response or attrition.

Multimorbidity definitions and measures. All studies operationalised multimorbidity as two ore more conditions within a patient, but not all limited the conditions to those that are long-term and the studies varied in the list of conditions that could be included. Only three of the studies (four articles) provided a clear definition.[17,18,20,22]

Two studies included people with less than one of five[19] or six[20] specific chronic diseases. In Schellevis *et al*'s[19] study, it is not clear why the specific diseases were chosen; Bayliss *et al*[20] chose high-prevalence conditions that frequently appear in the research literature on multimorbidity or chronic disease management. Three studies (four articles) had broader inclusion criteria with few limitations on which conditions were included.[17,18,21,22] Table 3 provides details of definitions and how multimorbidity was operationalised.

Sample size. None of the papers justified sample size. Cohort sizes ranged from 414 to 3745 patients at baseline and from 413 to 3551 patients at follow-up (Table 3). However, not all patients in the cohorts had, or developed, multimorbidity. One study did not state how many patients had multimorbidity,[21] the number was relatively small in three studies (four articles) (n = 216,[22] n = 268,[19] and n = 305[17,18]), and one study had a larger number (n = 686).[20] This meant that analyses by sub-group or sub-population (for example, type of condition,

Table 3. Methods

Author/ Methods	Van den Akker *et al*, 2001, 2006 'Registration Network Family Practices (RNH) Cohort'	Schellevis *et al*, 1994	Bayliss *et al*, 2004	Perkins *et al*, 2004	Parkerson *et al*, 1995
Location/s	South Netherlands	South-east Netherlands	US: Boston, MA; Chicago, IL; and Los Angeles, CA	US: Indiana state	US: Caswell County, NC
Primary care settings recruited	15 practices	7 practices	3 prepaid group practices (one from one HMO in each city) plus 23 of their satellite facilities; 25 multispecialty group facilities	1 practice	1 practice
Selection of primary care setting/s	Non random — 42 GPs in 15 practices registered with the RNH database.	Non random — Seven practices (15 GPs) from 103 that had taken part in a previous study selected based on them having participated in the previous study during a specific time period and the practice being located in the south-east of the Netherlands.	Non random — Selected study sites (cities) based on the size of the HMO, having both prepaid and fees-for-service arrangements, number of physicians, and willingness to take part. Three study sites met the criteria. In each city, five or six practice sites were sampled from each group practice HMO. Populations of clinicians were sampled according to specialty training, age and experience.	Not stated	Not stated
Number of GPs approached	n/a	18	1791	Not stated	Not stated
Number of GPs participating	42	15	225 contributed patients	Not stated	2 GPs & 2 general internists
Patient population studied	Sample at follow-up — mean age 52.4 years (SD 16.8), 22.3% of follow-up sample did not have any disease at the start of study, 21.4% had one disease, and 56.3% had two or more diseases	Hypertension, *n* = 549 (ages 22–92, 86.3% with single disease); chronic ischaemic heart disease, *n* = 183 (ages 34–97, 73.8% with single disease); diabetes mellitus, 119 (ages 29–88, 68.9% with single disease); CRD, *n* = 252 (ages 3–86, 88.9% with single disease); and osteoarthritis knee and/or hip, *n* = 80 (ages 39–87, 68.8% with single disease). Sample included people with one chronic disease and those with two or more.	Mean age 57.6 (SD 15.4); 58.3% married; 46.4% employed; 19.3% at or below 200% of poverty level; 82.5% white (versus non-white). 14.6% education less than high school; 28.5% high school graduate; 28.5% greater than high school; 12.1% college graduate; 16.3% greater than college; mean number of main diseases[a] 1.5; mean number of additional diseases[b] 0.7; hypertension alone (referent group) 0.3; remaining subjects 0.8.	Vulnerable older adults, average age was 68.9 years; 56% were African American. Approximately 75% of the patients had Medicare and 27% had Medicaid; 20% patients were smokers and 45% patients were obese. Patients averaged 7 medications, 6.4 unique pharmacy subclasses, and 5.2 chronic disease classes; and averaged eight ambulatory visits per year.	Ambulatory primary care patients aged 18–65 years
Number of patients approached	6113	Practice population of 23 534 whose records were searched or who were identified through a visit to /contact with the practice in first 3 months of study (identified by GPs).	3589 (eligible for longitudinal study out of 28 257 from which both a longitudinal and cross-sectional study would be recruited).	3601	561
Number of patients agreeing to participate	Not stated	Not stated	3589	3496	534 (95.2%)
Number of patients in study at baseline/ with baseline data collected	3745	962	2235	3496	414 (74%)
Patients sampled from where?	RNH database	GP	From MOS cohort study of primary care patients selected via HMOs 'facilities'	Primary care practice	Primary care practice

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Table 3 continued. Methods

How were patients sampled? (consecutive patients, mail out from practice list, self-reported, from electronic records)	Random sample of patients stratified to number of disease prior to study.	GPs identified from records (or through a visit to /contact with the practice in first 3 months of study) all patients for the study group. Control group selected using data from the Dutch National Survey of general practice.	Convenience sample — patients approached during a visit with a MOS clinician during a 2-week period in Feb 1986. Adults who visited healthcare provider in 9-day period starting in Feb 1986.	Convenience sample — patients aged ≥60 with a scheduled primary care appointment between 15 July 1999 and 31 August 2001, were eligible ending April 1991.	Convenience sample (12 age-sex-race categories) — patients approached by research assistant when presenting at clinic during 8-month period.
Selection of patients	Random	Non random	Non random	Non random	Non random
Method of randomisation	Not stated	Not applicable	Not applicable	Not applicable	Not applicable
Exclusion criteria (for patients)	Illiterate, spoke little or no Dutch, incapable of participating due to mental or physical status.	Patients who left the practice during the 21-month study period & patients who had received follow-up care from a specialist before the start of the study.	Cannot read English	Not stated	Illiterate, too sick to participate
Criteria for inclusion in cohort	Those on the RNH database aged ≥20. Cases were defined as subjects who had new multimorbidity, that is two or more new disorders registered on the problem list within a period of 3 years (1 September 1992–31 August 1995). Controls — no new disease in selection period. Additional control group — one new disease registered during selection period.	Diagnosis of at least one of the following diseases: hypertension, chronic ischaemic heart disease, diabetes mellitus, CRD (asthma, chronic bronchitis,emphysema), and osteoarthritis of knee and/or hip. Diagnosis made before 1 January 1988, diagnosis in agreement with the diagnostic inclusion criteria of ICHPPC-2-and patient not receiving follow-up care for the disease from a specialist at the start of the study.	Diagnosis with one or more of diabetes, CAD, CHF, CRD, musculoskeletal conditions, and depression. Referent population with a diagnosis of hypertension exclusive of any of the other major comorbid conditions. Completion of baseline data collection.	Community-dwelling patients ≥60 years of age with a scheduled primary care appointment between 15 July 1999 and 31 August 2001, were eligible.	Presenting to clinic for health care visit during 8-month period ending April 1991; age 18–65 years
Patient screening procedures	Searches of an electronic database.	Patient attendance at the practice during a specific time period.	Physician reports verified by study clinical staff and through a patient questionnaire.	Patient attendance at the practice during a specific time period.	Patient attendance at the practice during a specific time period.
Final cohort size (% female)	3551 (49.3%)[a] (2001), 3460 (49.8%)[b] (2006)	962 (overall not stated but 53.8%)	1574 (58.7%)	3496 (69%)	413 (58.6%)
Rationale for sample size	Not stated	Not stated	Not stated	Not stated	Not stated
Percentage of patients lost to follow-up overall	7.6% (285 out of 3745)	0%	29.6%	0%	0.2% (1 person)
Percentage of non-responders	5.2% could not be matched on database at follow-up (194 out of 3745).	Not applicable	Not described separately from drop outs.	0%	9% (50/534) illiterate and could not complete questionnaire at baseline.
Percentage dropped out of cohort	2.4% died (91/3745)	n/a	29.6% (661/2235)	0%	0.2% (1 person)
Retention rate	92.4%	100%	70.4%	100%	99.8%
Missing data	c. 40% questionnaires with missing data at baseline data collection — exact % not given.	c. 30% of consultations not recorded on research forms.	Not applicable	0%	7.9% (42/534) of patients consenting had excessive data missing from intake questionnaire.
Characteristics of the study subjects lost to follow-up	Not stated	Not applicable	Were younger and had lower income: no differences in initial health status.	Not applicable	Not stated
Reasons for drop out/loss to follow-up	91 died, for 194 data could not be matched on database at follow-up.	Not applicable	Variety of reasons including refusals and failure to contact (n = 661; 29.6%); 137 (6.1%) who died during follow-up were included in the analysis.	Not applicable	Records could not be found for 1 person at audit so incomplete follow-up data available.

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Table 3 continued. Methods

Number of patients in cohort with multimorbidity (at follow-up unless stated otherwise)	*n* = 305 (8.6%)[a] (2001); *n* = 290 (8.4%)[b] (2006) had new multimorbidity.	*n* = 268 (22.7%) had ≥2 chronic diseases at baseline.	*n* = 686 (43.6%)	Not stated	216
Total length of follow-up period	2 years	21 months	4 years	1 year	18 months
Number of follow-up points	Continuous	Continuous	1	Continuous	Continuous
Timing of each follow-up	2 years (continuous over period)	21 months (continuous over period)	4 years	1 year (continuous over period)	18 months (continuous over period)
Study period	January 1996/December 1997 (baseline) to January 1998/December 1999 (follow-up).	January 1988–October 1989	1986–1990	1999–2002 (followed for 1 year after patient index visit).	September 1990/April 1991 till February/September 1992 (followed for 18 months after recruitment).
Baseline data collection methods	Electronic record extraction/ patient report	Doctor report	Patient report/doctor report	Electronic record extraction	Patient report/doctor report/ record extraction
Baseline measurements	BMI (body mass index), smoking, alcohol use, sports, family medical history, long-term difficulties, life events, health locus of control, coping style, social network, values, morbidity and multimorbidity of chronic, recurrent and high impact diseases	Chronic diseases diagnosed from list of five diseases	Diagnoses; physical health status	Diagnostic ICD-9 codes, ambulatory visits and inpatient stays for year prior to index visit and all prescription medications for prior year. ACG categories & CCI. Calculated CDS, one to predict healthcare costs (CDS-HC) and one to predict mortality (CDS-M), to identify chronic disease class, then rated by physicians for likely healthcare utilisation and mortality over 1 year.	Health status and severity of illness
Self-reported or clinically determined diagnosis?	Clinically determined	Clinically determined	Clinically determined and self-reported	Clinically determined	Clinically determined
Outcomes data collection sources	Electronic record extraction/ patient report	Doctor report	Patient report/doctor report	Electronic record extraction	Doctor report/record extraction
Outcomes measurements	New multimorbidity, new morbidity 2001); International Classification of Primary Care (ICPC) codes representing a diagnosis for new diagnoses (2006).	Number/rate of consultations and episodes of disease, incidence rate and nature of 'intercurrent' morbidity (other new illnesses including acute ones).	Analysed categorical change (worse versus same/better) in Medical Outcomes Study SF-36 physical component summary (PCS) scores. Categorical change defined as a change of ≥6.5 points in PCS. Also assessed linear change in PCS scores.	All outpatient and inpatient visits and medical charges and death certificate information.	Frequency of primary care visits, severity of illness, health care charges, inpatient stays/ referrals, follow-up severity of illness, utilisation of office and referral services, cost of office health care during 18-month period.
Data collection methods/ tools	Patient reported: baseline data collected by patient self-completion postal questionnaire including: long-term difficulties questionnaire; VRMG — Recent events ; questionnaire Multidimensional health locus of control; Utrecht coping list. Record extraction: RNH database — initial data on morbidity/ multimorbidity and follow-up data on new morbidity and new multimorbidity	Doctor reported: recorded all consultations with cohort on special research forms; recorded ≥1 diagnosis at the highest diagnostic level appropriate, whether the episode was new or pre-existing.	Patient reported: SF36 Health Survey. Doctor reported: diagnoses confirmed by independent clinical exam by MOS staff.	Record extraction: using Regenstrief Medical Record system (RMRS) electronic medical record system for baseline and outcome measures. Diagnostic ICD-9 codes, ambulatory visits, inpatient stays, and all prescription medications from pharmacy database. Calculated ACG categories using outpatient data only and CCI using inpatient data only. Calculated CDS using prescription records.	Patient reported: DUKE (Duke Health Profile) questionnaire a 17-item generic functional health health measure including physical, mental & social health; Doctor reported: of illness using DUSOI; Record extraction: outcomes data — follow-up severity of illness, utilisation of office and referral services, cost of office health care during 18-month period by medical record audit. Audit check of severity of illness by research team to confirm severity rating by GPs.

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Table 3 continued. Methods

Definition of 'multimorbidity' (or 'comorbidity'[a] where this term was used instead)	Multiple diseases (2001), co-occurrence of diseases (2006).	Not stated	Inter-relationships between different diseases and between diseases and age or other health-related sociodemographic variables.	The total burden of illnesses across multiple potential conditions unrelated to the patient's principal or target diagnosis.	Not stated
How was 'multimorbidity' (or 'comorbidity') operationalised?	Two or more new diseases that are permanent, chronic, recurrent or have lasting consequences.	Included: hypertension, chronic ischaemic heart disease, diabetes mellitus, CRD and osteoarthritis.	Having one of the six chronic conditions of interest: diabetes, CAD, CHF, CRD, musculoskeletal conditions,and depression, plus at least one of 16 (unspecified) additional conditions on top of 'main diseases'. Chosen based on their high prevalence as well as frequent assessment in the literature oncomorbidity and chronic disease management.	Five measures of multimorbidity used. Number of chronic diseases out of 10 (arthritis, coronary artery disease, cancer, congestive heart failure, COPD, diabetes, hypertension, liver disease, renal disease, and stroke). ACG categories calculated by classifying patients into one of 34 diagnostic groups by clustering similar conditions based services resource. The CCI which assigns weights to 19 conditions, based on their risk of mortality, the weights are then summed for each patient. A CDS based on the number of different chronic diseases as inferred from the subject's prescribed medications.	Two or more health problems on the ICHPPC-2.
Criteria for inclusion in cohort	South Netherlands	Diagnosis of at least one of the following five diseases: hypertension, chronic ischaemic heart disease, diabetes mellitus, CRD, and osteoarthritis of knee and/or hip. Diagnosis made before 1 January 1988, diagnosis in agreement with the diagnostic inclusion criteria of ICHPPC-2-defined and patient not receiving follow-up care for the disease from a specialist at the start of the study.	Diagnosis with one or more of six conditions: diabetes, CAD, CHF, CRD, musculoskeletal conditions, and depression. Referent population with a diagnosis of hypertension exclusive of any of the other major comorbid conditions (but they could have other long-term conditions). Completion of baseline data collection.	Community-dwelling patients ≥60 years with a scheduled primary care appointment between 15 July 1999 and 31 August 2001, were eligible.	Presenting to clinic for health care visit during 8 month period ending April 1991; aged 18–65 years.Two or more health problems on ICHPPC-2

ACG = Ambulatory Care Group. CAD = coronary artery disease. CCI = Charlson Comorbidity Index. CDS = Chronic Disease Score. CHF = coronary heart failure. COPD = chronic obstructive pulmonary disease. CRD = chronic respiratory disease. DUSOI = Duke severity of illness checklist. HMO = health management organisation. ICHPPC-2 = (International Classification of Health Problems in Primary Care-2). PCS = physical component summary. RNH database = Research Networtk Family Practices database. SF-36 = 36-Item Short-Form Health Survey. [a]includes those who died in sample. [b]excludes those who died from sample.

type of disease susceptibility, age, or deprivation level) were not possible or had very limited statistical power.

Patient follow-up. Four of the studies (five articles)[17–19,21,22] carried out primary research; three analysed routinely collected data.[19,21,22] Two papers[17,18] drew on the same longitudinal dataset to carry out different analyses. One[20] carried out a secondary analysis of 4-year follow-up data, which had been collected in 1990 (some 14 years previously), as part of a longitudinal study called the Medical Outcomes Study. Table 3 shows, in detail for each study, the data that were gathered and from which sources they derived. The range of outcomes measured was limited, with studies mainly appearing to rely on routinely collected data.[19]

The study follow-up times ranged from 1–4 years, with four of the five studies following patients for 12–24 months.[17–19,21,22] One of the studies had only one follow-up point.[20]

Retention rates varied between 70% and 100% of the sample, depending on the follow-up methods; follow-up by record extraction resulted in little or no attrition.[19,21,22] Loss to follow-up contributed to the sample being unrepresentative in one study.[20]

Inclusion criteria and screening procedures. All studies — except that by Perkins *et al*,[21] which sampled on the basis of age — focused on identifying patients with clinically determined diagnoses of diseases; one also included self-reported diagnoses.[20] Patients were identified by a variety of means including: physician reports verified by study clinical staff and through a patient questionnaire;[20] searches of an electronic database;[17,18] a GP search of records;[19] or patient attendance at the practice during a specific time period.[19,21,22] Further details of the inclusion criteria are given in Table 3.

DISCUSSION

Summary

This review identified five cohort studies of multimorbidity in primary care; these derived from two countries (The Netherlands and the US). Substantial variation occurred in the conditions included. Multimorbidity predicted increased health service use and costs, mortality rates, and reduced physical function. Psychosocial risk factors for multimorbidity included negative life events, external health locus of control, and small social networks, which may be most important in conditions that lack a common pathophysiological origin. Although these pioneering studies offer valuable insights, important gaps were also identified: none of the studies focused on mental illness and multimorbidity, or the interaction with socioeconomic deprivation, and patients' views were notably absent. Methodologically, a clear conceptual framework was not always apparent and no study used random sampling of general practices and patients.

Strengths and limitations

The main limitation of any systematic review is the difficulty in ensuring that all of the relevant literature has been identified. This was maximised by combining a variety of search strategies. Abstracts were required to be in English, which could have excluded potentially relevant papers, however only two papers originally identified did not fulfil this criterion. The absence of consistent indexing in databases due to the lack of a key indexing term for 'multimorbidity' posed a difficulty, so comorbidity — which is often used synonymously — was searched for and variations of these search terms were used.[23]

Comparison with existing literature

As far as the authors are aware, this is the first systematic review on this topic. The inconsistency in defining and measuring multimorbidity has been reported by others.[23,24] Retrospective and cross-sectional studies support the findings on healthcare utilisation and costs, mortality, and physical functioning.[6,8,25,26] Since conducting this review, two other relevant cohort studies have been identified; one on the influence of multimorbidity on cognition in an aging population in one region of The Netherlands,[27] and the other on the impact of multimorbidity (as measured by the Ambulatory Care Group case mix system) on choice of primary care provider in two practices in one county of Sweden.[28] However, these two recently published papers do not change our conclusions or the implications for future research outlined below.

Implications for research

The studies identified tended to be limited in scope and size, with questionable generalisability relating to issues of sampling, inclusion criteria, patient attrition and non-response. Causal pathways, prognostic factors, treatment use, patient safety, service models, quality of care, and patient perceptions and experiences were not well documented. A need to focus on socioeconomic factors in future cohort studies is important as retrospective and

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prevalence studies in The Netherlands,[8] Scotland,[29] England,[9] and Ireland[25,26] all suggest a significant link between low socioeconomic status and the amount and burden of multimorbidity. Future research must also explore the longitudinal links between mental illness and multimorbidity, given the growing evidence on their interconnectedness.[29,30] Longitudinal studies on multimorbidity in primary care have important gaps in knowledge. A fuller understanding of personal experience, treatment burden and health service use, as well as the psychological, physical, and social factors that influence multimorbidity over time is needed.

REFERENCES

1. Mather CD, Lancar D. *Updated projections of global mortality and burden of disease, 2002–2030: data sources, methods, and results. Evidence and Information for Policy.* Geneva: World Health Organization, 2005.
2. World Health Organization. *The world health report 2008: Primary health care, now more than ever.* Geneva: WHO, 2008.
3. Starfield B, Shi L, Mackinko J. Contribution of primary care to health systems and health. *Milbank Q* 2005; **83(3):** 457–502.
4. Van Weel C, Schellevis FG. Comorbidity and guidelines: conflicting interests. *Lancet* 2006; **367(9510):** 550–551.
5. Fortin M, Bravo G, Hudon C, *et al.* Prevalence of multimorbidity among adults seen in family practice. *Ann Fam Med* 2005; **3(3):** 223–228.
6. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med* 2002; **162(20):** 2269–2276.
7. Britt HC, Harrison CM, Miller GC, Knox SA. Prevalence and patterns of multimorbidity in Australia. *Med J Aust* 2008; **189(2):** 72–77.
8. Salisbury C, Johnson L, Purdy S, *et al.* Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract* 2011; DOI: 10.3399/bjgp11X548929.
9. Mercer SW, Smith SM, Wyke S, *et al.* Multimorbidity in primary care: developing the research agenda. *Fam Pract* 2009; **26(2):** 79–80.
10. Smith SM, Soubhi H, Fortin M, *et al.* Interventions to improve outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database of Systematic Reviews: Protocols*; Issue 2. Chichester, UK: John Wiley & Sons, Ltd., 2007.
11. Gordis L. *Epidemiology*, 2nd edn. Philadelphia, PA: WB Saunders & Co, 2000.
12. Moons K, Royston P, Vergouwe Y, *et al.* Prognosis and prognostic research: what, why, and how? *BMJ* 2009; **338:** b375.
13. Fortin M, Lapointe L, Hudon C, *et al.* Multumorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes* 2004; **2:** 51.
14. Van den Akker M, Spigt M, De Raeve L, *et al.* The SMILE study: a study of medical information and lifestyles in Eindhoven, the rationale and contents of a large prospective dynamic cohort study. *BMC Public Health* 2008; **8:** 19.
15. Haggerty J, Fortin M, Beaulieu M, *et al.* At the interface of community and healthcare systems: a longitudinal cohort study on evolving health and the impact of primary healthcare from the patient's perspective. *BMC Health Serv Res* 2010, **10:** 258.
16. Schafer I, Hansen H, Schon G, *et al.* The German MultiCare-study: patterns of multimorbidity in primary health care — protocol of a prospective cohort study. *BMC Health Serv Res* 2009; **9:** 145.
17. Van den Akker M, Buntinx F, Metsemakers JF, *et al.* Psychosocial patient characteristics and GP-registered chronic morbidity: a prospective study. *J Psychosom Res* 2001; **50(2):** 95–102.
18. Van den Akker M, Vos R, Knottnerus JA. In an exploratory prospective study on multimorbidity general and disease-related susceptibility could be distinguished. *J Clin Epidemiol* 2006; **59(9):** 934–939.
19. Schellevis FG, Van de Lisdonk EH, Van der Velden J, *et al.* Consultation rates and incidence of intercurrent morbidity among patients with chronic disease in general practice. *Br J Gen Pract* 1994; **44(383):** 259–262.
20. Bayliss EA, Bayliss MS, Ware JE Jr, Steiner JF. Predicting declines in physical function in persons with multiple chronic medical conditions: what we can learn from the medical problem list. *Health Qual Life Outcomes* 2004; **2:** 47.
21. Perkins AJ, Kroenke K, Unutzer J *et al.* Common comorbidity scales were similar in their ability to predict health care costs and mortality. *J Clin Epidemiol* 2004; **57(10):** 1040–1048.
22. Parkerson GR Jr, Broadhead WE, Tse CK. Health status and severity of illness as predictors of outcomes in primary care. *Med Care* 1995; **33(1):** 53–66.
23. Van den Akker M, Buntinx F, Knottnerus J. Comorbidity or multimorbidity: what's in a name? A review of the literature. *Eur J Gen Pract* 1996; **2(2):** 65–70.
24. Valderas JM, Starfield B, Sibbald B, *et al.* Defining comorbidity: implications for understanding health and health services. *Ann Fam Med* 2009; **7(4):** 357–363.
25. Smith S, Ferede A, O'Dowd T. Multimorbidity in younger deprived patients. An exploratory study of research and service implication in general practice. *BMC Fam Pract* 2008; **9:** 6.
26. Glynn LG, Valderas JM, Healy P, *et al.* The prevalence of multimorbidity in primary care and its effect on health care utilization and cost. *Fam Pract* 2011; **28(5):** 516–523.
27. Aarts S, van den Akker M, Tan FE, *et al.* Influence of multimorbidity on cognition in a normal aging population: a 12-year follow-up in the Maastricht Aging Study. *Int J Geriatr Psychiatry* 2011; **26(10):** 1046–1053.
28. Zielinski A, Håkansson A, Beckman A, Halling A. Impact of comorbidity on the individual's choice of primary health care provider. *Scand J Prim Health Care* 2011; **29(2):** 104–109.
29. Mercer SW, Watt GCM. The inverse care law: clinical primary care encounters in deprived and affluent areas of Scotland. *Ann Fam Med* 2007; **5(6):** 503–510.
30. Gunn JM, Ayton DR, Densley K, *et al.* The association between chronic illness, multimorbidity and depressive symptoms in an Australian primary care cohort. *Soc Psychiatry Psychiatr Epidemiol* 2012; **47(2):** 175–184.