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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
M. Snowden led the systematic literature review, including finalizing the design and methods for article screening, abstraction and rating; participated on the expert panel; provided oversight for the updated literature review; and wrote, reviewed and edited the manuscript.
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.
M. Cherrier 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.
K. Greenlund 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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C. Levy 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.
C. Copeland conducted the article screening and abstraction for the literature review; prepared summary data tables with key data from included studies; and reviewed and edited the manuscript.
M. Vogel conducted the article screening and abstraction for the updated literature review; prepared summary data tables with key data from included studies; and reviewed and edited the manuscript.
L. Anderson advised the literature review design, methods and evidence rating; and wrote, reviewed and edited the manuscript.
D. Atkins advised the research team on the literature review design, methods and evidence rating; 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.
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 Recherché 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
An 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; Llinás-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.

Acknowledgments

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References


Fleming J, Brayne C. Cambridge city over-75s cohort (CC75C) study collaboration. Inability to get up after falling, subsequent time on floor, and summoning help: prospective cohort study in people over 90. BMJ. 2008; 337:a2227. [PubMed: 19015185]


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

<table>
<thead>
<tr>
<th>Construct</th>
<th>Search terms</th>
</tr>
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<tbody>
<tr>
<td>Older adults</td>
<td>Aged[mh]</td>
</tr>
<tr>
<td></td>
<td>Aged, 80 and over[mh]</td>
</tr>
<tr>
<td></td>
<td>Frail Elderly[mh]</td>
</tr>
<tr>
<td></td>
<td>elderly[tiab]</td>
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<tr>
<td></td>
<td>older adults[tiab]</td>
</tr>
<tr>
<td></td>
<td>seniors[tiab]</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Dementia[mh]</td>
</tr>
<tr>
<td></td>
<td>“cognitive impairment”[tiab]</td>
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<td>CLIND[tiab]</td>
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<tr>
<td>Chronic conditions and geriatric syndromes</td>
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<td>Emphysema[Majr]</td>
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<td>Brain ischemia[Majr]</td>
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<td></td>
<td>Stroke[Majr]</td>
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<td>Heart disease[tiab]</td>
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<td>Sleep disorders[Majr]</td>
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<td>Neoplasms[Majr]</td>
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<td>Osteoporosis[Majr]</td>
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<td>Comorbidity[Majr]</td>
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<td></td>
<td>Manic depressive disorder[tiab]</td>
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<tr>
<td></td>
<td>Chronic disease[Majr]</td>
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</table>

[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.

Note: Limits of English-only studies were also set.
### Table 2

**Chronic conditions and geriatric syndromes**

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<th>Chronic conditions</th>
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<td>Asthma</td>
<td>Falls, fractures, and other injuries</td>
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<td>Frailty</td>
</tr>
<tr>
<td>Bone diseases (e.g., osteoporosis)</td>
<td>Functional impairments</td>
</tr>
<tr>
<td>Brain diseases (e.g., Parkinson’s)</td>
<td>Polypharmacy/High-risk medications</td>
</tr>
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<td>Cancer</td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>Cardiovascular diseases (e.g., CAD, hypertension, and hyperlipidemias)</td>
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</tr>
<tr>
<td>Cerebrovascular diseases (e.g., stroke)</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
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<tr>
<td>Chronic pain</td>
<td></td>
</tr>
<tr>
<td>Dental problems</td>
<td></td>
</tr>
<tr>
<td>Depression and other chronic mental illness (PTSD, schizophrenia, and bipolar)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Emphysema/COPD</td>
<td></td>
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<tr>
<td>Neurological conditions (epilepsy and multiple sclerosis)</td>
<td></td>
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<tr>
<td>Sleep disorders</td>
<td></td>
</tr>
<tr>
<td>Substance abuse</td>
<td></td>
</tr>
<tr>
<td>Risk factors if a chronic conditions is present (e.g., obesity, smoking, and gait)</td>
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</table>
### Table 3

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

<table>
<thead>
<tr>
<th>Outcome/Chronic condition</th>
<th># of Studies</th>
<th>Sample Size</th>
<th>Author, Year</th>
<th>Quality Rating</th>
<th>Effectiveness Rating</th>
</tr>
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<tbody>
<tr>
<td><strong>Mortality MCC</strong></td>
<td>19</td>
<td>50,218</td>
<td>Bruce et al., 1995; Cacciatoare et al., 2005; Feil et al., 2003; Fitzpatrick et al., 2005; Ganguli et al., 2002; Gombojav et al., 2011; Gubine et al., 2006; Helmer et al., 2001; Kakull et al., 1994; Nikolet et al., 2011; Lhnäs-Regla et al., 2007; Lyketsos et al., 2007; Millán-Calenti et al., 2011; Nguyen et al., 2003; Rothman et al., 2008; Tschunz et al., 2004; Wang et al., 2010a</td>
<td>Agüero-Torres et al., 1999; Arfken et al., 1995; Bursi et al., 2006; Foley et al., 1999; Freels et al., 2002; Gale et al., 1996; Kammoun et al., 2000; Lavretsky et al., 2010; Magaziner et al., 2005; Meerman et al., 2008; Stump et al., 2001; Zekry et al., 2009</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Mortality Parkinson’s disease</strong></td>
<td>8</td>
<td>4,513</td>
<td>Butter et al., 2008; Ebmeier et al., 1990; Hobson et al., 1994; Lo et al., 2009; Marder et al., 1991; Mitchell and Rockwood, 2000; Parashos et al., 2002</td>
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<td>Fair</td>
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<tr>
<td><strong>Mortality Stroke</strong></td>
<td>6</td>
<td>2,302</td>
<td>Desmond et al., 1998; Desmond et al., 2002</td>
<td>Liebetrau et al., 2003; Melkas et al., 2009; Oksala et al., 2009; Tatemichi et al., 1994</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Service utilization: length of stay institutions/NH MCC</strong></td>
<td>3</td>
<td>3,423</td>
<td>Desmond et al., 1998; Desmond et al., 2002</td>
<td>Magaziner et al., 2005; Rothman et al., 2008; Smith et al., 2000</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Function MCC</strong></td>
<td>19</td>
<td>37,446</td>
<td>Cankurtaran et al., 2008; Covinsky et al., 2003; Gombojav et al., 2011; Lykotsos et al., 2005; Millán-Calenti et al., 2011; Nikolet et al., 2011; Rothman et al., 2008; Sousa et al., 2009; Stewart et al., 2009; Wang et al., 2010b</td>
<td>Agüero-Torres et al., 1998; Agüero-Torres et al., 2002; Erksson et al., 2008; Feng et al., 2010; Lyketsos et al., 2007; Magaziner et al., 2005; Zekry et al., 2008; Zekry et al., 2009; Zhu et al., 1998</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>CVD medications</strong></td>
<td>7</td>
<td>7,196</td>
<td>Andersson et al., 2008; Barzilay et al., 2008; Bursa et al., 2006; Cankurtaran et al., 2008; Rastas et al., 2007</td>
<td>Freels et al., 2002; Loopenon et al., 2005</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>anti-hypertensive medications</strong></td>
<td>7</td>
<td>10,552</td>
<td>Barzilay et al., 2008; Gombojav et al., 2011; Huang et al., 2009</td>
<td>Freels et al., 2002; Hanou et al., 2006; Vinyoles et al., 2008</td>
<td>Fair</td>
</tr>
</tbody>
</table>

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

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

*b* Quality 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.

*c* CVD 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*.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Chronic condition</th>
<th># of studies</th>
<th>Sample size</th>
<th>Author, Year</th>
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<tr>
<td>Mortality</td>
<td>Mortality</td>
<td>4</td>
<td>3,283</td>
<td>Arfken et al., 1995; Lavretsky et al., 2010; Millán-Calenti et al., 2011; St. John and Montgomery, 2009</td>
</tr>
<tr>
<td>Mortality</td>
<td>Depression</td>
<td>4</td>
<td>3,283</td>
<td>Arfken et al., 1995; Lavretsky et al., 2010; Millán-Calenti et al., 2011; St. John and Montgomery, 2009</td>
</tr>
<tr>
<td>Mortality</td>
<td>Cancer</td>
<td>2</td>
<td>3,278</td>
<td>Robb et al., 2010; Roe et al., 2010</td>
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<tr>
<td>Mortality</td>
<td>Atrial Fib</td>
<td>1</td>
<td>2,837</td>
<td>Miyasaka et al., 2007</td>
</tr>
<tr>
<td>Mortality</td>
<td>CHF</td>
<td>1</td>
<td>142</td>
<td>Haydar et al., 2004</td>
</tr>
<tr>
<td>Mortality</td>
<td>COPD</td>
<td>1</td>
<td>134</td>
<td>Antonelli-Incalzi et al., 2006</td>
</tr>
<tr>
<td>Mortality</td>
<td>Hip fracture</td>
<td>1</td>
<td>558</td>
<td>Cree et al., 2000</td>
</tr>
<tr>
<td>Mortality</td>
<td>Hypertension</td>
<td>1</td>
<td>2,496</td>
<td>Gombojav et al., 2011</td>
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</table>

Service utilizations/institutionalizations

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<th>Outcome</th>
<th>Chronic condition</th>
<th># of studies</th>
<th>Sample size</th>
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</tr>
</thead>
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<tr>
<td>Hospitalizations</td>
<td>MCC</td>
<td>3</td>
<td>13,334</td>
<td>Feil et al., 2003; McCormick et al., 2001; Welmerink et al., 2010</td>
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<td>3,020</td>
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<td>CHD</td>
<td>2</td>
<td>7,188</td>
<td>Bursi et al., 2006; Welmerink et al., 2010</td>
</tr>
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<td>Diabetes</td>
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<td>Sinclair et al., 2000</td>
</tr>
<tr>
<td>Length of stay, hospital</td>
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<td>2</td>
<td>1,343</td>
<td>Lang et al., 2006; Zekry et al., 2009</td>
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<tr>
<td>Other medical care</td>
<td>MCC</td>
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<td>779</td>
<td>McCormick et al., 1994; McCormick et al., 2001</td>
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<td>Cancer</td>
<td>1</td>
<td>258</td>
<td>Robb et al., 2010</td>
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<tr>
<td>Other medical care</td>
<td>Diabetes</td>
<td>2</td>
<td>1,188</td>
<td>Quinn et al., 2009; Sinclair et al., 2000</td>
</tr>
<tr>
<td>Other medical care</td>
<td>Myocardial infarction</td>
<td>1</td>
<td>1,832</td>
<td>Bursi et al., 2006</td>
</tr>
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<td>MCC</td>
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<td>2,361</td>
<td>Guhne et al., 2006; Meerman et al., 2008; Smith et al., 2000; Zekry et al., 2009</td>
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<td>Diabetes</td>
<td>1</td>
<td>789</td>
<td>Sinclair et al., 2000</td>
</tr>
<tr>
<td>Institutionalization/NH</td>
<td>Hip fracture</td>
<td>1</td>
<td>558</td>
<td>Cree et al., 2000</td>
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<td>178</td>
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<td>399</td>
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<tr>
<td>Hospice</td>
<td>CHF</td>
<td>1</td>
<td>142</td>
<td>Haydar et al., 2004</td>
</tr>
<tr>
<td>Advanced medical planning</td>
<td>CHF</td>
<td>1</td>
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<td>Haydar et al., 2004</td>
</tr>
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<td>Use of social services</td>
<td>Diabetes</td>
<td>1</td>
<td>789</td>
<td>Sinclair et al., 2000</td>
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<tr>
<td>Costs</td>
<td>MCC</td>
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<td>1.101</td>
<td>McCormick et al., 2001; Scuvée-Moreau et al., 2002</td>
</tr>
<tr>
<td>Cost</td>
<td>Diabetes</td>
<td>1</td>
<td>399</td>
<td>Quinn et al., 2009</td>
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</table>

Medications

*Int J Geriatr Psychiatry. Author manuscript; available in PMC 2018 May 22.*
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Chronic condition</th>
<th># of studies</th>
<th>Sample size</th>
<th>Author, Year</th>
</tr>
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<tr>
<td>Medications-polypharmacy</td>
<td>MCC</td>
<td>7</td>
<td>8,527</td>
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<td>Medications-polypharmacy</td>
<td>Falls</td>
<td>3</td>
<td>411</td>
<td>Eriksson et al., 2008; Morris et al., 1987; Van Iersel et al., 2006</td>
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<tr>
<td>High-risk medications</td>
<td>Falls</td>
<td>4</td>
<td>590</td>
<td>Allan et al., 2009; Eriksson et al., 2008; Morris et al., 1987; Van Iersel et al., 2006</td>
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<td>Antidepressants</td>
<td>Depression</td>
<td>2</td>
<td>3,228</td>
<td>Blazer et al., 2005; Janzing et al., 2000</td>
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<td>2</td>
<td>1,886</td>
<td>Okura et al., 2009; Sinclair et al., 2000</td>
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<td>1</td>
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<td>Vik et al., 2007</td>
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<td>7,940</td>
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<td>Robb et al., 2010</td>
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<td>1</td>
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<td>Vinyoles et al., 2008</td>
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<tr>
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<td>Parkinson’s disease</td>
<td>3</td>
<td>555</td>
<td>Aarsland et al., 2001a, 2001b; Melton et al., 2006</td>
</tr>
<tr>
<td>Disease-specific</td>
<td>Stroke</td>
<td>3</td>
<td></td>
<td>Desmond et al., 1998; Harris et al., 1994; Melkas et al., 2009</td>
</tr>
<tr>
<td>Function</td>
<td>CVD</td>
<td>3</td>
<td>852</td>
<td>Freels et al., 2002; Haydar et al., 2004; Lopponen et al., 2005</td>
</tr>
<tr>
<td>Function</td>
<td>Depression</td>
<td>3</td>
<td>3,517</td>
<td>Feng et al., 2010; Fuhrer et al., 1992a, 1992b; Millán-Calenti et al., 2011</td>
</tr>
<tr>
<td>Function</td>
<td>Diabetes</td>
<td>3</td>
<td>2,285</td>
<td>Okura et al., 2009; Quinn et al., 2009; Sinclair et al., 2000</td>
</tr>
<tr>
<td>Function</td>
<td>Falls</td>
<td>3</td>
<td>490</td>
<td>Allan et al., 2009; Eriksson et al., 2008; van Iersel et al., 2006</td>
</tr>
<tr>
<td>Function</td>
<td>Stroke</td>
<td>2</td>
<td>303</td>
<td>Harris et al., 1994; Stott et al., 2001</td>
</tr>
<tr>
<td>Function</td>
<td>Cancer</td>
<td>1</td>
<td>258</td>
<td>Robb et al., 2010</td>
</tr>
<tr>
<td>Function</td>
<td>Hypertension</td>
<td>1</td>
<td>782</td>
<td>Huang et al., 2009</td>
</tr>
</tbody>
</table>

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

*Article 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.

*At 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)