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Health Care Utilization and Costs of Elderly Persons With Multiple Chronic Conditions

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Abstract

This systematic literature review identified and summarized 35 studies that investigated the relationship between multiple chronic conditions (MCCs) and health care utilization outcomes (i.e. physician use, hospital use, medication use) and health care cost outcomes (medication costs, out-of-pocket costs, total health care costs) for elderly general populations. Although synthesis of studies was complicated because of ambiguous definitions and measurements of MCCs, and because of the multitude of outcomes investigated, almost all studies observed a positive association of MCCs and use/costs, many of which found that use/costs significantly increased with each additional condition. Several studies indicate a curvilinear, near exponential relationship between MCCs and costs. The rising prevalence, substantial costs, and the fear that current care arrangements may be inappropriate for many patients with MCCs, bring about a multitude of implications for research and policy, of which the most important are presented and discussed.

Keywords

multiple chronic conditions, multimorbidity, health care utilization, health care costs, aged

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Introduction

Multiple chronic conditions (MCCs) pose a substantial health and health care problem, especially among the aged (Schoen, Osborn, How, Doty, & Peugh, 2009; Thorpe & Howard, 2006; van den Akker, Buntinx, Metsemakers, Roos, & Knottnerus, 1998). MCCs (also referred to as multimorbidity) constitute a specific comorbidity construct, which relates to the co-occurrence of two or more chronic conditions (CCs) in one person without reference to an index disease (Valderas, Starfield, Sibbald, Salisbury, & Roland, 2009). Research has linked MCCs to poor outcomes in various dimensions of health, for example, disability (Fuchs et al., 1998), quality of life (Fortin, Dubois, Hudon, Soubhi, & Almirall, 2007), and mortality (Gijssen et al., 2001), among others. Patients with MCCs are at risk for insufficient care and adverse treatment effects, for example, adverse drug events caused by polypharmacy (Akazawa, Imai, Igarashi, & Tsutani, 2010; Qato et al., 2008; Simonson & Feinberg, 2005; Zhang et al., 2009).

Because of successes of both preventive and curative medicine, combined with widespread technological advances, the life expectancy in developed countries has steadily risen over the past 60 years (Christensen, Doblhammer, Rau, & Vaupel, 2009). Amplified by declining fertility rates, this ongoing development is causing a progressive increase in the proportion of elderly people (G. F. Anderson & Hussey, 2000). In the process, the number of people with MCCs has steadily increased (Fortin, Bravo, Hudon, Vanasse, & Lapointe, 2005; Paez, Zhao, & Hwang, 2009). The prevalence of MCCs among persons 65 and older has been widely reported to exceed 65% (G. Anderson, 2010; Hoffman, Rice, & Sung, 1996; van den Akker et al., 1998; Wolff, Starfield, & Anderson, 2002; Yu, Ravelo, Wagner, & Barnett, 2004). In trying to meet the care demands of large numbers of individuals with MCCs, health care systems originally designed to handle acute and episodic illnesses are faced with substantial organizational and financial challenges (Fortin, Soubhi, Hudon, Bayliss, & van den Akker, 2007; Schoen et al., 2009; Stevenson, Abernethy, Miller, & Currow, 2004). The focus of treatment is more and more shifting from cure to slowing the progression of diseases and to confine the functional limitations resulting from MCCs (Warsaw, 2006).

Consequently, multimorbidity is increasingly recognized as a major health problem for which more research and sound policy implications are highly demanded (G. F. Anderson, 2005; Fuster & Voute, 2005; Norris et al., 2008; Sippkoff, 2003). While much is known about the care of older people with individual CCs, the care of persons with MCCs is less well studied. This article will contribute to the current state of knowledge by systematically reviewing studies in which the relationship between MCCs and health care use (HCU) and health care costs (HCCs) was investigated for elderly general populations. Based on the results, the authors will identify implications for policy and research.

New Contribution

Despite the widespread recognition that MCCs pose an extensive health and health care problem, research is not very extensive (Fortin, Lapointe, Hudon, & Vanasse, 2005).

A rich resource containing numerous charts and straightforward conclusions on the impact of MCCs on individuals, their caregivers, and the U.S. health care system is the 2010 revision “Chronic Conditions: Making the Case for Ongoing Care” (G. Anderson, 2010). It constitutes an update of the original 2002 report, created by the *Partnership for Solutions: Better Lives for People With Chronic Conditions*, a Robert Wood Johnson Foundation national program. Its main focus is on the impact of MCCs on HCU/HCCs, and it furthermore highlights current problems encountered by individuals living with CCs as they attempt to obtain a continuum of health care services. Data from the 2006 Medical Expenditure Panel Survey, the 2007 Medicare Standard Analytical file, the 1996 Survey of Income and Program Participation, and from three opinion surveys were used to develop this chartbook (G. Anderson, 2010).

Very little has been done to systemize and synthesize existing empirical evidence (Fortin, Lapointe, et al., 2005). Notable exceptions are Fortin et al. (2004), who reviewed studies investigating MCCs and quality of life in primary care; Gijzen et al. (2001), who summarized studies on causes and consequences (e.g., mortality, functional status/quality of life, HCU, complications) of comorbidity in several somatic diseases (e.g., cancers, diabetes, ischaemic heart disease); and Vogeli et al. (2007), who conducted a narrative review with studies on the prevalence, health consequences, and care management of MCCs. In contrast to the former articles, and in light of an increasing life expectancy and aging populations in many developed countries, this current review is exclusively concerned with peer-reviewed studies in which the relationship between MCCs and HCU/HCCs was examined for elderly general populations. The main contribution lies in the accumulation and summarization of the available empirical evidence on the relationship between MCCs and HCU (physician use, hospital use, medication use) and HCCs to give specific recommendations for future research and health care practice. By learning about the nature of the relationship between CCs and HCU/HCCs, and in particular the incremental service use and costs associated with additional CCs in elderly general populations, this review also contributes to research on the projection of future HCCs.

Conceptual Framework

The behavioral model by R. Andersen and Newman (1973) represents a causal ordering of health service use within an integrated framework. Because the model has been previously described and discussed (R. M. Andersen, 1995; Linden, Horgas, Gilberg, & Steinhagen-Thiessen, 1997; Pitkin Derose, Bahney, Lurie, & Escarce, 2009), we will only outline its basic components relevant for the application to MCCs. In the context of this model, it is assumed that individuals' use of services is a function of their predisposition to use services (predisposing factors), factors that support or impede use (enabling factors), and their need for health care (illness level). MCCs can be understood as one particular concept reflecting patients' illness level, that is, objective evaluations of patient's health, based on the number of concurrent CCs. Because patients' illness level is considered to be the prime determinant of use, one

major implication of the behavioral model is that MCCs should have a stronger impact on HCU than variables operationalizing predisposing and enabling factors (R. Andersen & Newman, 1973). Predisposing variables pertain to sociodemographic (e.g., age, sex, education, occupation, ethnicity, religion, marital status) and belief characteristics (e.g., values concerning health and illnesses), while enabling factors are those that support or impede use (e.g., income, type of health insurance, and price of health services).

The concept of MCCs, when related to global outcome measures of service utilization, such as physician, hospital, or medication use, can be useful in informing national health policy and in monitoring policy changes. It holds particular meaning for primary care and health services research in general populations, where the emphasis is on care and costs of the patient as a whole, not on treatment of a particular disease. It offers new opportunities for quantifying and monitoring population health and its impact on additional HCU/HCC (Schneider, O'Donnell, & Dean, 2009; Valderas, Starfield, & Roland, 2007). This is particularly relevant since future costs may not be well represented as the sum of the costs of separate illnesses. Depending on the nature of the interactions among coexisting diseases, HCCs could either be greater or less than the sum of the cost of individual diseases (Valderas et al., 2009). Measures of MCCs can take these interactions and their effect on HCU/HCCs into consideration. Similar to other authors before us (Pitkin Derose et al., 2009), we included HCCs into the review because of its close relationship with HCU, although the behavioral model in its original form did not recognize cost.

Methods

The procedure of this article was based on established guidelines for systematic literature reviews (Centre for Reviews and Dissemination, 2008). Three measures were used to identify relevant articles that investigated the relationship between MCCs and HCU/HCCs. First, a computerized literature search within the electronic database PubMed was performed, using the following search terms: ((multimorbid*) OR (comorbid*) OR (multiple chronic condition*) OR (multiple chronic disease*)) AND ((utilisation) OR (utilization) OR (expenditure*) OR (expense*) OR (economic*)) AND (aged[MeSh Terms]).

The search process ended on November 1, 2010. Two of the authors (TL and HHK) independently evaluated the first 100 articles by examining title and abstract. Discrepancies were discussed, and the criteria were refined. Subsequently, the main author of this article (TL) screened the remaining set. Second, we reviewed the e-library section of the International Research Community on Multimorbidity (IRCMo) at the Université de Sherbrooke, Canada (http://www.med.usherbrooke.ca/cirmo/centre_documentation_anglais.htm) for additional publications. Third, a bibliographic search was conducted within all potentially eligible articles. Published journal articles were included if they met the following criteria:

1. The relationship between MCCs and HCU/HCCs was examined for an elderly general population (not defined by sharing a particular index disease).
2. Original cross-sectional or longitudinal study published in a peer-reviewed journal.
3. A clearly described measure of MCCs was included as an explanatory variable.
4. Primary study outcome was an aggregate measure of HCU (e.g., physician use, hospital use, use of pharmaceuticals) or HCCs.
5. The article was in English or German language.

Data extraction was primarily concerned with study design, methodological information on sampling, definition and measurement of explanatory variables (in particular MCCs) and outcome variables, and statistical data analysis and findings (Table 1). To facilitate comparisons, all cost estimates were transformed to 2009 U.S. dollars using the Consumer Price Index (OECD, 2010).

Results

Study Selection

The systematic PubMed search produced 3,338 publications, of which a total of 3,157 articles were excluded during the initial screening. The remaining ($n = 181$) were retrieved in full text and closely examined. Of these, 63 were studies on HCU and/or HCCs for populations sharing an index disease, while 100 did not meet the inclusion criteria for other reasons, for example, no aggregate HCU outcome, highly selective sample and/or no elderly population, methodological study. The residual 18 articles were included into the review. Next, we searched the IRCMo virtual library, looking for further studies not yet identified by the PubMed search. From a list of approximately 500 publications exclusively concerned with various aspects of co- and multimorbidity, we selected another 22 studies, of which five were eventually included. The subsequent bibliographic search yielded 12 more studies. Altogether we included 35 studies. The search process and systematization of analyses is depicted in Figure 1. Searches within the Cochrane Database of Systematic Reviews (CDSR) and the Centre for Reviews and Dissemination (CRD) did not yield any extra results.

In the next step, we examined all included studies for analyses concerned with our research question. An analysis was defined as a distinct investigation exploring the association of MCCs (and possibly further explanatory variables) and a particular HCU/HCC outcome. We organized analyses by outcome categories, that is, physician use, hospital use, use and costs pharmaceuticals, HCCs, and out-of-pocket expenditures. An analysis was considered adjusted when all explanatory (confounding) variables included in a statistical model were simultaneously controlled for. Note that several authors investigated more than one HCU/HCC outcome.

Table 1. Summary of Included Articles on the Association of Multiple Chronic Conditions (CCs) and Health Care Utilization and Costs^a (n = 35)

Author (Year) and Country	Study Type and Data Source	Sample Description	Independent Variable (CCs)	Dependent Variable	Principal Findings
Chan et al. (2002), Australia	Cross-sectional study with data from a household survey in the Randwick municipality of Sydney (Australia), March 1998 to June 1999	Sample of noninstitutionalized elderly subjects aged 55 and older (n = 526); survey was supplemented with admission records from the Prince of Wales Hospital (major emergency center in the Randwick municipality)	Count of 9 self-reported diseases	Hospital admissions (HAs) via emergency department (within 14-month study period) ^b	Multiple (three or more) CCs were a strong and significant predictor of emergency department admissions.
Chu and Pei (1999), Hong Kong	Prospective case-control study with emergency admissions (using administrative data) at Queen Mary Hospital of Hong Kong, 1996	Sample of elderly patients aged 65 and older (n = 380) who were emergency readmissions within 28 days of previous discharge from any hospital in Hong Kong (cases); a sex- and age-matched control was recruited for every case (n = 380)	Count of 10 diseases (based on self-report and administrative records)	Early unplanned hospital readmission within 28 days ^{b,c}	Compared with controls, readmission cases had significantly more CCs (3.1 vs. 2.6). Number of CCs was a significant risk factor for early unplanned readmission in a multivariate analysis (OR 1.30).
Condelius et al. (2008), Sweden	Cross-sectional study with administrative registry data (2001) from four municipalities in southern Sweden	Sample of elderly patients aged 65 and older (n = 4,907) who had one or more HA in 2001	CCs based on a count of 17 ICD-10 main chapters (based on presence of diseases in different organ systems)	Number of planned, ^c acute, ^c and total HAs ^{b,c}	Elders with three or more HAs had significantly more CCs (3.45) than those with one (1.64) or two stays (2.61). In multivariate analyses, the number of CCs was significantly associated with acute and total number of admissions, and (less strongly) with planned HAs.
Crystal et al. (2000), United States	Cross-sectional study with 1995 Medicare Current Beneficiary Survey data (use and cost files)	Nationwide sample of Medicare-enrolled elderly patients aged 65 and older (n = 7,886)	Count (number not specified) of self-reported diseases	Annual out-of-pocket (OPE), ^{b,c} annual health care costs (HCCs) ^{b,c}	The number of CCs was significantly and positively associated with total HCCs, annual OPE, and OPE as percentage of income (persons without CCs spent 13.8% of their income, those with five or more CCs 25.5%).

(continued)

Table 1. (continued)

Author (Year) and Country	Study Type and Data Source	Sample Description	Independent Variable (CCs)	Dependent Variable	Principal Findings
Fahlman et al. (2006), United States	Retrospective review (cross-sectional) of retail and mail order prescription claims data from Medicare + Choice (collected between January 1998 and December 2000), United States	Sample made up of drug claims and enrollment data of Medicare + Choice decedents (n = 4,602) in their last year of life (65 and older), supplemented by the Medicare denominator file and 1990 Census data	Charlson Comorbidity Index (CCI) based on diagnosis codes and utilization data	Medication use, ^{b,c} annual prescription drug spending, ^{b,c} OPE for prescription drugs ^{b,c}	Beneficiaries with higher numbers of comorbidities had significantly greater numbers of prescriptions (8 prescriptions for each additional comorbidity) and higher annual prescription drug expenditures and higher OPE.
Fishman et al. (1997), United States	Cross-sectional study with diagnostic and procedural data (1992) from Group Health Cooperative (GHC) of Pudget Sound (western Washington State, United States)	GHC enrolled patients 18 years and older (n = 258,015); sample stratified by age: 65 to 74 (n = 27,222), 75 to 84 (n = 14,039), 85 and older (n = 3,078)	Count of 18 diseases (based on registry data and diagnostic codes from utilization data)	Annual HCCs ^b	An additional CC resulted in an expected increase in annual HCCs of 80% to 300%, depending on age, sex, and CC profile.
Hessel et al. (2000), Germany	Cross-sectional study with data from a household survey by the University of Leipzig, Germany, March/April 1996	Nationwide sample of noninstitutionalized elderly persons aged 60 and older (n = 349)	Count of self-reported diseases (number not specified)	Annual number of physician visits, ^c daily number of medications ^c	The number of medical conditions was significantly and positively associated with the annual number of physician visits and number of medications taken on a daily basis (CCs were strongest predictor in each of the multiple regression analyses).
Hoffman et al. (1996), United States	Cross-sectional study with data from the 1987 National Medical Expenditure Survey (household component)	Nationwide sample of noninstitutionalized persons of all ages (n = 27,705), sample stratified by age: 65 and older (n = 3,710)	Count (not specified) of self-reported diseases (distinguished by chronic vs. acute conditions)	Annual HCCs ^b	In comparison with acute conditions only (\$2,713), those with one CC had annual HCCs about 1.8 times (\$4,887), and those with two or more CCs had costs about 3.6 times as high (\$9,881).
Hwang et al. (2001), United States	Cross-sectional study with 1996 Medicare Expenditure Panel Survey data (household component)	Nationwide sample of noninstitutionalized persons of all ages (n = 22,326), sample stratified by age: 65 and older (n = 2,686)	Using the clinical classification system, self-reported diseases were aggregated into clinically	Annual OPE ^b	OPE increased with each additional CC and was about twice as high for elders with two CCs compared with those without CCs. This association was found for OPE for prescription drugs.

(continued)

Table 1. (continued)

Author (Year) and Country	Study Type and Data Source	Sample Description	Independent Variable (CCs)	Dependent Variable	Principal Findings
Ionescu-Ittu et al. (2007), Canada	Cross-sectional study with random sample drawn from provincial administrative databases in Quebec, Canada, for 2000-2001	Sample of persons aged 65 and older ($n = 95,173$) who had at least one medical charge in 2000 or 2001	homogeneous categories CCI based on diagnosis codes and utilization data; Chronic Disease Score (CDS) based on drug prescriptions	Rate of emergency department use (number of days on which a visit was made to an emergency department per 1,000 days) ^{b,c}	home health, office visits, hospital use, and medical equipment but not for OPE for dental services and vision aids. Comorbidity was a significant independent predictor of emergency department use. In a multivariate analysis, comorbidity had a comparatively weak effect on emergency department use. One additional score on CCI increased the rate of emergency department use by 7%, one score on the CDS by 4%.
Landi et al. (2004), Italy	Observational cohort study with administrative data from six Italian home health care agencies (longitudinal data, 1997-2002)	Community-dwelling frail persons aged 65 and older cared for by six Italian home care agencies ($n = 1,291$)	Count (number not specified) of all clinically diagnosed diseases	HAs at baseline and during 1-year follow-up ^{b,c}	Elders with any HA (at baseline) had significantly more CCs (3.9) than those without HA (3.2). In a multivariate analysis, elderly persons with five or more CCs were more than twice as likely to incur an HA, compared with those without CCs (during 1-year follow-up).
Librero et al. (1999), Spain	Cross-sectional study with administrative (hospital discharge) data from Valencia Health Service, Spain, 1993-1994	Discharge data from 1993 of $n = 106,673$ patients (1994 data was used for the identification of readmission only) aged 16 or older; analysis for readmission at 1 year was stratified by age	Adaptation of Charlson Comorbidity Index (CCIa) based on clinical diagnosis	Hospital readmission at 1 year ^c	Results from logistic regression with age comorbidity interaction: Patients aged 65 to 79 in the highest morbidity group (5+) had significantly lower chances of being hospitalized (OR 0.51) than those without CCs, whereas patients with moderate morbidity burden (1 to 2) had significantly higher chances (OR 1.24).

(continued)

Table 1. (continued)

Author (Year) and Country	Study Type and Data Source	Sample Description	Independent Variable (CCs)	Dependent Variable	Principal Findings
Linden et al. (1997), Germany	Cross-sectional study with survey data from a randomly drawn sample from the city registry of West Berlin	Sample of elderly patients aged 70 and older (n = 516)	Count of number of diseases (based on physical examinations by medical doctors)	Annual physician visits, ^{b,c} medication use ^{b,c}	Number of CCs was significantly and positively associated with number of physician visits and number of medications in a multiple regression analysis.
Liu-Ambrose et al. (2010), Canada	Cross-sectional study with data from a survey in the metropolitan area of greater Vancouver; British Columbia, Canada, in May 2005	Convenience sample (n = 209) of community-dwelling elders aged 65 and older recruited from local pharmacies	Count (number not specified) of self-reported chronic conditions	Three month HCCs ^c	Number of CCs was significantly associated with HCCs: An additional CC was associated with additional \$98.12 in three month direct HCCs (number of CCs was strongest predictor in a linear regression analysis).
Marcantonio et al. (1999), United States	Case-control study of emergency admission patients in a Medicare managed care plan (using administrative data, that is, medical records)	Sample of patients aged 65 and older (n = 154) who were emergency readmissions within 30 days of previous discharge from an academic hospital (primary hospital for members of this care plan); a control matched by principal diagnosis was recruited for every case (n = 154)	Count of 16 clinically diagnosed conditions	Early unplanned hospital readmission within 30 days ^c	CCs were independently associated with early unplanned readmission. Patients with five or more CCs were 2.6 times more likely to incur an early readmission compared with those without CCs.
M. Y. Martin et al. (2006), United States	Cross-sectional study with survey data from the Birmingham Study of Aging (University of Alabama), 1999-2001	Sample of community-dwelling elders 65 and older (based on a random sample of Medicare beneficiaries) from five counties in central Alabama (n = 1,000)	CCI based on self-reported physician diagnosis	Annual emergency department visits, ^c number of HAs, ^c nights spent at hospital, ^c physician visits ^c	Number of CC was significantly and positively associated with each of the outcomes (HAs, emergency department admissions, nights spent at hospital, physician visits). The risk to incur an emergency department admission increased by 27% with each additional score on the CCI.

(continued)

Table 1. (continued)

Author (Year) and Country	Study Type and Data Source	Sample Description	Independent Variable (CCs)	Dependent Variable	Principal Findings
Moxey et al. (2003), United States	Cross-sectional study with 1996 Medicare Current Beneficiary Survey data	Nationwide sample of community-dwelling Medicare-enrolled elderly patients aged 65 and older (n = 7,789)	Definition of three health status categories (HSC) based on number of self-reported diseases and difficulties with activities of daily living (ADL)	Annual HCCs, ^b annual outpatient drug expenditures ^b	Persons with more CCs had significantly higher drug expenditures and total health care expenditures.
Mueller et al. (1997), United States	Cross-sectional study with data from the 1987 National Medical Expenditure Survey (household component)	Nationwide sample of noninstitutionalized persons of all ages (n = 36,000), sample stratified by age: 65 and older (size not specified)	Count of 11 self-reported diseases	Annual pharmaceutical expenditures ^b	Mean per capita pharmaceutical expenditures increased with each additional CC (no CCs \$172, one CC \$370, two CCs \$606, three or more CCs \$980).
Paez et al. (2009), United States	Cross-sectional study with data from the 2005 Medical Expenditure Panel Survey	Nationwide sample of noninstitutionalized persons of all ages (size not specified), sample stratified by age: 65 to 79, 80 or older	Using the clinical classification system, self-reported diseases were aggregated into clinically homogeneous categories	Annual OPE ^b	Mean OPE increased with each additional CC. OPE for persons aged 65 to 79 with three or more CCs was about 2.7 times higher than for those without CCs. The positive association was persistent for all analyzed services (e.g., inpatient, outpatient, medications), except vision aids.
Qato et al. (2008), United States	Cross-sectional study with data from the National Social Life, Health and Aging Project population based survey, July 2005 to March 2006	Nationwide sample of community-dwelling persons aged 57 to 84 (n = 3,005)	CCI based on self-reported physician diagnosis	Medications used on a regular schedule (daily or weekly) ^{b,c}	Medication use was more likely among persons with more comorbid conditions. Compared with elders without CCs, those with one to four CCs odds of 0.33 to not have taken any medications.

(continued)

Table 1. (continued)

Author (Year) and Country	Study Type and Data Source	Sample Description	Independent Variable (CCs)	Dependent Variable	Principal Findings
Ramage-Morin (2009), Canada	Cross-sectional study with data from the National Population Health Survey (household file, 1998-1999, and health institutions file, 1996-1997)	Nationwide sample of elderly persons aged 65 and older (n = 2,851)	Count of 22 self-reported diseases	Multiple medication use (last 2 days) ^{b,c}	Noninstitutionalized respondents with CCs were much more likely to have used medications and to have used multiple medications. Elders with three or more CCs were 1.48 more likely to have used multiple medications compared with those with none or one CC. For institutionalized persons, the association had the same direction but less strength.
Rapoport et al. (2004), Canada	Cross-sectional study with data from the National Population Health Survey (general health component), 1998-1999	Nationwide sample of persons of all ages (n = 17,244), stratified by age: 60 to 79 (n = 2,995), 80 and older (n = 659)	Count of 19 self-reported diseases	Annual number of HAs, ^c nights spent at hospital, ^c physician visits ^c	The number of CCs was a highly significant predictor of health care utilization. An additional CC was associated with 1.29 more physician visits and 0.60 more hospital nights a year. An additional CC was associated with a 76% increase to have had more than 12 physician visits a year and a 27% increase for any hospitalization
Rice and LaPlante (1992), United States	Cross-sectional study with data from the 1980 National Medical Care Utilization and Expenditure Survey (household component)	Nationwide sample of noninstitutionalized persons of all ages (n = 6,000 households), sample stratified by age: 65 and older (size not specified)	Count of self-reported disabling diseases (number not specified)	Annual HCCs ^b	HCCs were positively and significantly associated with number of CCs. Expenditures for elderly persons with two or more CCs were about 2.9 times higher than for those without CCs.
Rogowski et al. (1997), United States	Cross-sectional study with survey data from the Panel Study of Income Dynamics (Elderly Health Supplement, 1990)	Nationwide sample of persons aged 66 and older (n = 996)	Count of 8 self-reported diseases (with prevalence of at least 10% in the elderly population)	Medication use, ^c prescription drug expenditures (PDE), ^{b,c} out-of-pocket expenditures for prescription drugs (OPE-PD) ^b	Annual PDE/OPE-PD increased with each additional CC in a descriptive analysis. In a multivariate analysis, the presence of two or more CCs increased the odds of prescription drug use by 2.3 (reference category: no CCs).

(continued)

Table 1. (continued)

Author (Year) and Country	Study Type and Data Source	Sample Description	Independent Variable (CCs)	Dependent Variable	Principal Findings
Ruger and Kim (2007), South Korea	Gross-sectional study with data from the 1998 Korean National Health and Nutrition Survey	Nationwide sample of noninstitutionalized persons of all ages ($n = 39,060$), sample stratified by age: 66 to 79 ($n = 4,726$), 80 and older ($n = 469$)	Count of 14 self-reported diseases	Annual OPE ^a	OPE was positively associated with number of CCs. Mean OPE did not increase with each additional CC but was substantially higher for persons with one or more CCs compared with those without CCs.
Sambamoorthi et al. (2003), United States	Cross-sectional study with 1997 Medicare Current Beneficiary Survey (cost and use data)	Nationwide sample of community-dwelling Medicare-enrolled elderly persons aged 65 and older ($n = 8,814$)	Count of 10 self-reported diseases	Medication Use, ^c annual PDE, ^{b,c} OPE-PD ^{b,c}	PDE/OPP-PD were positively associated with CCs. In adjusted analysis, expenditures increased by \$202 (PDE) and \$78 (OPP-PD) with each additional CC.
Schneider et al. (2009), United States	Cross-sectional study with 2005 Chronic Condition Data Warehouse data	5% random sample of Medicare population, of which 84.6% were aged 65 and older ($n = 1,649,574$)	Count of 21 clinically diagnosed diseases (based on utilization data for treatment of these diseases)	Annual HCCs, ^b HAs and days at hospital, ^b home health visits, ^b physician (office) visits ^b	Total HCCs and utilization within each care setting increased with each additional CC. Compared with elders without CCs, those with three or more CCs had about 11.5 times higher HCC, had 25 times more hospital nights, 14.6 times more hospital stays, 16.5 times more home health visits, and 2.3 times more physician office visits.
Schoenberg et al. (2007), United States	Study with longitudinal survey data from the Health Retirement Study (1998, 2002)	Nationwide sample of elderly persons aged 65 and older ($n = 8,180$)	Count (and common combinations) of 8 self-reported diseases	Annual OPE ^{a,c}	OPE increased with each additional CC in unadjusted analysis and was positively and significantly associated with CCs in adjusted analysis. Cost increases over the time period 1998 to 2002 were more pronounced for persons with CCs than for those without (+19.8% without CCs vs. +64.6% for those with five or more CCs).

(continued)

Table 1. (continued)

Author (Year) and Country	Study Type and Data Source	Sample Description	Independent Variable (CCs)	Dependent Variable	Principal Findings
Shah et al. (2001), United States	Cross-sectional study with data from the 1993 Medicare Current Beneficiary Survey	Nationwide sample of noninstitutionalized Medicare-enrolled elderly persons aged 66 and older ($n = 9,784$)	CCla based on self-reported diseases	Annual emergency department admissions ^b	Emergency department admissions were significantly and positively associated with CCs (CCla score groups). Compared with persons without CCs (reference category), those within CCla score group 5 were more than 8.5 times as likely to have used the emergency department.
Shelton et al. (2000), United States	Prospective cohort study based on survey and administrative claims data (1993-1994)	Elderly disabled patients aged 65 and older ($n = 411$) in the development cohort) participating as control patients in the Generalist Physician Initiative, Carle Clinic site, Illinois	Count of 6 self-reported diseases	Annual hospital or emergency department admissions ^c	Result from cross-sectional analysis with data from the development cohort: Participants with two or more CCs had an increased risk of having been admitted to hospital.
Starfield et al. (2005), United States	Cross-sectional study with (administrative claims data from the 1999 Medicare Standard Analytical File	5% random sample of Medicare population aged 65 and older in 1999 ($n = 1,133,030$)	John Hopkins Adjusted Clinical Group (ACG) case-mix system (based on 179 diagnosis groups)	Annual physician visits (primary and specialist care) ^b	Average number of visits markedly increased with increasing morbidity burden (ACG), with larger increases for specialists than for primary care physicians.
Weiner et al. (2003), United States	Cross-sectional study with survey data from the Women's Health and Aging Study I (1991-1994), Urban community in Baltimore, Maryland, United States; supplemented with Medicare claims data	Sample of community-dwelling elderly disabled women aged 65 and older in an urban community in Baltimore, Maryland, United States ($n = 902$)	Count of 16 self-reported diseases	Annual HCCs (total, inpatient, outpatient, home health care, nursing facility) ^{b,c} , HAs ^b , physician visits ^b	Number of CCs was positively and significantly associated with HAs and total HCCs in unadjusted analyses. In adjusted multivariate analysis, CCs were not associated with increased expenditures.

(continued)

Table 1. (continued)

Author (Year) and Country	Study Type and Data Source	Sample Description	Independent Variable (CCs)	Dependent Variable	Principal Findings
Wolff et al. (2002), United States	Cross-sectional study with (administrative claims) data from Medicare beneficiaries (based on enrollment and claims files)	5% random sample of Medicare population aged 65 and older in 1999 ($n = 1,217,013$)	Major Diagnostic Categories (MDC) based on Ambulatory Diagnostic Group clusters that involve CCs	Annual health care expenditures, ^b HA for ambulatory care sensitive conditions (HA-ACSC), ^c HA with a preventable complication ^c	Health care expenditures exponentially increased with each additional CCs. The odds of incurring a HA for an ACSC were 7.5 times greater among persons with one CC and 98.5 times greater among those with four or more CCs compared with those without CCs. Similar findings were presented for HAs with a preventable complication.
Xakellis (2005), United States	Cross-sectional study with data from the 1998 Medicare Current Beneficiary Survey	Nationwide sample of noninstitutionalized Medicare-enrolled elderly persons aged 65 and older ($n = 7,928$)	Count of 15 self-reported diseases	Annual physician visits ^b	Persons who saw both types of physicians (generalist and specialist) had significantly more CCs, while persons who saw no physician had significantly fewer CCs than persons who saw a generalist or specialist physician only. This result was confirmed and extended adjusted analyses.
Yu et al. (2004), United States	Cross-sectional study with administrative data from Veterans Affairs electronic medical records, 2000	Electronic medical records of all veterans aged 65 and older who received care in 2000 ($n = 1,596,789$)	Count of 29 diseases (based on utilization data for treatment of these diseases)	Annual HCCs ^b	The mean costs for persons with one or more CCs were about 3.5 times greater than for those without CCs.

a. All cost estimates were transformed to 2009 U.S. dollars using the Consumer Price Index (OECD, 2010).

b. Denotes articles that contain unadjusted analyses (e.g., bivariate analyses).

c. Denotes articles that contain adjusted analyses (i.e., adjusted for confounders) for the particular health care outcome (e.g., regression analyses).

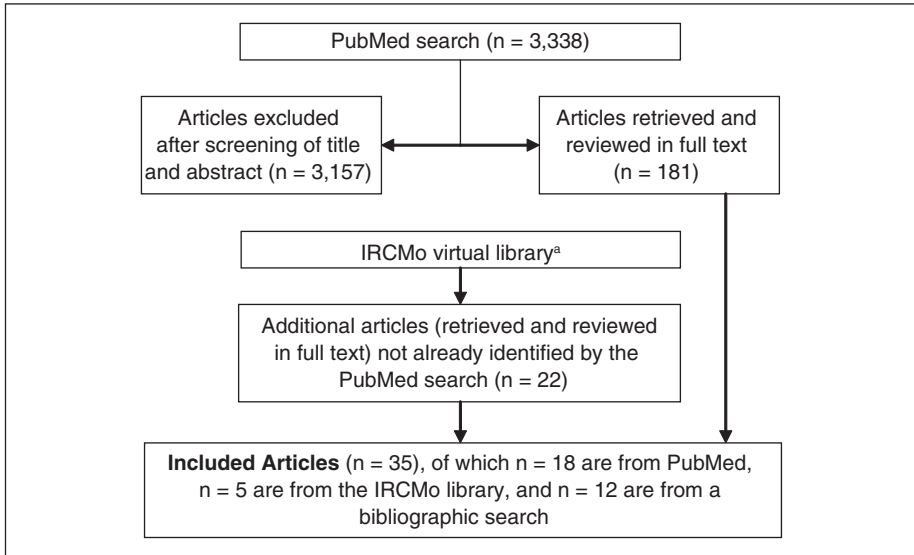


Figure 1. Flowchart illustrating the search process

a. International Research Community on Multimorbidity (IRCMo) at the Université de Sherbrooke, Canada (http://www.med.usherbrooke.ca/cirmo/centre_documentation_anglais.htm)

Methodological Overview

The majority of studies come from the United States ($n = 23$), the remaining are from Europe ($n = 5$), Canada ($n = 4$), Asia ($n = 2$), and Australia ($n = 1$). All have been published between 1992 and 2009, and analyzed data from 1980 to 2005. Most included studies were cross-sectional in nature ($n = 30$). Of the remaining five studies, three were cohort studies (Landi et al., 2004; Schoenberg, Kim, Edwards, & Fleming, 2007; Shelton et al. 2000), while two were case-control studies (Chu & Pei, 1999; Marcantonio et al., 1999), respectively. The data analyzed were based on surveys ($n = 21$) drawn from administrative files ($n = 12$) or combined both sources ($n = 2$).

Measurement of MCCs substantially varied between studies. The bulk of studies using survey data assessed CCs by self-report of respondents, few of which verified respondent information, for example, by physicians' diagnosis, medications used, or physical examinations. Studies that used administrative records identified chronic illnesses from medical records or from specific diagnosis linked to claims data. Oftentimes, these were based on *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis codes.

Different measures of MCCs were subsequently used to analyze HCU/HCCs. Since these have been extensively discussed elsewhere (de Groot, Beckerman, Lankhorst, & Bouter, 2003; Guralnik, 1996; Piccirillo & Costas, 2004), and some authors provided limited and incomplete information, we will only describe them briefly. About two

thirds ($n = 24$) of the studies employed a simple disease or diagnosis count in which a list of diseases or diagnoses was drawn on to identify concurrent CCs. Unfortunately, the lists from which CCs were drawn differed in number and types of CCs, impeding comparisons. What is more, there was no homogeneous definition of what constitutes as a CC in the included studies. For example, Ruger and Kim (2007) defined a CC “as one that lasted or was expected to last 3 or more months,” (p. 805), while Hwang, Weller, Ireys, and Anderson (2001) defined a person as having a CC “if that person’s condition had lasted or was expected to last twelve or more months and resulted in functional limitations and/or the need for ongoing medical care.” (P. 268). Only 11 studies explicitly defined what constitutes as a CC, albeit the majority provided information on which diseases were included in the study.

Other measures, including indices, were employed in studies that did not use a disease count ($n = 11$). A widely used index, developed by Charlson, Pompei, Ales, and MacKenzie (1987), is the Charlson Comorbidity Index (CCI), originally introduced to predict mortality in hospital patients. This weighted index was implemented in three studies (Fahlman, Lynn, Doberman, Gabel, & Finch, 2006; Ionescu-Ittu et al., 2007; M. Y. Martin, Powell, Peel, Zhu, & Allman, 2006). Another two authors calculated a multimorbidity score based on the adaptations of the Deyo, Cherkin, and Ciol (1992) and Romano, Roos, and Jollis (1993) versions of the CCI (Librero, Peiro, & Ordinana, 1999; Shah, Rathouz, & Chin, 2001). Additionally to the CCI, Ionescu-Ittu et al. (2007) calculated a medication-based Chronic Disease Score (CDS) developed by Von Korff, Wagner, and Saunders (1992). Wolff et al. (2002) grouped individual ICD-9 diagnosis by main organ system involvement into 23 major diagnostic categories (MDCs). Starfield, Lemke, Herbert, Pavlovich, and Anderson (2005) applied the ambulatory care groups (ACG) case-mix system to separate patients into three overall morbidity burden groups. A similar approach was followed by Moxey, O’Conner, Novielli, Teutsch, and Nash (2003) who used 10 prevalent CCs and information on activities of daily living (ADL) to develop three health status categories (HSCs). Persons with no CCs and no problems with ADL were allocated to HSC I, those with one or two CCs and no problems with ADL to HSC II, and those with three or more CCs and/or difficulties with ADL to HSC III (Moxey et al., 2003). Two studies used the clinical classification system (CCS) in which ICD-9 codes were aggregated into mutually exclusive, clinical homogeneous categories (Hwang et al., 2001; Paez et al., 2009).

Association of MCC With Health Care Utilization

The following subsections will separately discuss results by outcome categories, that is, physician use, hospital use, pharmaceuticals, HCCs, out-of-pocket costs.

Physician use. The relationship between MCCs and use of physician services was analyzed within seven studies. It was consistently found that elders with more CCs had significantly more physician visits. Two studies conducted bivariate analyses and observed an increasing mean number of physician visits by number of CCs (Schneider et al., 2009; Starfield et al., 2005). For example, in a descriptive analysis using a large

sample of Medicare beneficiaries, the mean annual number of physician visits increased from 4.86 for persons without CCs to 11.36 for those with three and more CCs (Schneider et al., 2009). MCCs were moreover associated with significant differences in the utilization of primary and specialist physician services (Starfield et al., 2005; Xakellis, 2005). Xakellis (2005) compared the number of CCs by visits to primary and specialist physicians and found that persons who did not see any type of physician within 1 year had on average 1.66 (± 1.5) CCs, while those who saw both types of physicians had 2.67 (± 1.7).

Multivariate models were employed within four studies, all of which observed a positive association of MCCs and annual number of physician visits (Hessel, Gunzelmann, Geyer, & Brahler, 2000; Linden et al., 1997; Martin et al., 2006; Rapoport, Jacobs, Bell, & Klarenbach, 2004). For example, in a study of Canadian elders by Rapoport et al. (2004), an additional CC was associated with 1.29 more physician visits per year. These models moreover indicate that health state measures had a relatively stronger impact on physician use than predisposing (i.e., sociodemographic and attitudinal) factors. Within these elderly populations, typical confounders such as age, gender, and income, which had been controlled for in all four models, did exhibit inconsistent and partly insignificant effects on the number of physician visits, whereas the illness level, measured through presence of MCCs and self-rated health, had been a consistent and highly significant predictor of physician use.

Hospital use. The impact of MCCs on utilization of hospital care was addressed within 13 studies. Of these, nine were population based (Chan, Chong, Basilikas, Mathie, & Hung, 2002; Condelius, Edberg, Jakobsson, & Hallberg, 2008; Ionescu-Iltu et al., 2007; Landi et al., 2004; M. Y. Martin et al., 2006; Rapoport et al., 2004; Schneider et al., 2009; Shah et al., 2001; Wolff et al., 2002), while four were based on patients recruited from hospital(s) (Chu & Pei, 1999; Librero et al., 1999; Marcantonio et al., 1999; Shelton et al., 2000). The majority of studies investigated the annual number of hospital admissions, emergency department admissions, or unplanned hospital readmissions within 1 year. Two studies were concerned with early unplanned readmissions within 28 days (Chu & Pei, 1999) and 30 days (Marcantonio et al., 1999), respectively. Further outcomes researched were days/nights spent in a hospital (M. Y. Martin et al., 2006; Rapoport et al., 2004; Schneider et al., 2009) and planned hospital admissions (Condelius et al., 2008).

All studies that explored hospital admissions or days/nights spent at hospital asserted a positive association, many of which found that hospital use increased with each additional CC. Schneider et al. (2009) observed that persons with three or more CCs had 14.6 times more hospital stays and 25 times more hospital nights than those without CCs. In a study with elders from southern Sweden (Condelius et al., 2008), those with three or more hospital admissions had significantly more CCs (3.45) than those with one (1.64) or two (2.61) stays.

Studies that conducted adjusted analyses likewise demonstrated that the number of CCs was a highly significant predictor of hospital use (Chu & Pei, 1999; Condelius et al., 2008; Landi et al., 2004; Marcantonio et al., 1999; M. Y. Martin et al., 2006; Rapoport

et al., 2004; Shelton et al., 2000). Condelius et al. (2008) compared the effects of a set of significant explanatory variables (of which a measure of MCCs was one) on total number of hospital admissions, emergency department admissions, and planned admissions, and found the impact of multiple CCs on planned admissions to be much weaker than the effect on total admissions and on emergency department admissions. Seemingly, MCCs led to frequent hospitalizations through unexpected negative health events. In light of this finding, results from Wolff et al. (2002), who explored the risk for incurring hospital admissions for ambulatory care sensitive conditions (ACSC), that is, hospitalizations that are considered preventable with adequate ambulatory care, strongly suggest that ambulatory care may be insufficient especially for highly multimorbid patients. Patients with four or more CCs had odds more than 90 times greater than individuals without CCs to incur hospital admissions for ACSCs and to have preventable complications while hospitalized (Wolff et al., 2002).

All but one study that explored the impact of MCCs on emergency department admissions or unplanned hospital readmissions found a positive association. Librero et al. (1999) conducted a logistic regression analysis with age-comorbidity interaction. Surprisingly, patients aged 65 to 79 years in the highest morbidity group (5+) were significantly less likely to have had an emergency department admission (odds ratio [OR] = 0.51) than those without CCs, whereas patients with moderate morbidity burden (1 to 2) had significantly higher chances (OR = 1.24). The authors concluded that intermediate levels of age-comorbidity showed a discrete increase in the risk of unplanned hospital readmission at one year, while high levels age-comorbidity behaved as a protective factor from readmission (Librero et al., 1999). Despite this unusual finding, the remaining studies vary only in magnitude of the positive associations observed, which ranged from weak effects (OR = 1.07; Ionescu-Ittu et al., 2007) to strong effects in which the odds of elderly subjects to be hospitalized via the emergency department were more than eight times as high for those in the highest multimorbidity category compared with those without CCs (Shah et al., 2001).

Furthermore, several studies observed a positive significant association between two predisposing factors and hospitalizations independent of the number of CCs, that is, age (Ionescu-Ittu et al., 2007; Librero et al., 1999; Marcantonio et al., 1999; Rapoport et al., 2004; Shah et al., 2001), as well as living alone (Landi et al., 2004; Shah et al., 2001; Shelton et al., 2000). Beyond that, no other likely confounding variables (e.g., gender, education) consistently influenced hospital use. Unfortunately, many possible confounders were not included regularly, while a variety of predisposing factors did exhibit inconsistent or insignificant effects.

Pharmaceuticals. Nine studies were concerned with use and/or costs of prescription medications, all of which asserted a positive association. While about 60% of elderly respondents with zero or one CC reported taking prescription medications, this percentage went up to more than 90% for those with two or three CCs, and approached 100% for those with more than five CCs (Qato et al., 2008; Ramage-Morin, 2009; Rogowski, Lillard, & Kington, 1997; Sambamoorthi, Shea, & Crystal, 2003). Thus, almost all severely multimorbid individuals reported using some type of prescription

medication. Subjects with MCCs also filled significantly more prescription medications (Fahlman et al., 2006; Hessel et al., 2000; Linden et al., 1997) and had an increased risk of taking multiple medications (Ramage-Morin, 2009). Noninstitutionalized elderly Canadians with three or more CCs had about 15 times the odds of having used five or more medications (odds of 2.3 for institutionalized elders) within the past 2 days compared with those with none or one CC (Ramage-Morin, 2009).

Mean annual costs for prescription medications were calculated within five studies (Fahlman et al., 2006; Moxey et al., 2003; Mueller, Schur, & O'Connell, 1997; Rogowski et al., 1997; Sambamoorthi et al., 2003), all of which found that spending significantly increased with each additional CC. Of all included studies, Fahlman et al. (2006) reported the lowest prescription drug expenditures of \$482 for individuals with none or one CC and \$755 for those with five CCs. The study by Moxey et al. (2003) observed the highest drug expenditures and the strongest increase of costs for each additional CC: \$471, \$1,503, and \$3,112 for subjects with zero, one or two, and three and more CCs, respectively. Additional mean per capita costs for prescription drugs associated with the presence of two or more CCs (in comparison with subjects without CCs) were between 134% (Rogowski et al., 1997) and 260% (Sambamoorthi et al., 2003).

Similar to findings for utilization of physician and hospital care, measures of MCCs (and other health status measures) did exhibit the strongest and most consistent influence on use and costs of prescription pharmaceuticals in adjusted analyses. However, an increased use/costs of medications was also observed for females (Fahlman et al., 2006; Hessel et al., 2000; Sambamoorthi et al., 2003) with statistically insignificant effects in two models (Linden et al., 1997; Rogowski et al., 1997), and individuals with supplementary or employer sponsored insurance (Fahlman et al., 2006; Rogowski et al., 1997; Sambamoorthi et al., 2003).

Total health care costs. Mean annual HCCs were investigated within 10 studies. Of these, 6 were based on surveys (Crystal, Johnson, Harman, Sambamoorthi, & Kumar, 2000; Hoffman et al., 1996; Liu-Ambrose, Ashe, Marra, & Physical Activity and Chronic Conditions Research Team, 2010; Moxey et al., 2003; Rice & LaPlante, 1992; Weiner, Amick, & Lee, 2008), while the remaining 4 analyzed U.S. administrative data from Medicare (Schneider et al., 2009; Wolff et al., 2002), Group Health Cooperative of Pudget Sound (Fishman, Von Korff, Lozano, & Hecht, 1997), and the Department of Veterans Affairs (Yu et al., 2004).

Two studies simply compared mean expenditures of individuals without CCs with those with one or more CCs and reported additional costs of 285% (Yu et al., 2004) and 400% (Fishman et al., 1997). Several studies calculated HCCs associated with each additional CC, many of which asserted a curvilinear, near exponential relationship in which costs about doubled for an additional CC (Crystal et al., 2000; Fishman et al., 1997; Hoffman et al., 1996; Moxey et al., 2003; Rice & LaPlante, 1992; Schneider et al., 2009; Wolff et al., 2002). For instance, in the study by Schneider et al. (2009) Medicare beneficiaries with zero, one, two, and three and more CC accumulated expenditures of \$3,079, \$7,879, \$16,402, and \$35,701, respectively. Wolff et al. (2002) calculated lower mean expenditures (\$272 for one CC vs. \$17,996 for four and more CCs),

the percentage increase in HCCs attributable to an additional CC was similar to that found by Schneider et al. (2009), however. A consequence of increasing incremental costs with each additional CC was that resources were allocated very unequally between beneficiaries. As for the study of Wolff et al. (2002), individuals without CCs accounted for 18% of the sample but only 1% of the expenditures. The majority of expenditures (95%) were attributed to the group of individuals with two or more CCs, which accounted for 65% of the sample. About one fourth of the sample had four or more CCs. This group consumed about two thirds of the total funds (Wolff et al., 2002).

Three studies explored the impact of MCCs on self-reported HCCs using multivariate models. MCCs were independently predictive of total health care expenditures in two of these (Crystal et al., 2000; Liu-Ambrose et al., 2010), whereas Weiner et al. (2003) did not find any association between MCCs and HCCs for a population of severely disabled elderly women. Higher expenditures were also observed for the oldest of these elderly subjects (Fishman et al., 1997; Moxey et al., 2003; Yu et al., 2004).

Out-of-pocket payments. The impact of MCCs on out-of-pocket payments was investigated within eight studies, three of which were focused on out-of-pocket payments for prescription drugs solely (Fahlman et al., 2006; Rogowski et al., 1997; Sambamoorthi et al., 2003), while the remaining were concerned with total out-of-pocket payments (Crystal et al., 2000; Hwang et al., 2001; Paez et al., 2009; Ruger & Kim, 2007; Schoenberg et al., 2007).

Similar to findings for HCCs, annual out-of-pocket payments likewise substantially increased as the number of CCs rose (Crystal et al., 2000; Fahlman et al., 2006; Sambamoorthi et al., 2003; Schoenberg et al., 2007). A descriptive study by Paez et al. (2009) with data from the 2005 Medical Expenditure Survey found that for persons aged 65 to 79 with three or more CCs (\$2,251), out-of-pocket expenditures were about 3.3 times higher than for those without CCs (\$681; Paez et al., 2009). Schoenberg et al. (2007) conducted a cohort study and calculated that out-of-pocket expenditures were about 3.6 times higher for persons with five or more CCs (\$6,091) than for individuals without CCs (\$1,702). It was moreover observed that increases in payments over the period 1998 to 2002 were much more pronounced for persons with CCs than for those without: 19.8% for those without CCs and 64.6% for those with five or more CCs, respectively (Schoenberg et al., 2007). This finding gains importance in light of the positive association of CCs and out-of-pocket payment burden, which was observed within two studies (Crystal et al., 2000; Rogowski et al., 1997). Out-of-pocket payment burden is indicated by the ratio of out-of-pocket payments to income and represents the burden of health care-related expenditures a person or household has to bear. Recent empirical findings suggest that elderly women, individuals with less education, small available income, inadequate health insurance, and MCCs are especially at risk of insufficient medical care because of a large out-of-pocket burden (Corrieri et al., 2010). The heavy financial burden could discourage especially the highly multimorbid with little education and income from seeking necessary medical services and products.

Discussion

This systematic literature review identified and summarized 35 studies in which the relationship between MCCs, HCU, and HCCs outcomes was researched for elderly general populations. Almost all included studies asserted a positive association between MCCs and HCU outcomes (physician visits, hospitalizations, use of medications) and HCC outcomes (medication, out of pocket, total health care expenditures). In particular HCU/HCCs significantly increased with each additional CC in almost all studies. Ambiguous findings were presented in three of the included studies (Librero et al., 1999; Ruger & Kim, 2007; Weiner et al., 2008).

In terms of HCU, all the evidence points to more complex in- and outpatient care scenarios (G. Anderson, 2010). Elders with MCCs have an increased need of physician services, which disproportionately affects use of services by specialists (Starfield et al., 2005; Xakellis, 2005). In addition, elderly patients with MCCs see a multitude of physicians (G. Anderson, 2010) and confront them with more problems at each encounter (Beasley et al., 2004). They use significantly more prescription medications and have higher prescription drug expenditures (Moxey et al., 2003; Mueller et al., 1997; Sambamoorthi et al., 2003). Individuals who use multiple medications (polypharmacy) are at increased risk for adverse drug events (Gandhi et al., 2003; Lin, Liao, Cheng, Wang, & Hsueh, 2008; Qato et al., 2008; Simonson & Feinberg, 2005; Zhang et al., 2009; Zhen et al., 2001), while adverse drug events pose a significant cost to health care systems (Akazawa et al., 2010; Burton, Hope, Murray, Hui, & Overhage, 2007). In adjusted analyses, measures of MCCs typically had a much stronger impact on HCU outcomes than predisposing and enabling factors. Studies that controlled for a variety of demographic, socioeconomic, and attitudinal variables observed no change in the effect direction of MCCs on HCU outcomes. However, age and living arrangement (i.e., living alone) were positively associated with hospital use (Ionescu-Ittu et al., 2007; Landi et al., 2004; Librero et al., 1999; Rapoport et al., 2004; Shelton et al., 2000), and female gender and supplementary insurance were associated with an increased use of prescription medications (Fahlman et al., 2006; Hessel et al., 2000; Sambamoorthi et al., 2003), independent of the number of CCs.

Because of its close relationship with HCU, elders with MCCs also accumulated substantial HCCs. Several of the included studies observed a curvilinear (near exponential) relationship, in which expenditures about doubled with each additional CC (Hoffman et al., 1996; Schneider et al., 2009; Wolff et al., 2002). Generally, the more CCs a patient had, the higher the costs of an additional CC. This suggests that costs do not simply add up, but that CCs may interact in some way to make costs rise exponentially. Patients with several concurrent CCs may therefore be at risk of incurring very high additional costs when obtaining an additional CC. Necessarily, the group of individuals with many concurrent CCs consumed a large proportion of the total funds, which led to an unequal distribution of available health care resources (Schneider et al., 2009; Wolff et al., 2002).

While two decades ago the majority of growth in health care spending was attributed to intensive inpatient services, Thorpe and Howard (2006) found that much of the spending growth among Medicare beneficiaries over the past 15 years could be traced to the medical treatment of increasing numbers of persons with MCCs. Treatment of these patients takes place chiefly in outpatient settings and by patients at home with prescription drugs rather than in hospitals (Thorpe, Ogden, & Galactionova, 2010). Yet elderly subjects with MCCs are also high users of hospital care; in particular emergency department services (Shah et al., 2001). They exhibit alarmingly high rates of hospital admissions for adverse events; more than 90 times as high for those with four or more CCs compared with those without CCs (Wolff et al., 2002). This strongly suggests that current ambulatory care and self-care arrangements are insufficient or inappropriate for at least some patients with MCCs.

The findings of this review indicate that multimorbid subjects with high out-of-pocket payment burden (i.e., ratio of out-of-pocket payments to available income) are especially at risk for insufficient care. Out-of-pocket payment burden increases as the number of CCs rises, and it is moreover significantly larger for females, persons with little education and small available income, and those with incomprehensive and/or without supplementary health insurance (Corrieri et al., 2010; Crystal et al., 2000; Cunningham, 2009). High out-of-pocket burden may bring about insufficient ambulatory care by discouraging highly burdened persons to seek necessary medical products/services and by noncompliance of physician recommendations (Paez et al., 2009). Highly burdened individuals may not be able or willing to pay a large part of their available income for necessary medical services (G. Anderson, 2010). While out-of-pocket payments are intended to discourage subjects from unnecessary spending, large expenses of multimorbid individuals with little income may keep them from seeking even the most necessary medical services.

Unfortunately, synthesis of studies was complicated, impeding generalizations and quantifications of additional service use and additional costs attributable to additional CCs. This is because each outcome was only researched within a few studies, yet the precise impact of MCCs will most likely vary for different HCU/HCC outcomes. Furthermore, there was substantial methodological heterogeneity between studies, especially with regard to measures of MCCs. Studies differed in the definition of CCs itself, in the amount and type of CCs considered to construct a measure of MCCs, and in the measures themselves (e.g., disease count, CCI, CDS). The lack of methodological standardization was the result of varying research objectives (in many studies, MCCs were not the primary focus but a secondary explanatory variable), extensiveness of available data and type and number of explanatory variables included in the analyses, and the diversity of institutional and service settings, which may explain part of the observed variance in studies that examined the same outcome (R. Anderson, 2009; Bodenheimer, 2005; Reinhardt, Hussey, & Anderson, 2002).

The prevalence of MCCs has steadily increased in the past years and continues to rise (G. Anderson, 2010). Individuals with MCCs show substantial additional HCU/HCCs. In addition, empirical findings presented in this review suggest that current

ambulatory- and self-care arrangements are inappropriate and possibly even harmful for patients with MCCs. Even physicians themselves report that they have difficulties coordinating care for multimorbid persons and believe that these patients have unmet needs (G. Anderson, 2010). This should not be surprising since evidence-based medical treatment is still largely rooted in care of acute and episodic health problems, with a strong focus on single diseases (Tinetti, Bogardus, & Agostini, 2004). Elderly individuals with MCCs have different clinical and long-term care needs, not well recognized by the current organization, though (Boyd et al., 2005; Mercer, Smith, Wyke, O'Dowd, & Watt, 2009; Starfield, 2007). The literature suggest that these needs are primarily determined by the illness level, that is, the number, particular combination, and severity of diseases and to a much lesser extent by predisposing and enabling factors. Overall, the MCC population is characterized by enormous clinical heterogeneity, and varies by the number of concurrent CCs, severity of illnesses, functional limitations, and the specific clustering of conditions (U.S. Department of Health and Human Services, 2010).

Little is known about the natural clustering of diseases, little more about the prevalence of specific disease combinations. Existing research on disease clusters is not extensive and methodologically heterogeneous (Britt, Harrison, Miller, & Knox, 2008; John, Kerby, & Hennessy, 2003; Marengoni, Winblad, Karp, & Fratiglioni, 2008; van den Akker et al., 1998; Weiss, 2007; Wolff et al., 2002). Because of the multitude of possible disease combinations and large gaps in knowledge to that effect, research has mostly been aimed at identifying general basic needs of persons with MCCs (Bayliss, Edwards, Steiner, & Main, 2008; Boyd et al., 2007; Fried, Bradley, Towle, & Allore, 2002; Norris et al., 2008; Wagner et al., 2001). One broad issue shared by many patients with MCCs is transition between different care settings. Transitions often go along with adverse treatment effects (e.g., through medication errors), unnecessary utilization (e.g., duplication diagnostic tests), and are stressing and very time consuming to patients. Coleman, Parry, Chalmers, and Min (2006) evaluated the Care Transitions Intervention, which was "designed to address potential threats to quality and safety during care transitions by providing patients and their caregivers with tools and support to encourage them to more actively participate in their care transitions." (P. 1823). The intervention was found to be effective and cost-effective, that is, intervention group subjects had significantly lower rates of hospital readmissions and lower mean hospital costs. Although several other care concepts have been introduced and evaluated (Boyd et al., 2007; Boyd et al., 2008; Chalmers & Coleman, 2006; Levine, Phelan, Balderson, & Wagner, 2006; Trice, 2006; Von Korff, Gruman, Schaefer, Curry, & Wagner, 1997), adoption outside research settings has been slow (Norris et al., 2008).

Limitations

The inability to find all available articles meeting the inclusion criteria is the main limitation of this review. Given the diversity of studies on MCCs, as well as definitional ambiguities with respect to (multiple) CCs and HCU, we purposely employed a

search strategy, in which a variety of broad terms were used. Inserting more specific search terms, commonly used in research within each outcome category, might have generated more matches. To test this conjecture, we replaced the broad utilization terms of our initial PubMed search with key words pertinent for each outcome category (e.g., ambulatory care, primary care, specialist care, and outpatient utilization as keywords for outcome category “physician use”). This nonexhaustive *ex post* search produced a total of 509 articles, most of which had been identified by our initial search. The remaining did not include any additional studies that met our inclusion criteria. Although some articles may have been overlooked, especially those without reference to MCCs in the title or abstract, we cautiously conclude that our initial PubMed search produced a fairly unbiased sample of relevant publications. However, the procedure of article selection from the PubMed search may have introduced a bias in the selection of publications, since the majority of studies had been evaluated (by examining title and abstract) solely by the main author (TL). This procedure had to be adopted because of limited resources.

Another limitation is given by the fact that we did not conduct a quality ranking of the included articles. Because of the methodological diversity and variety of outcomes researched, it was difficult to establish reasonable quality criteria applicable to all, or even a subset of the included articles. Future systematic reviews should identify and list criteria to perform a quality ranking of included studies.

Implications for Policy and Research

Current evidence-based health care, reimbursement schemes, and scientific research methods are insufficient and partially inappropriate for (elderly) people with MCCs (G. Anderson, 2010; Boyd et al., 2005; Smith & O’Dowd, 2007). That is because these guidelines are still largely rooted in the treatment of acute and episodic single diseases (Iezzoni, 2010; Norris et al., 2008; Tinetti et al., 2004). This puts (elderly) multimorbid patients at serious risk for deteriorating health over time and leads to additional and possibly unnecessary HCU/HCCs. The societal and economic burden associated with current practice guidelines and care arrangements could therefore be immense.

Doubtlessly, the greatest research priorities should be given to the development of new and novel health care interventions for disease treatment and management and for primary, secondary, and tertiary preventions. Ideally, the etiology and pathogenesis of individual CCs (and disease clusters) would be sufficiently understood to impede disease development and progress via primary preventions. For example, in research on the metabolic syndrome, a combination of cardiometabolic risk determinants (including central obesity, insulin resistance, glucose intolerance, dyslipidemia, nonalcoholic fatty liver disease, and hypertension), recent biochemical and molecular findings emphasize that pharmacological intervention at critical periods during fetal development is a promising area of potential therapeutic benefit (Bruce & Hanson, 2010). In consideration of the fact that many (elderly) people are living with MCCs today, secondary and

tertiary prevention strategies should be designed that slow disease progression and the onset of functional limitations. Specific interventions and (screening) programs may be more cost-effective for patients with several concurrent CCs, because in these patients obtaining another CC is associated with very high incremental costs.

Although a few care models have been introduced and evaluated (Boyd et al., 2007; Chalmers & Coleman, 2006; Levine et al., 2006; Trice, 2006), more comprehensive approaches that cut across diseases, settings (in- and outpatient care), providers, and sites (medical and social services) are needed. Novel needs-based medical health and long-term care models should find a balance between the goals of the patient, caregivers and family, health care providers, and the health care system (Singer et al., 2011). A possible starting point could be to identify and evaluate current best practices and to incorporate them into new and more comprehensive patient-centered models of care (Norris et al., 2008). Naturally, before implemented into the health care system, their effectiveness and cost-effectiveness should be demonstrated (Iezzoni, 2010).

Based on the findings of this review, interventions improving outpatient care of older people with MCCs may prove particularly beneficial, since treatment of these patients takes place primarily in outpatient settings and at home with prescription medications (Thorpe et al., 2010). Especially, elderly individuals with high out-of-pocket burden, that is, those with less education and income, no supplementary health insurance, and/or activity limitations, may profit from special programs. Empirical evidence indicates that these patients regularly experience insufficient care as a result of cost-related nonadherence (Corrieri et al., 2010; Zivin, Ratliff, Heisler, Langa, & Piette, 2010). However, even those patients who comply with physician recommendations are at risk of inappropriate care, since most currently available treatment guidelines are based on the results from randomized controlled trials that typically exclude older patients with MCCs (Gross, Mallory, Heiat, & Krumholz, 2002; Tinetti et al., 2004). Because the generalizability of results from such trials to patient subpopulations that had been excluded is questionable, future research should explore the effectiveness of single-disease guidelines in patients with MCCs (Smith & O'Dowd, 2007).

There are large gaps in knowledge particularly with regard to how the exposition to multiple medications may be influenced by the presence of MCCs. Research has shown that older persons with MCCs are at serious risk of adverse drug events (Lin et al., 2008), which in turn impose substantial costs to the health care system (Burton et al., 2007; Wehling, 2009). The prevalence of adverse events may even be underestimated since the broader physical, cognitive, and psychological effects associated with the use of multiple medications are unknown (Tinetti et al., 2004). Tinetti et al. (2004) proposed research targets regarding polypharmacy in subjects with MCCs, whose results could substantially improve pharmacological treatment toward a patient-centered instead of a disease-oriented prescribing routine. Most important, clinical research needs to decipher how the effects of multiple medications that act simultaneously are altered by genetic, physiological, disease-related, and other factors. Subsequently, randomized controlled trials or appropriately designed observational studies should be conducted to compare multidrug regimens directly with simpler regimens.

All patients expected to use the medications (or combinations) should participate in these studies, and a broad range of physical, psychological, cognitive, and other outcomes should be included and evaluated, allowing integration of patients' preferences and the trade-offs patients are willing to make in terms of the risk of various health outcomes.

The main implication of this review in light of the behavioral model of health care utilization (R. Andersen & Newman, 1973) is that the illness level, as measured by disease counts or indices, is a much more meaningful predictor of additional HCU/HCCs than predisposing and enabling factors. Hence, future studies investigating HCU/HCCs should take MCCs into account, for example, as a confounder. How to best define and measure MCCs in this context is uncertain and needs further investigation. Research comparing the predictive ability of various multimorbidity measures on different health (care) related outcomes has produced inconclusive results (Baser, Palmer, & Stephenson, 2008; Byles, D'Este, Parkinson, O'Connell, & Treloar, 2005; Farley, Harley, & Devine, 2006; Perkins et al., 2004; Tooth, Hockey, Byles, & Dobson, 2008), suggesting that no single measure of multimorbidity will completely capture the differences in the study subjects' underlying health status and that the predictive ability of a specific measure/index depends on the outcome investigated.

To enhance comparability of study results, a standardized methodology with regard to the definition and inclusion of (measures of multiple) CCs in studies investigating particular health and health care-related outcomes would prove beneficial (Iezzoni, 2010). On that account new patient-centric process and outcome measures for persons with MCCs need to be developed, validated, and regularly included into data sets. These measures should reflect the impact of interactions between CCs on outcomes, ought to be sensitive to changes on function and quality of life as prioritized by persons with MCCs themselves, and be useful for clinical and policy-related decision making (Smith & O'Dowd, 2007). Generally, the reorganization and integration of available data sets and the creation of novel ones tailored to the multimorbid population will allow the identification of homogeneous subgroups within the heterogeneous group of people with MCCs and will simplify subsequent research efforts as well as the direction of appropriate care intervention programs to these patients.

There are many more policy implications and areas in which more research would be useful. Because of the urgency and magnitude of the problem of MCCs in the United States, the U.S. Department of Health and Human Services (HHS) issued a Strategic Framework on Multiple Chronic Conditions in December 2010 (<http://www.hhs.gov/ash/initiatives/mcc/index.html>), which aims at catalyzing change within the context of how CCs are addressed in the United States. Four interdependent domains were elucidated that would benefit the individual with MCCs: Strengthening the health care and public systems; empowering the individual to use self-care management; equipping care providers with tools, information, and other interventions; supporting targeted research about individuals with MCCs and effective interventions. For each domain, a variety of interlinked strategies were developed, which can help individual patients with MCCs, their caretakers, health care providers, and health care and public

health systems to identify and implement approaches to optimize health and quality of life. Several HHS agencies are involved in this project, for example, Administration of Aging, Centers for Medicare and Medicaid, Centers for Disease Control and Prevention, Food and Drug Administration, Agency for Healthcare Research and Quality (AHRQ). Previously, the AHRQ together with the Society of General Internal Medicine and the John A. Hartford Foundation had sponsored two meetings in response to the changing care demands of elders with MCCs in the United States, which led to the development of a research agenda. Norris et al. (2008) summarized the consensus on research priorities that need to be addressed to optimize health care for older adults with MCCs. The multitude of research questions in each topic area (e.g., health care systems, pharmacotherapy, prevention, long-term care) show how manifold and extensive the implications of caring for subjects with MCCs for research and policy are (Norris et al., 2008).

It will take great efforts to gain further insight into the various aspects of multimorbidity and to learn how to best organize health and long-term care for rising numbers of people with MCCs. The problem is large and affects not only patients and physicians but society as a whole. We know that the direct costs of care for patients with MCCs are substantial. Additional (intangible) costs because of adverse treatment effects and reduced quality of life and disability have yet to be comprehensively explored. Although some initiatives are currently under way, by and large and in relation to its economic and societal impact, the problem is still partly ignored by science, funding, and especially the broad public. Further research is urgently needed.

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