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Dementia and co-occurring chronic conditions: a systematic literature review to identify what is known and where are the gaps in the evidence?

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Conflict of Interest

None declared.

Author contributions

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L. Steinman coordinated and conducted the article screening and abstraction for the literature review; prepared summary data tables with key data from included studies; coordinated the rating of the evidence by the expert panel; coordinated the update to the literature review; and wrote, reviewed, and edited the manuscript.

L. Bryant conducted the article screening and abstraction for the literature review; participated on the expert panel that advised on the design of the literature review (including the inclusion and exclusion criteria), reviewed the summary tables of key data from included studies, rated the strength and quality of the evidence, prioritized the gaps in the literature; and reviewed and edited the manuscript.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web site.

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Abstract

Objective—The challenges posed by people living with multiple chronic conditions are unique for people with dementia and other significant cognitive impairment. There have been recent calls to action to review the existing literature on co-occurring chronic conditions and dementia in order to better understand the effect of cognitive impairment on disease management, mobility, and mortality.

Methods—This systematic literature review searched PubMed databases through 2011 (updated in 2016) using key constructs of older adults, moderate-to-severe cognitive impairment (both diagnosed and undiagnosed dementia), and chronic conditions. Reviewers assessed papers for eligibility and extracted key data from each included manuscript. An independent expert panel rated the strength and quality of evidence and prioritized gaps for future study.

Results—Four thousand thirty-three articles were identified, of which 147 met criteria for review. We found that moderate-to-severe cognitive impairment increased risks of mortality, was associated with prolonged institutional stays, and decreased function in persons with multiple chronic conditions. There was no relationship between significant cognitive impairment and use of cardiovascular or hypertensive medications for persons with these comorbidities. Prioritized areas for future research include hospitalizations, disease-specific outcomes, diabetes, chronic pain, cardiovascular disease, depression, falls, stroke, and multiple chronic conditions.

Conclusions—This review summarizes that living with significant cognitive impairment or dementia negatively impacts mortality, institutionalization, and functional outcomes for people living with multiple chronic conditions. Our findings suggest that chronic-disease management interventions will need to address co-occurring cognitive impairment.

Keywords

dementia; cognitive impairment; multiple chronic conditions; systematic literature review; public health; aging

Introduction

There are currently 44 million people living with dementia worldwide (5 million in the U.S. (Hebert *et al.*, 2013), with numbers expected to more than triple by 2050 (Prince *et al.*, 2013). Dementia is the largest single contributor to disability and needs for care among older adults out of any chronic disease (Wimo and Prince, 2010), and total monetary costs of dementia represent a similar financial burden as heart disease and cancer (Hurd *et al.*, 2013). Dementia has recently been identified as an important chronic condition (CC) to target for public health interventions (Machlin and Soni, 2009; Goodman *et al.*, 2013).

Current increases in the numbers of older adults and prevalence of CCs as leading causes of death have led to the recognition of the challenges faced by people living with multiple CCs (Goodman *et al.*, 2013). A growing body of evidence indicates a higher burden of CCs in older adults with dementia (Hill *et al.*, 2002; Bynum *et al.*, 2004); recent U.S. Medicare beneficiary data suggest that one in four persons with dementia have co-occurring stroke (24%) and one in three have co-occurring coronary artery disease (33%) (National Academy on an Aging Society, 2000). People in more advanced stages of dementia often have difficulty recognizing and reporting symptoms and/or side effects, adhering to medication, and complying with treatment and follow-up recommendations because of deficits in memory, language, judgment, and reasoning ability (McGuire *et al.*, 2006; Boustani *et al.*, 2007; Arlt *et al.*, 2008; Punthakee *et al.*, 2012). Older adults with dementia also have higher health care expenditures than those without impairment (Hill *et al.*, 2002; Frytak *et al.*, 2008; Kuo *et al.*, 2008; Zhao *et al.*, 2008; Marengoni *et al.*, 2009; Suehs *et al.*, 2013). At the same time, persons with multiple CCs consume a disproportionate number of health care (Thorpe *et al.*, 2010; Centers for Medicare and Medicaid Services (CMMS), 2012), and more care coordination and greater self-management skills are required for those with multiple CCs (Redelmeier *et al.*, 1998; Committee on Quality of HealthCare in America, 2001).

A better understanding is needed to better understand the relationships between dementia and co-occurring CCs from a public health standpoint. *The Healthy Brain Initiative: The Public Health Road Map for State and National Partnerships, 2013–2018* ((Alzheimer's Association (AA) and Centers for Disease Control and Prevention (CDC), 2013) has called for "A review of the literature on co-occurring CCs and dementia, including Alzheimer's disease, to understand the effect of dementia on various outcomes such as depression, disease management, morbidity, and mortality." This systematic literature review examines the effects of moderate-to-severe cognitive impairment (including both diagnosed and undiagnosed dementia) on co-occurring CCs to document what is currently known and what gaps remain in the research literature.

Methods

This review was guided by a multidisciplinary seven-member expert panel of health services and cognitive health researchers from around the U.S. The conceptual framework (Figure 1) was developed based on the National Institutes of Health (NIH) Cognitive and Emotional Health Project, which identified how moderate-to-severe cognitive impairment might influence co-occurring CCs through shared risk factors (such as hypertension) and/or disease

management (such as symptom recognition, reporting, or treatment adherence) (NIH, 2001; Hendrie *et al.*, 2006). Outcomes of interest include disease-specific outcomes (e.g., recurrent strokes for persons with moderate to severe cognitive impairment and a history of stroke), healthcare costs (e.g., outpatient or inpatient care costs), service utilization (e.g., hospitalizations and institutionalizations), mortality, and function.

Review methods were derived from the *Guide to Community Preventive Services* “The Guide” (Briss *et al.*, 2000; Norris *et al.*, 2002) and previously conducted systematic reviews (Frederick *et al.*, 2007; Snowden *et al.*, 2011), and align with PRISMA guidelines (Moher *et al.*, 2009). We searched peer-reviewed literature from inception (1967) through 2011 using PubMed. Subject headings and text words reflected key constructs of older adults, moderate-to-severe cognitive impairment, and CCs (Table 1). References to meta-analyses, review papers, and included articles were also examined to identify possible articles.

Inclusion/exclusion criteria

Study inclusion criteria were: (i) sample size of 100 or more; (ii) participants aged 50 and older, (iii) data on populations both with and without moderate to severe cognitive impairment; (iv) a valid and reliable measure of dementia or moderate-to-severe cognitive impairment; (v) at least one other CC or geriatric syndrome or measure of comorbidity; and (vi) a description of the prevalence or effect of cognitive impairment on co-occurring CCs.

To define cognitive impairment, the article must include a valid and reliable clinical diagnosis of dementia (e.g., the Diagnostic Statistical Manual criteria, fourth edition (DSM-IV) (American Psychiatric Association, 2000); the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria for Alzheimer’s disease (McKhann *et al.*, 1984); or the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia (Erkinjuntti, 1994) or valid and reliable measures of moderate-to-severe cognitive impairment that captured memory and at least one other cognitive domain such as executive function or language. These could include both multidimensional measures (e.g., Mini-Mental Status Examination (MMSE)) (Folstein *et al.*, 1975) or multiple individual measures of cognitive function with at least one focused on memory. The review focused on moderate-to-severe cognitive impairment, including persons with and without official dementia diagnoses. We included the latter group given the high rate of persons without a formal diagnosis; currently, less than half of those in high income countries and less than 10% in low-income and middle-income countries have received a dementia diagnosis (Prince *et al.*, 2013).

Using the definition of CCs as “conditions that last a year or more and require ongoing medical attention and/or limit activities of daily living (ADL’s)” (Warshaw, 2006; US DHHS, 2010) the expert panel created a list of common CCs (Table 2) from The NIH Cognitive and Emotional Health Project (Hendrie *et al.*, 2006), the U.S. DHHS multiple chronic conditions (MCC) Strategic Framework (US DHHS, 2010), and disease categories in PubMed. Geriatric syndromes (e.g., frailty and polypharmacy) were included as well given their large impact on quality of life and disability (Inouye *et al.*, 2007). Geriatric

syndromes are conditions that are common in older adults but do not fit into discrete disease categories (Ahmed *et al.*, 2007; Inouye *et al.*, 2007; Chaudhry *et al.*, 2010). To be included in this review, the article had to include people living with at least one CC condition or geriatric syndrome (Table 2), or evidence of co-morbid conditions via a valid and reliable measure of comorbidity (e.g., Charlson's Comorbidity Index) (Charlson *et al.*, 1987).

Articles included both community-based and institutionalized populations from around the globe. We excluded articles not published in English, that only used an ICD diagnosis for cognitive impairment or dementia, that defined cognitive impairment as delirium, traumatic brain injury, developmental disorders, or MCI, and that reported only reviews, commentaries, or meta-analyses.

Data collection

We used a two-step screening process to assess whether articles met inclusion criteria. We first reviewed titles and abstracts. Articles that could not be included or excluded based on abstracts were retrieved to examine the full text in a second screening phase. Screening of titles and abstracts was conducted jointly by members of the research team (LS, LB, and CC) until 80% agreement was reached; subsequent title and abstract screening was conducted separately. Articles were screened by individual reviewers. A different research team member abstracted data from accepted articles to double check whether an article met eligibility criteria. The reviewers met weekly to discuss title/abstract and article screening. The principal investigator (MS) made final determinations when questions or disagreements between reviewers could not be resolved.

Rating the evidence

We used a standardized form to systematically collect data from each article, including study design, sample size, setting, co-occurring chronic disease, outcome measures, results, and indicators of study quality (e.g., adjustment for possible confounders). Data were compiled in summary tables for evidence rating (see Appendices). We grouped articles into chronic condition-outcome pairings to categorically rate the evidence, and panelists rated the overall evidence within each group; for example, rating the evidence for how cognitive impairment impacted mortality for persons with multiple CCs, stroke, or depression.

Expert panel members rated both the quality and strength of evidence across articles in each chronic condition-outcome pairing using a qualitative approach from previous systematic literature reviews (Frederick *et al.*, 2007; Snowden *et al.*, 2011). *Indicators of quality* included sample size and generalizability, appropriate measurement of cognitive impairment and of CCs, use of multivariable analysis, and controlling specifically for age, gender, and education. For quality rating, panel members independently rated each condition-outcome pairing as “good”, “fair”, or “limited”.

Indicators of strength of evidence included the study quality and design, the number of studies in the chronic condition-outcome pairing, consistency across studies, and statistical findings. For strength of evidence ratings, the panel members independently rated each condition-outcome pairing as “strong”, “sufficient”, or “insufficient” (recording whether the

insufficient rating was due to an insufficient number of at least fair quality studies or a sufficient number of available studies but inconclusive data).

Final determination of quality and strength of evidence was based on 80% agreement among panel members (i.e., agreement among six out of the seven panelists). The panel met to discuss areas of disagreement, and panel members were allowed to change their votes after the discussion; however, to reduce persuasion bias, they were not required to reach consensus.

Identifying and prioritizing gaps where evidence was rated “insufficient”

The panel also identified and prioritized the areas for which there was insufficient evidence. We used Q-sort ranking (Brown, 1996), a method for rank-ordering items, to prioritize the gaps in which panelists assigned a rank (“5”=highest priority to “1”=least priority) to each of the 42 outcomes and CCs/geriatric syndromes with insufficient evidence in order of priority for further research (“5”=highest priority to “1”=least priority). Using the Q-sort method, informants were given a limited, normally distributed allotment of 1s, 2s, 3s, 4s, and 5s to create a normal distribution of rankings.

Results

Four thousand thirty-three articles were identified in the literature review: 4,005 in the PubMed search and 28 from reference lists of review articles or meta-analyses (Figure 2). Forty-eight articles met inclusion criteria after Level 1 screening of abstracts, and 99 articles met inclusion criteria after Level 2 screening of abstracts, yielding 147 included articles. Articles were excluded primarily due to small sample size or the omission of both persons with and without dementia/cognitive impairment.

The 147 included articles were grouped into 62 chronic condition-outcome pairings, or categories, for rating the evidence. Nine percent ($N=7$) of the categories were rated as having sufficient evidence (Table 3); all of which were rated at least fair quality. Sufficient evidence was found for the impact of moderate-to-severe cognitive impairment on mortality, length of stay in institutional settings, function, and cardiovascular medication use, for persons with certain co-occurring CCs. The other pairings were deemed to have insufficient evidence, due to lack of studies (two or fewer) or inconclusive evidence (mixed results within or across studies) (Table 4).

Mortality

Twenty-nine studies (Kukull *et al.*, 1994; Arfken *et al.*, 1995; Bruce *et al.*, 1995; Gale *et al.*, 1996; Agüero-Torres *et al.*, 1999; Foley *et al.*, 1999; Kammoun *et al.*, 2000; Helmer *et al.*, 2001; Stump *et al.*, 2001; Freels *et al.*, 2002; Ganguli *et al.*, 2002; Feil *et al.*, 2003; Nguyen *et al.*, 2003; Tschanz *et al.*, 2004; Cacciatore *et al.*, 2005; Fitzpatrick *et al.*, 2005; Magaziner *et al.*, 2005; Bursi *et al.*, 2006; Guhne *et al.*, 2006; Llinàs-Regla *et al.*, 2007; Lyketsos *et al.*, 2007; Meerman *et al.*, 2008; Rothman *et al.*, 2008; Zekry *et al.*, 2009; Lavretsky *et al.*, 2010; Wang *et al.*, 2010a; Gombojav *et al.*, 2011; Millán-Calenti *et al.*, 2011; Nikolova *et al.*, 2011) compared mortality rates for persons with multiple CCs and with and without moderate-to-severe cognitive impairment or dementia. Seventeen used community-based

samples and 12 used clinic-based samples. Most studies had a sample size greater than 500 (79%) with 52,644 subjects across all studies. A majority of studies used a multivariable analysis (90%) and almost half of these (46%) adjusted for age, gender, and education (the remaining studies adjusted for just one or two of these demographic covariates).

Mortality was measured in terms of mortality rates, risk for mortality (e.g., hazard ratios (HRs)), or survival rates. Percent mortality ranged from 40.2% to 82% for persons with moderate-to-severe cognitive impairment and 16.0% to 37.7% for persons without significant cognitive impairment (Stump *et al.*, 2001; Nguyen *et al.*, 2003; Tschanz *et al.*, 2004; Guhne *et al.*, 2006; Llinàs-Regla *et al.*, 2007; Lavretsky *et al.*, 2010; Wang *et al.*, 2010a). Six studies (Bruce *et al.*, 1995; Stump *et al.*, 2001; Fitzpatrick *et al.*, 2005; Llinàs-Regla *et al.*, 2007; Meerman *et al.*, 2008; Lavretsky *et al.*, 2010) reported unadjusted relative risks (RR) for mortality (95% confidence interval (CI)), ranging from 2.3 (1.7–3.2) (Llinàs-Regla *et al.*, 2007) to 7.4 (4.9–11.4) (Lavretsky *et al.*, 2010).

Fourteen studies (Helmer *et al.*, 2001; Stump *et al.*, 2001; Freels *et al.*, 2002; Feil *et al.*, 2003; Nguyen *et al.*, 2003; Tschanz *et al.*, 2004; Fitzpatrick *et al.*, 2005; Bursi *et al.*, 2006; Guhne *et al.*, 2006; Llinàs-Regla *et al.*, 2007; Meerman *et al.*, 2008; Rothman *et al.*, 2008; Lavretsky *et al.*, 2010; Gombojav *et al.*, 2011) reported the adjusted HR for significant cognitive impairment on risk of mortality (95% CI) ranging from 1.5 (1.1–2.1) (Rothman *et al.*, 2008) to 2.99 (2.53–3.53) (Tschanz *et al.*, 2004); covariates may have included demographics, CCs, and six other frailty criteria (Rothman *et al.*, 2008). The percent attributable risk (PAR%) of death related to dementia diagnosis ranged from 11.8% (Guhne *et al.*, 2006; Llinàs-Regla *et al.*, 2007) to 16.6% (Tschanz *et al.*, 2004). Tschanz (Tschanz *et al.*, 2004) and Feil (Feil *et al.*, 2003) compared mortality RR and PAR for dementia versus other CCs: In addition, two studies (Feil *et al.*, 2003; Tschanz *et al.*, 2004) found that dementia or moderate-to-severe cognitive impairment had a greater RR of mortality than other CCs (e.g., an RR two to three times higher) and higher mortality PAR% than other CCs.

In addition, persons with moderate-to-severe cognitive impairment had shorter average survival times, ranging from 3.0 to 7.1 years compared with 4.0 to 11.0 years for persons without cognitive impairment (Agüero-Torres *et al.*, 1999; Fitzpatrick *et al.*, 2005; Guhne *et al.*, 2006; Lavretsky *et al.*, 2010; Wang *et al.*, 2010a). Persons with moderate-to-severe cognitive impairment also had lower survival rates: the adjusted 5-year survival for persons with moderate-to-severe cognitive impairment was 16.1% versus 28.5% for normal cognition (Wang *et al.*, 2010a); unadjusted survival rates were 22% versus 39% (Bursi *et al.*, 2006) and lower (poorer) scores on the MMSE decreased likelihood of survival (Bruce *et al.*, 1995).

Several studies reported non-significant or negative relationships. For example, in 2005, Magaziner *et al.*, (2005) reported an unadjusted RR for mortality of 0.61 (0.53–0.71) and adjusted RR for mortality of 0.63 (0.51–0.77) for persons with dementia and multiple CCs. This study included persons living in nursing homes ($N=2,153$, mean age > 80), almost half of which were diagnosed with dementia using DSM criteria. In this study, the group without dementia included people who were difficult to diagnose.

The expert panel also found sufficient evidence that moderate-to-severe cognitive impairment increases mortality in persons with Parkinson's disease (Ebmeier *et al.*, 1990; Marder *et al.*, 1991; Mitchell and Rockwood, 2000; Levy *et al.*, 2002; Parashos *et al.*, 2002; Buter *et al.*, 2008; Lo *et al.*, 2009; Hobson *et al.*, 2010, $N = 4,513$) and stroke (Tatemichi *et al.*, 1994; Desmond *et al.*, 1998; Desmond *et al.*, 2002; Liebetrau *et al.*, 2003; Melkas *et al.*, 2009; Oksala *et al.*, 2009, $N = 2,302$). These were the only specific co-occurring CCs for which sufficient evidence was found to examine mortality outcomes. Other articles included people with dementia or moderate-to-severe cognitive impairment from various etiologies (stroke, Parkinson's disease, and other).

Service utilization

Three studies (Smith *et al.*, 2000; Magaziner *et al.*, 2005; Rothman *et al.*, 2008, ($N = 3,423$) examined length of stay in an institution for persons with multiple CCs (Inouye *et al.*, 2007). In 2008, Rothman *et al.*, (2008) reported an adjusted HR for long-term nursing home stay of 3.7 (95% CI) 2.5–5.4) for persons with cognitive impairment (MMSE < 24) versus those without impairment. In 2000, Smith *et al.*, (2000) found an unadjusted median length of stay in nursing homes for those with dementia (diagnosed using DSM-III-R criteria) of 946 days compared with those without dementia at 579 days. Lastly, Magaziner and colleagues reported a decreased likelihood of being discharged to home (adjusted RR of 0.23 (95% CI 0.17–0.31)) for those with dementia (DSM-III-R criteria) compared with those without.

Function

Nineteen studies (Agüero-Torres *et al.*, 1998; Zhu *et al.*, 1998; Agüero-Torres *et al.*, 2002; Covinsky *et al.*, 2003; Lyketsos *et al.*, 2005; Magaziner *et al.*, 2005; Lyketsos *et al.*, 2007; Cankurtaran *et al.*, 2008; Rothman *et al.*, 2008; Zekry *et al.*, 2008; Huang *et al.*, 2009; Sousa *et al.*, 2009; Stewart *et al.*, 2009; Zekry *et al.*, 2009; Feng *et al.*, 2010; Wang *et al.*, 2010b; Gombojav *et al.*, 2011; Millán-Calenti *et al.*, 2011; Nikolova *et al.*, 2011) ($N = 37,466$) examined the impact of significant cognitive impairment and co-occurring multiple comorbidities on function. Function was typically defined as basic activities of daily living (ADL's) or instrumental ADL's (IADLs). Nine studies included samples with a dementia diagnosis and seven included institutionalized persons. Half of the studies used multivariable analysis, with half of these adjusting for age, sex, and education. Persons with dementia and multiple CCs had significantly more IADL and ADL impairments than those without significant cognitive impairment.

Medication use

Seven studies (Freels *et al.*, 2002; Lopponen *et al.*, 2005; Bursi *et al.*, 2006; Rastas *et al.*, 2007; Andersson *et al.*, 2008; Barzilay *et al.*, 2008; Cankurtaran *et al.*, 2008) ($N = 5,245$) examined the degree to which dementia affected cardiovascular medication use (other than that for hypertension) in persons with co-occurring cardiovascular disease (CVD). Only one (Barzilay *et al.*, 2008) found statistically significant differences between people with dementia (VaD, AD, and not otherwise specified) and use of CVD medications such as beta-blockers, ACE inhibitors, or aspirin.

In addition, the expert panel agreed on sufficient evidence that moderate-to-severe cognitive impairment had no impact on hypertension medication use in people with co-occurring hypertension (Freels *et al.*, 2002; Hanon *et al.*, 2006; Barzilay *et al.*, 2008; Vinyoles *et al.*, 2008; Huang *et al.*, 2009; Stewart *et al.*, 2009; Gombojav *et al.*, 2011) with five of the seven studies (Freels *et al.*, 2002; Hanon *et al.*, 2006; Huang *et al.*, 2009; Stewart *et al.*, 2009; Gombojav *et al.*, 2011) ($N = 8,236$) reporting no statistically significant differences for persons with and without moderate-to-severe cognitive impairment.

Prioritizing the gaps in the evidence

The expert panel identified 55 pairings with insufficient or no evidence (Table 4). These included 18 outcomes (e.g., cost and function) and 10 CCs or geriatric syndromes (e.g., cancer and chronic obstructive pulmonary disease (COPD)) with insufficient evidence, and no evidence was found for the impact of significant cognitive impairment on 14 additional conditions/syndromes: asthma, arthritis, bone diseases, chronic kidney disease, chronic pain, dental problems, other chronic mental illness, neurological conditions, sleep disorders, substance abuse, risk factors if another CC was present (e.g., obesity and smoking), frailty, functional impairments, and urinary incontinence.

After the expert panel prioritized these gaps, the following were identified as highest priority for future research: service utilization-hospitalizations and disease-specific outcomes, and diabetes, chronic pain, CVD, depression, falls or fractures, stroke, and multiple CCs (the presence of moderate-to-severe cognitive impairment and more than two other CCs).

Updating the review

We were recently asked to update the literature review to include more recent articles published between mid-2011 and June of 2016. Twenty-two additional articles met our criteria and two new chronic condition-outcome pairings had sufficient evidence. The first looked at the impact of cognitive impairment and co-occurring CVD on mortality. Two studies (O'Donnell *et al.*, 2012 and Huijts *et al.*, 2013) found an over 50% increase in mortality risk for people living with moderate-to-severe cognitive impairment (adjusted HRs 1.53 (95% CI 1.02–2.30) to 1.68 (1.49–1.90)). The second new outcome was disease-specific; namely that living with dementia and diabetes increased the risk for severe hypoglycemia compared with persons living with diabetes and without dementia (Abbatecola *et al.*, 2015; Prinz *et al.*, 2015). Fourteen new articles (Chang *et al.*, 2012; Chen *et al.*, 2014; Huijts *et al.*, 2013; Llibre *et al.*, 2014; Katsoulis *et al.*, 2014; Lee *et al.*, 2015; Mignardot *et al.*, 2014; Murao *et al.*, 2014; O'Donnell *et al.*, 2012; Park *et al.*, 2016; Sanyal *et al.*, 2014; Warchol-Celinska *et al.*, 2015; van Asch *et al.*, 2013) fell into existing chronic condition-outcome pairings and did not change the quality or strength of the evidence, and four articles (Hawkins *et al.*, 2012; Jacobs *et al.*, 2012; Hajduk *et al.*, 2013; Provencher *et al.*, 2015) were found in separate areas where there was previously no evidence.

Discussion

This review found sufficient evidence that moderate-to-severe cognitive impairment (including both diagnosed and undiagnosed dementia) in the presence of co-occurring CCs

had a significant effect on increasing mortality, increasing length of stay in institutional settings, and decreasing function. In addition, there was sufficient evidence that moderate-to-severe cognitive impairment was not associated with cardiovascular or hypertension medication use. For all other outcome-chronic condition pairings, the panel found insufficient evidence or no evidence.

Previous studies in older adults have identified multiple risk factors for co-occurring cognitive decline and other CCs such as CVD (NIH, 2001). Comparisons between older adults with significant cognitive impairment and those without suggest that the former tend to be sicker and more likely to suffer from multiple CCs and greater functional impairment (Hill *et al.*, 2002; Bynum *et al.*, 2004; Frytak *et al.*, 2008; Kuo *et al.*, 2008; Zhao *et al.*, 2008; Marengoni *et al.*, 2009). The current review partially confirmed these earlier findings (specifically for risks of mortality, institutional length of stay, and decreased function) and further affirmed that significant cognitive impairment itself may have an impact on the subsequent development of other CCs and syndromes in older adults. Most of the sufficient evidence found in this review was for moderate-to-severe cognitive impairment and multiple CCs; there was insufficient evidence to support a relationship between significant cognitive impairment and course of specific CCs (e.g., depression).

Moderate-to-severe cognitive impairment (including both diagnosed and undiagnosed dementia) is associated with clinical deterioration. Significant cognitive impairment also makes it more likely that individuals will not recognize or respond appropriately to early symptoms of CCs, geriatric syndromes, and decreasing function. Greater severity of illness at diagnosis and the inability to maintain medication regimens and management of side effects may lead, at least in part, to the increased costs of health care for older adults with significant cognitive impairment compared with those without (Guterman *et al.*, 1999). Policies and procedures that improve surveillance among those with significant cognitive impairment may encourage timely diagnosis and treatment that with sufficient support can reduce severity and promote improved health. In addition, the assessment of cognitive abilities in those with multiple CCs would potentially assist health care providers in improved disease management. Although it is perhaps reassuring that difficulty managing medications does not appear to affect access to them, affected individuals may need additional supports to maintain control over their conditions.

Reviewing existing evidence and identifying gaps is the first step toward assisting clinicians, investigators, and policy makers at international, national, and local levels to understand the effects of significant cognitive impairment on CCs, and then design and deliver relevant evidence-based programs for disease management. Several national entities such as the NIH's *Cognitive and Emotional Health Project* (NIH, 2001; Hendrie *et al.*, 2006) and the CDC's *Healthy Brain Initiative* (CDC and the AA, 2007; AA and CDC, 2013) emphasize the identification and use of existing datasets to answer these important research gaps. Our research team and advisory committee created an inventory of existing major datasets that include measures of both cognitive impairment and CCs (Bell *et al.*, 2015); these datasets can be used to conduct secondary data analyses to address research gaps identified by our review team (e.g., Snowden *et al.*, 2015). Findings from this review can also inform *Healthy People 2020* objectives' (US DHHS ODPHP, 2010) to increase the proportion of older adults

with one or more CCs who report confidence in managing their conditions, and to decrease the numbers of preventable hospitalizations (many for co-occurring CCs) for people living with Alzheimer's disease and other dementias.

The strengths of this systematic review are its focus on the effects of significant cognitive impairment on CCs, the use of a formal process derived from the *Guide to Community Preventive Services* (Briss *et al.*, 2000; Norris *et al.*, 2002), an experienced study team (Frederick *et al.*, 2007; Snowden *et al.*, 2011), and input from a multidisciplinary expert panel to identify relevant studies, assess quality, and summarize the evidence. There is far more literature to date that looks at how CCs impact moderate-to-severe cognitive impairment. In practice, it is important to consider both, or bidirectionality (Mercer *et al.*, 2012)-that physical conditions can affect mental conditions, and vice versa. Concordant conditions, such as stroke and cognitive impairment, are those in which management of one of these conditions is likely to impact management for the other CC.

This review has several limitations. While we aligned with most PRISMA recommended guidelines (Moher *et al.*, 2009), we did not assess for risk of bias within and across studies. We did provide our expert panel with details on study design, sample, measures, analysis, and outcomes in order to inform their ratings of the strength and quality of evidence. Second, we reviewed only one database (PubMed) due to limitations on time and resources to conduct the review. This database was chosen given our focus on the public health implications of addressing both cognitive impairment and co-occurring CCs together. In addition, we recognize the complexity of including function both as a key outcome of interest and a geriatric syndrome, in light of functional impairment being part of the criteria for a dementia diagnosis. While complicated, function (and functional impairments) was viewed as important outcomes of interest given their significant impact on chronic disease management which in turn impacts other outcomes such as mortality and service utilization. Similarly, because Parkinson's disease and stroke are established causes of dementia with their own significant mortality risk, our finding of increased mortality in these conditions may be expected. Finally, our exclusion criteria, in particular the exclusion of MCI as a potential contributor to other CCs, may have eliminated potentially informative studies, but the expert panel found the lack of an established definition or screening criteria too vague for its evaluation as a contributing factor.

Key findings from this review include the significant impact of cognitive impairment on mortality, service utilization, and functional outcomes for people living with co-occurring CCs, and that there was not strong evidence to support the association between moderate-to-severe cognitive impairment and medication use for co-occurring CCs. In addition, this review identified and prioritized gaps in the evidence to help guide future research including secondary data analyses. The results of this systematic review and the identification of gaps in the literature will strengthen the ability of clinicians, researchers, and policy makers to respond to the growing burden of CCs in older adults attributable to increasing rates of cognitive impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Living with significant cognitive impairment and co-occurring CCs is an important issue for public health in aging society.
- Little is known about how dementia and other significant cognitive impairment impacts morbidity, mortality, and other outcomes for people with multiple CCs.
- This systematic review found sufficient evidence that moderate to severe cognitive impairment (including dementia) increased risks of mortality, was associated with prolonged institutional stays, and decreased function in persons with multiple CCs. There was no relationship between significant cognitive impairment and use of cardiovascular or hypertensive medications for persons with these comorbidities.
- Further study is needed to better understand how dementia and other significant cognitive impairment influences hospitalizations, disease-specific outcomes, diabetes, chronic pain, CVD, depression, falls, and stroke for people living with multiple CCs.

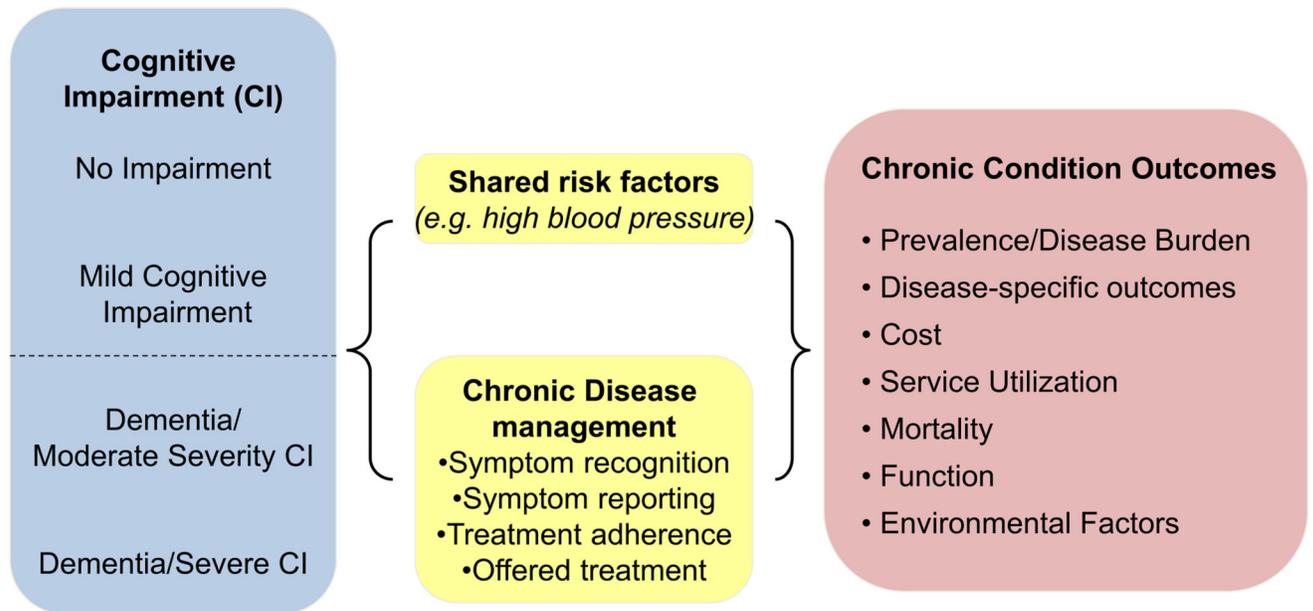


Figure 1. Conceptual Framework. [Colour figure can be viewed at wileyonlinelibrary.com]

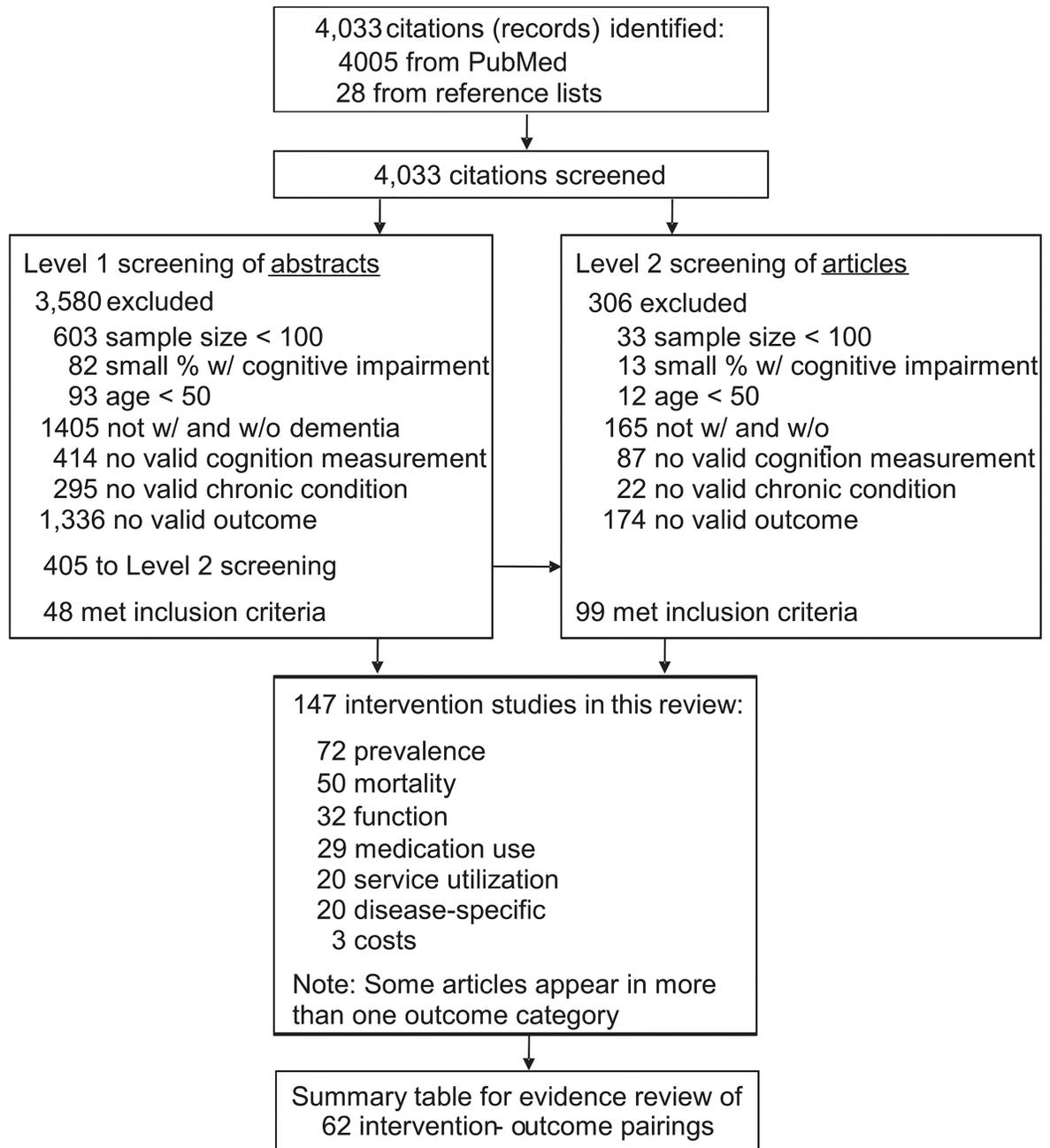


Figure 2.
Literature search flow chart.

Table 1

PubMed search terms

Construct	Search terms	
Older adults	Aged[mh]	
	Aged, 80 and over[mh]	
	Frail Elderly[mh]	
	elderly[tiab]	
	older adults[tiab]	
Cognitive impairment	seniors[tiab]	
	Dementia[mh]	
	“cognitive impairment”[tiab]	
	MCI[tiab]	
Chronic conditions and geriatric syndromes	CIND[tiab]	
	Accidental falls[Majr]	Depression[Majr]
	Hyperlipidemias[Majr]	Schizophrenia[Majr]
	Pulmonary disease, chronic obstructive[Majr]	Multiple sclerosis[Majr]
	Emphysema[Majr]	Bone diseases[Majr]
	Diabetes mellitus[Majr]	Chronic pain[tiab]
	Cardiovascular diseases[Majr]	Osteoarthritis[Majr]
	cardiovascular disease[tiab]	Frailty[tiab]
	Intracranial arterial Diseases[Majr]	Epilepsy[Majr]
	Carotid artery diseases[Majr]	Brain ischemia[Majr]
	Hypertension[tiab]	Stroke[Majr]
	Heart disease[tiab]	Sleep disorders[Majr]
	Neoplasms[Majr]	Oral health[Majr]
	Parkinsonian disorders[Majr]	Urinary incontinence[Majr]
	Asthma[Majr]	Osteoporosis[Majr]
	Substance-related disorders[Majr]	Comorbidity[Majr]
	Stress disorders, Post-traumatic[Majr]	co-morbidity[tiab]
	Bipolar disorder[tiab]	comorbidity[tiab]
	Manic depressive disorder[tiab]	Chronic disease[Majr]
	Study design	Cross-sectional studies[Mesh] OR cross-sectional stud*[tiab] OR cohort studies[Mesh] OR cohort stud*[tiab] OR case-control studies[Mesh] OR case-control stud*[tiab] OR longitudinal stud*[tiab] OR longitudinal stud*[tiab] OR prospective stud*[tiab] OR retrospective stud*[tiab]

[Mesh], Medical subject headings; [mh] is used to search a MeSH heading; [majr] is used to search a MeSH heading that is a major topic of an article; [tiab], Title or abstract.

^aNote: Limits of English-only studies were also set.

Table 2

Chronic conditions and geriatric syndromes

Chronic conditions	Geriatric syndromes
Asthma	Falls, fractures, and other injuries
Arthritis	Frailty
Bone diseases (e.g., osteoporosis)	Functional impairments
Brain diseases (e.g., Parkinson's)	Polypharmacy/High-risk medications
Cancer	Urinary incontinence
Cardiovascular diseases (e.g., CAD, hypertension, and hyperlipidemias)	
Cerebrovascular diseases (e.g., stroke)	
Chronic kidney disease	
Chronic pain	
Dental problems	
Depression and other chronic mental illness (PTSD, schizophrenia, and bipolar)	
Diabetes	
Emphysema/COPD	
Neurological conditions (epilepsy and multiple sclerosis)	
Sleep disorders	
Substance abuse	
Risk factors if a chronic conditions is present (e.g., obesity, smoking, and gait)	

Table 3

Summary of evidence rating for chronic condition-outcome pairings with sufficient evidence

Outcome/ Chronic condition	# of Studies	Sample Size	Author, Year ^d		Quality Rating ^b	Effectiveness Rating ^b
			Community sample	Clinical sample		
Mortality MCC	19	50,218	Bruce <i>et al.</i> , 1995 Cacciatore <i>et al.</i> , 2005 Feil <i>et al.</i> , 2003 Fitzpatrick <i>et al.</i> , 2005 Ganguli <i>et al.</i> , 2002 Gombojav <i>et al.</i> , 2011 Guhne <i>et al.</i> , 2006 Helmer <i>et al.</i> , 2001 Kukull <i>et al.</i> , 1994 Nikolova <i>et al.</i> , 2011 Linnäs-Regla <i>et al.</i> , 2007 Lyketsos <i>et al.</i> , 2007 Millán-Calenti <i>et al.</i> , 2011 Nguyen <i>et al.</i> , 2003 Rothman <i>et al.</i> , 2008 Tschanz <i>et al.</i> , 2004 Wang <i>et al.</i> , 2010a	Agüero-Torres <i>et al.</i> , 1999 Arfken <i>et al.</i> , 1995 Bursi <i>et al.</i> , 2006 Foley <i>et al.</i> , 1999 Freels <i>et al.</i> , 2002 Gale <i>et al.</i> , 1996 Kammoun <i>et al.</i> , 2000 Lavretsky <i>et al.</i> , 2010 Magaziner <i>et al.</i> , 2005 Meerman <i>et al.</i> , 2008 Stump <i>et al.</i> , 2001 Zekry <i>et al.</i> , 2009	Fair	Sufficient
Mortality Parkinson's disease	8	4,513	Buter <i>et al.</i> , 2008 Ebmeier <i>et al.</i> , 1990 Hobson <i>et al.</i> , 2010 Levy <i>et al.</i> , 2002 Lo <i>et al.</i> , 2009 Marder <i>et al.</i> , 1991 Mitchell and Rockwood, 2000 Parashos <i>et al.</i> , 2002	None	Fair	Sufficient
Mortality Stroke	6	2,302	Desmond <i>et al.</i> , 1998 Desmond <i>et al.</i> , 2002	Liebetrau <i>et al.</i> , 2003 Melkas <i>et al.</i> , 2009 Oksala <i>et al.</i> , 2009 Tatemichi <i>et al.</i> , 1994	Fair	Sufficient
Service utilization: length of stay institutions/NH MCC	3	3,423		Magaziner <i>et al.</i> , 2005 Rothman <i>et al.</i> , 2008 Smith <i>et al.</i> , 2000	Fair	Sufficient
Function MCC	19	37,446	Cankurtaran <i>et al.</i> , 2008 Covinsky <i>et al.</i> , 2003 Gombojav <i>et al.</i> , 2011 Lyketsos <i>et al.</i> , 2005 Millán-Calenti <i>et al.</i> , 2011 Nikolova <i>et al.</i> , 2011 Rothman <i>et al.</i> , 2008 Sousa <i>et al.</i> , 2009 Stewart <i>et al.</i> , 2009 Wang <i>et al.</i> , 2010b	Agüero-Torres <i>et al.</i> , 1998 Agüero-Torres <i>et al.</i> , 2002 Enksson <i>et al.</i> , 2008 Feng <i>et al.</i> , 2010 Lyketsos <i>et al.</i> , 2007 Magaziner <i>et al.</i> , 2005 Zekry <i>et al.</i> , 2008 Zekry <i>et al.</i> , 2009 Zhu <i>et al.</i> , 1998	Fair	Strong
CVD medications ^c CVD	7	7,196	Andersson <i>et al.</i> , 2008 Barzilay <i>et al.</i> , 2008 Bursi <i>et al.</i> , 2006 Cankurtaran <i>et al.</i> , 2008 Rastas <i>et al.</i> , 2007	Freels <i>et al.</i> , 2002 Lopponen <i>et al.</i> , 2005	Fair	Sufficient
anti-hypertensive medications Hypertension	7	10,552	Barzilay <i>et al.</i> , 2008 Gombojav <i>et al.</i> , 2011 Huang <i>et al.</i> , 2009 Stewart <i>et al.</i> , 2009	Freels <i>et al.</i> , 2002 Hanon <i>et al.</i> , 2006 Vinyoles <i>et al.</i> , 2008	Fair	Sufficient

CVD, cardiovascular disease; MCC, multiple chronic conditions; NH, nursing home.

^aSome of the 147 studies are listed in more than one chronic condition-outcome pairing. Some articles include both community and clinical populations.

^bQuality ratings included Good, Fair, and Limited. Effectiveness ratings included Strong, Sufficient, and Insufficient. Seven expert panelists rated quality and effectiveness individually and then met to reach consensus.

^cCVD medications includes those besides anti-hypertensives.

Table 4

Summary of evidence rating for chronic condition-outcome pairings with insufficient evidence due to not enough studies. Categories with insufficient evidence due to mixed or inconclusive findings are listed in *italics*)

Outcome	Chronic condition	# of studies	Sample size	Author, Year
Mortality				
Mortality	Depression	4	3,283	Arfken <i>et al.</i> , 1995; Lavretsky <i>et al.</i> , 2010; Millán-Calenti <i>et al.</i> , 2011; St. John and Montgomery, 2009
Mortality	Cancer	2	3,278	Robb <i>et al.</i> , 2010; Roe <i>et al.</i> , 2010
Mortality	Atrial Fib	1	2,837	Miyasaka <i>et al.</i> , 2007
Mortality	CHF	1	142	Haydar <i>et al.</i> , 2004
Mortality	COPD	1	134	Antonelli-Incalzi <i>et al.</i> , 2006
Mortality	Hip fracture	1	558	Cree <i>et al.</i> , 2000
Mortality	Hypertension	1	2,496	Gombojav <i>et al.</i> , 2011
Service utilizations/institutionalizations				
Hospitalizations	MCC	3	13,334	Feil <i>et al.</i> , 2003; McCormick <i>et al.</i> , 2001; Welmerink <i>et al.</i> , 2010
Hospitalizations	Cancer	1	3,020	Roe <i>et al.</i> , 2010
Hospitalizations	CHD	2	7,188	Bursi <i>et al.</i> , 2006; Welmerink <i>et al.</i> , 2010
Hospitalizations	Diabetes	1	789	Sinclair <i>et al.</i> , 2000
Length of stay, hospital	MCC	2	1,343	Lang <i>et al.</i> , 2006; Zekry <i>et al.</i> , 2009
Other medical care	MCC	2	779	McCormick <i>et al.</i> , 1994; McCormick <i>et al.</i> , 2001
Other medical care	Cancer	1	258	Robb <i>et al.</i> , 2010
Other medical care	Diabetes	2	1,188	Quinn <i>et al.</i> , 2009; Sinclair <i>et al.</i> , 2000
Other medical care	Myocardial infarction	1	1,832	Bursi <i>et al.</i> , 2006
Institutionalization/NH	MCC	4	2,361	Guhne <i>et al.</i> , 2006; Meerman <i>et al.</i> , 2008; Smith <i>et al.</i> , 2000; Zekry <i>et al.</i> , 2009
Institutionalization/NH	Diabetes	1	789	Sinclair <i>et al.</i> , 2000
Institutionalization/NH	Hip fracture	1	558	Cree <i>et al.</i> , 2000
Institutionalization/NH	Parkinson's disease	1	178	Parashos <i>et al.</i> , 2002
Length of stay, institution/NH	Diabetes	1	399	Quinn <i>et al.</i> , 2009
Amount of care at institutions	MCC	1	198	Lyketsos <i>et al.</i> , 2007
Home care	MCC	1	435	Zekry <i>et al.</i> , 2009
Home care	Diabetes	1	789	Sinclair <i>et al.</i> , 2000
Caregiver burden	MCC	1	198	Lyketsos <i>et al.</i> , 2007
Medicare qualified stay	Diabetes	1	399	Quinn <i>et al.</i> , 2009
Hospice	CHF	1	142	Haydar <i>et al.</i> , 2004
Advanced medical planning	CHF	1	142	Haydar <i>et al.</i> , 2004
Use of social services	Diabetes	1	789	Sinclair <i>et al.</i> , 2000
Costs				
Cost	MCC	2	1,101	McCormick <i>et al.</i> , 2001; Scuvée-Moreau <i>et al.</i> , 2002
Cost	Diabetes	1	399	Quinn <i>et al.</i> , 2009
Medications				

Outcome	Chronic condition	# of studies	Sample size	Author, Year
Medications-polypharmacy	MCC	7	8,527	Doruk <i>et al.</i> , 2010; Lopponen <i>et al.</i> , 2005; Lyketsos <i>et al.</i> , 2005; Lyketsos <i>et al.</i> , 2007; Millán-Calenti <i>et al.</i> , 2011; Wang <i>et al.</i> , 2010b; Zekry <i>et al.</i> , 2008
Medications-polypharmacy	Falls	3	411	Eriksson <i>et al.</i> , 2008; Morris <i>et al.</i> , 1987; Van Iersel <i>et al.</i> , 2006
High-risk medications	Falls	4	590	Allan <i>et al.</i> , 2009; Eriksson <i>et al.</i> , 2008; Morris <i>et al.</i> , 1987; Van Iersel <i>et al.</i> , 2006
Antidepressants	Depression	2	3,228	Blazer <i>et al.</i> , 2005; Janzing <i>et al.</i> , 2000
Diabetes medications	Diabetes	2	1,886	Okura <i>et al.</i> , 2009; Sinclair <i>et al.</i> , 2000
Osteoporosis medications	Hip and other fractures	1	15,718	Vik <i>et al.</i> , 2007
Anti Parkinson's medications	Parkinson's disease	1	130	Aarsland <i>et al.</i> , 2001a
Part D Medicare coverage	MCC	1	13,160	Zivin <i>et al.</i> , 2009
Disease-specific				
Disease-specific	MCC	6	7,940	Eriksson <i>et al.</i> , 2008; García-Lara <i>et al.</i> , 2010; Magaziner <i>et al.</i> , 2005; Rothman <i>et al.</i> , 2008; Sambrook <i>et al.</i> , 2007; Wang <i>et al.</i> , 2010c
Disease-specific	Cancer	1	258	Robb <i>et al.</i> , 2010
Disease-specific	Falls	4	1,723	Chen <i>et al.</i> , 2005; Chen <i>et al.</i> , 2010; Fleming and Brayne, 2008; van Iersel <i>et al.</i> , 2006
Disease-specific	Depression	1	121	Janzing <i>et al.</i> , 2000
Disease-specific	CVD	1	1,832	Bursi <i>et al.</i> , 2006
Disease-specific	Diabetes	1	1,097	Okura <i>et al.</i> , 2009
Disease-specific	Hypertension	1		Vinyoles <i>et al.</i> , 2008
Disease-specific	Parkinson's disease	3	555	Aarsland <i>et al.</i> , 2001a, 2001b; Melton <i>et al.</i> , 2006
Disease-specific	Stroke	3		Desmond <i>et al.</i> , 1998; Harris <i>et al.</i> , 1994; Melkas <i>et al.</i> , 2009
Function				
Function	CVD	3	852	Freels <i>et al.</i> , 2002; Haydar <i>et al.</i> , 2004; Lopponen <i>et al.</i> , 2005
Function	Depression	3	3,517	Feng <i>et al.</i> , 2010; Fuhrer <i>et al.</i> , 1992a, 1992b; Millán-Calenti <i>et al.</i> , 2011
Function	Diabetes	3	2,285	Okura <i>et al.</i> , 2009; Quinn <i>et al.</i> , 2009; Sinclair <i>et al.</i> , 2000
Function	Falls	3	490	Allan <i>et al.</i> , 2009; Eriksson <i>et al.</i> , 2008; van Iersel <i>et al.</i> , 2006
Function	Stroke	2	303	Harris <i>et al.</i> , 1994; Stott <i>et al.</i> , 2001
Function	Cancer	1	258	Robb <i>et al.</i> , 2010
Function	Hypertension	1	782	Huang <i>et al.</i> , 2009

CHF, congestive heart failure; CVD, cardiovascular disease; NC, no consensus; MCC, multiple chronic conditions; NH, nursing home.

^aArticle citations for each chronic condition-outcome pairing are available by contacting the corresponding author. Some of the 147 studies are listed in more than one chronic condition-outcome pairing.

^bAt least six expert panelists rated insufficient evidence due to not enough studies (typically 2 or less). Categories with mixed evidence are presented in italics.

* Some studies are described in more than one article (e.g., References 132 and 133 describe the same study)