

# **Effectiveness of interventions for managing multiple high-burden chronic diseases affecting older adults: A systematic review and meta-analysis**

Monika Kastner<sup>1,2\*</sup>, Roberta Cardoso<sup>1</sup>, Yonda Lai<sup>1</sup>, Victoria Treister<sup>1</sup>, Jemila S. Hamid<sup>1,3</sup>, Leigh Hayden<sup>2</sup>, Geoff Wong<sup>4</sup>, Noah M. Ivers<sup>5</sup>, Barbara Liu<sup>6</sup>, Sharon Marr<sup>7</sup>, Jayna Holroyd-Leduc<sup>8</sup>, Sharon E. Straus<sup>1,10</sup>

<sup>1</sup>Li KaShing Knowledge Institute. St. Michael's Hospital, 209 Victoria Street, Toronto, Ontario, M5B 1W8, Canada

<sup>2</sup>Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, 6th floor, 155 College St, Toronto, Ontario, M5T 3M7, Toronto, Ontario, Canada

<sup>3</sup>Clinical Epidemiology and Biostatistics, McMaster University, 1280 Main Street West, Hamilton, Ontario, Canada

<sup>4</sup>Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, OX2 6GG, United Kingdom

<sup>5</sup>Department of Family Medicine, Women's College Hospital – University of Toronto, 76 Grenville Street, Toronto, Ontario, M5S1B3 Canada

<sup>6</sup>Regional Geriatric Program of Toronto; Sunnybrook Health Sciences, Geriatric Medicine, 2075 Bayview Avenue, Toronto, ON, M4N 3M5, Canada

<sup>7</sup>St. Peter's Hospital/Hamilton Health Sciences, Division of Geriatric Medicine McMaster University, 88 Maplewood Avenue, Hamilton, Ontario, office 160. L8M 1W9.

<sup>8</sup>Departments of Medicine and Community Health Sciences, University of Calgary, Foothills Hospital 1403-29<sup>th</sup> Street NW, Calgary, Alberta, T2N 2T9, Canada

<sup>9</sup>Department of Family and Community Medicine, St. Michael's Hospital, Toronto, ON

<sup>10</sup> Department of Medicine, University of Toronto, 200 Elizabeth Street, Toronto, Ontario, M5G 2C4, Canada

**\*Corresponding Author:** Monika Kastner ([monika.kastner@utoronto.ca](mailto:monika.kastner@utoronto.ca))

**Key words:** chronic disease management, older adults, multimorbidity; systematic review

**Word count:** 3005

## **ABSTRACT:**

**Introduction:** More than half of older adults (age  $\geq 65$  years) have two or more high burden multimorbidity conditions (highly prevalent chronic diseases, which are associated with increased health care utilization such as diabetes [DM], dementia (DEM), depression [DEP], chronic obstructive pulmonary disease [COPD], cardiovascular disease [CVD], arthritis [AT], and heart failure [HF]), yet most existing chronic disease management (CDM) interventions focus on a single disease or don't respond to the specialized needs of older adults. We conducted a systematic review and meta-analysis to identify effective multimorbidity interventions compared with a control or usual care strategy for older adults.

**Methods:** We searched bibliometric databases for randomized controlled trials (RCTs) evaluating multi-CDM interventions in any language from 1990 to December 2017. Primary outcome was any multi-disease specific chronic disease management outcome as reported by studies. Reviewer pairs independently screened citations and full-text articles, extracted data, and assessed risk of bias. We assessed statistical and methodological heterogeneity and performed a meta-analysis of RCTs with similar interventions and components.

**Results:** Twenty-five studies (including 15 RCTs and 6 cluster RCTs) were included (12,579 older adults; mean age 67.3 years). In patients with [DEP + COPD] or [CVD + DM], care coordination strategies significantly improved depressive symptoms (standardized mean difference -0.41; CI -0.59 to -0.22;  $I^2 = 0\%$ ) and reduced HbA1c levels (mean difference -0.51; CI -0.90 to -0.11;  $I^2 = 0\%$ ) but not mortality (relative risk [RR] 0.79; CI 0.53 to 1.17;  $I^2 = 0\%$ ). Among secondary outcomes, care coordination strategies reduced functional impairment in patients with [AT + DEP] (between group difference [BGD] -0.82; CI -1.17 to -0.47) or [DM + DEP] (BGD 3.21; CI 1.78 to 4.63); improved cognitive functioning in patients with [DM + DEP] (BGD 2.44; CI 0.79 to 4.09) or [HF + COPD] ( $p = 0.006$ ); and increased mental health service use in those with [DM + (CVD or DEP)] (RR 2.57; CI 1.90 to 3.49;  $I^2 = 0\%$ ).

**Interpretation:** Subgroup analyses showed that older adults with [DM + (DEP or CVD)] or [COPD + HF] can benefit from care coordination strategies with or without education to lower HbA1c, reduce depressive symptoms, improve health-related functional status, and increase the use of mental health services.

**Registration:** PROSPERO (No CRD42014014489).

**Abbreviations:**

AT = arthritis; BGD = between group difference; CADTH = Canadian Agency for Drugs and Technologies in Health; CDM = chronic disease management; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DEP = depression; DM = diabetes mellitus; DMC = difference in mean change; HF = heart failure; QOL = quality of life; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference.

## INTRODUCTION

By the year 2050, two billion people worldwide will be 60 years of age and older<sup>1,2</sup>. In Canada, older adults (age  $\geq 65$  years) represent the fastest growing proportion of the population – by 2036, they will make up 25% of the population and consume 62% of the healthcare budget<sup>2</sup>. These projections coupled with a rise in global life expectancies<sup>1</sup>, will lead to an increased number of people who will develop high burden chronic diseases (i.e., highly prevalent and associated with premature death and increased health care utilization)<sup>3</sup>. The burden of chronic disease is a global phenomenon, with more than half of older adults living with multimorbidity<sup>4</sup> (i.e., co-existence of two or more chronic diseases)<sup>5</sup>. These trends are similar in Canada (42.6%)<sup>6,7</sup>, the United States (62.5%)<sup>8</sup>, and the United Kingdom (46.5% to 64.1%)<sup>9</sup>. Moreover, older adults with multimorbidity have greater health care needs, are at higher risk for adverse health outcomes, and experience more frequent hospitalizations<sup>10</sup>, yet only 55% receive appropriate care<sup>7,8</sup>. In response, different chronic disease management (CDM) interventions have been created (i.e., those that facilitate ongoing, proactive and preventive support for optimal disease management. These strategies have potential to improve care for older adults<sup>11,12</sup> but are not usually developed for older adults or sustainable, and focus only on a single disease<sup>8,13,14</sup>. We know very little about the potential impact of interventions for managing multiple chronic diseases, and no existing systematic review focuses exclusively on older adults. To address these gaps, we conducted a systematic review and meta-analysis to identify effective multimorbidity interventions (those that integrate the care of two or more high-burden chronic diseases) compared with a control or usual care strategy in older adults (age  $\geq 65$  years), and to determine which components of these interventions optimise their impact.

## METHODS

Our systematic review protocol has been published<sup>15</sup>, and is registered with PROSPERO (the international prospective register of systematic reviews): registration number CRD42014014489). We applied the PRISMA<sup>16</sup> quality and publication standards.

## Data Sources and Searches

An experienced information specialist executed our search strategy (Appendix 1) and a second information specialist appraised it using the PRESS checklist<sup>17</sup>. We searched Medline, Embase, Cinahl, AgeLine and the Cochrane Library for studies in any language from 1990 to December 2017. This date restriction was applied because few multimorbidity studies were published before 1990<sup>18</sup>. We applied a validated, age-specific search filter to focus our studies on older adults (i.e., age  $\geq 65$  years)<sup>19</sup>. We searched the grey literature using the Canadian Agency for Drugs and Technologies in Health (CADTH) grey matter approach<sup>20</sup>; and scanned reference lists of included studies to identify additional articles.

## Study Selection

Reviewer pairs were calibrated to ensure screening reliability. This exercise was repeated until there was at least 80% agreement, after which reviewer pairs selected the remainder of potentially relevant articles independently. The same procedure was used for selecting full-text articles. Disagreements at both levels were resolved through discussion.

Our eligibility criteria were informed by the PICO criteria<sup>21</sup>. We included older adults age  $\geq 65$  years with multimorbidity (two or more high-burden chronic conditions) as suggested by national and international public health agencies<sup>22,23</sup>; we also considered age  $< 60$  to over 60 years of age as long as the mean age of the study population was  $\geq 65$  years. We considered CDM interventions that were *deliberately* created to address multimorbidity<sup>5</sup> whereby all study participants had to have the *same* chronic disease dyad or triad combination (e.g., DM + DEP). We excluded interventions with co-morbidity cases (i.e., an index disease + different co-existing conditions)<sup>24</sup>. CDM interventions could be complex (i.e., multiple components or targets), facilitate ongoing and proactive support for optimal disease management; and include quality improvement components<sup>25,26</sup>. The *comparator* could be any control or usual care strategy. The primary outcome could be any patient relevant CDM outcome as reported by studies (e.g., glycaemic control as part of diabetes care). Secondary outcomes included quality of life (QOL), functional status (cognitive, physical, social, psychological functioning), treatment adherence, harms, satisfaction, health services utilization (e.g., hospital admission, emergency department

visits), and costs. We included randomized controlled trials (RCTs), quasi-experimental trials, and mixed-methods studies that included an RCT.

### **Data Extraction and Quality Assessment**

Data were abstracted in duplicate using a standardized, pilot-tested form on study characteristics, population and intervention characteristics, outcomes, follow-up and risk of bias. Outcomes were classified using the Cochrane Consumer and Communication group taxonomy<sup>27,28</sup> (Appendix 2). Risk of bias was independently assessed by two reviewers using the Cochrane Risk of Bias tool<sup>29</sup>, Mixed Method Appraisal Tool<sup>30</sup>, and GRADEPro (overall quality of evidence across our meta-analyses)<sup>31</sup>. Conflicts for all assessments were resolved through team discussion.

### **Deconstruction of CDM interventions**

To determine which component or combination of components contributed to outcomes, each CDM strategy was deconstructed by reviewer pairs using content analysis<sup>32</sup>. This involved extracting the description of the CDM intervention from each article, identifying individual components, and assigning a code to each (e.g., education, case management) drawing on the EPOC taxonomy of quality improvement strategies<sup>25,26</sup>. This process led to the iterative development of a codebook of intervention components (Appendix 3).

### **Data Synthesis and Analysis**

We descriptively summarized studies according to study and patient characteristics and assessed the effects of CDM interventions across different outcomes. We explored the potential sources of statistical, methodological and clinical heterogeneity, and considered performing a meta-analysis for studies with the same outcome and similar combination of intervention components (e.g., education + case management). We defined high statistical heterogeneity as  $I^2 \geq 75\%$ <sup>29</sup>. We used random effects model given the expected high heterogeneity among complex interventions. For continuous outcomes, mean differences or standardized mean differences were used as effect measures, and relative risk (RR) with their confidence intervals (CIs) were used for binary outcomes. Planned subgroup analyses were to investigate outcomes by disease cluster, type of

intervention, and similar disease component combinations. All analyses were conducted using the R statistical package.

## RESULTS

Figure 1 shows the flow of article selection. We screened 53,465 abstracts and identified 1878 potentially relevant full-text articles. Of these, 25 studies and 3 companion reports were included in the systematic review representing 12,579 older adults (mean age 67.3 years, range 61-86 years; 55% women)<sup>33-61</sup>. Designs were RCTs (n = 15), cluster RCTs (n = 6), mixed-methods (n = 3), and uncontrolled (n = 1) studies published between 2003-2018 in the US (n = 11), Australia (n = 7), Europe (n = 6) and Canada (n = 1). Follow-up ranged 2-52 weeks (mean 26.3 weeks). The most common chronic conditions occurring in disease clusters were DM (n = 13), DEP (n = 10), HF (n = 7), and COPD (n = 7). The most frequently occurring disease dyads were [DM + DEP (n = 4)<sup>44,49,60</sup> or CVD (n = 4)]<sup>40,49,53,56</sup> and [HF + COPD (n = 3)]<sup>46,52,57</sup>.

CDM intervention types are described in Appendix 3. The majority of studies were classified as care coordination (n = 10) or information and health technology (n = 7). Deconstruction of these interventions revealed nine components, of which the most frequently occurring were education targeting patients, providers or both (88%); disease management (52%); and self-management (48%). Interventions were delivered in primary care (n = 8), at home (n = 7), and in outpatient clinics (n = 5), hospitals (n = 3), and nursing homes (n = 2).

The risk of bias assessment for the 21 included RCTs are shown in Appendix 5. The majority of studies had low risk of bias for random sequence generation (86%), blinding of outcome assessors (62%), incomplete or selective reporting of outcomes (88%), and other biases (86%); and unclear risk of bias for allocation sequence (48%) and blinding of patients or personnel (48%). Two studies (10%) had high risk of bias for blinding of participants and personnel.

### Primary outcomes: Chronic disease management (Table 1)

**Depression:** Of 14 studies investigating depression, six studies evaluating care coordination interventions (n = 3314)<sup>33,45,47,48,55,60</sup> and two studies of cognitive-behavioural interventions<sup>43,44</sup> (n = 400) significantly reduced depressive symptoms in patients with [DEP +

another disease (COPD<sup>33,44</sup>, AT<sup>55</sup>, DEM<sup>43,47</sup> or DM<sup>44,60</sup>); and for patients with [DM + CVD]<sup>48</sup> (p-value range < 0.001 to 0.021); the remainder of studies did not report effect sizes. A subgroup of two trials (n = 448)<sup>33,48</sup> of case management + self-management + education that were pooled in a meta-analysis showed significantly improved depressive symptoms in patients with [DEP + COPD] or [CVD + DM] (SMD -0.41; CI -0.59 to -0.22; I<sup>2</sup> = 0%) (Figure 2a).

**HbA1c:** Three pooled studies (n = 2222)<sup>48,50,60</sup> evaluating care coordination with education did not reduce HbA1c levels in patients with [DM + another disease (mean difference -0.27; CI -0.66 to 0.13; I<sup>2</sup> = 50.12%)]. A subgroup of these (n = 421; 2 RCTs)<sup>48,50</sup> consisting of case management + self-management in addition to education significantly reduced HbA1c levels (mean difference -0.51; CI -0.90 to -0.11; I<sup>2</sup> = 0%) (Figure 2b).

**Systolic blood pressure:** Meta-analysis of two RCTs (n = 365)<sup>48,58</sup> evaluating an education + self-management strategy showed no difference between groups for reducing systolic blood pressure in patients with [DM + CVD or chronic kidney disease] (difference in mean change [DMC] -0.44; CI -4.49 to 3.61; I<sup>2</sup> = 0%) (Figure 2c).

**Mortality:** Meta-analysis of four RCTs of care coordination interventions with at least education as a component (n = 550)<sup>33,36,38,46</sup> showed decreased mortality across trials in patients with [COPD + (DEP or HF)] or [HF + DEP], but it did not reach significance (relative risk [RR] 0.79; CI 0.53 to 1.17; I<sup>2</sup> = 0%) (Figure 2d).

## Secondary outcomes

**Quality of life:** Care coordination strategies reduced functional impairment among patients with [AT + DEP] (between group difference [BGD] -0.82; CI -1.17 to -0.47)<sup>45</sup> or [DM + DEP] (BGD 3.21; CI 1.78 to 4.63)<sup>60</sup>. Among three studies (n = 1913) targeting patients with at least diabetes, care coordination significantly improved cognitive functioning (BGD 2.44; CI 0.79 to 4.09)<sup>60</sup> and a self-management strategy reduced diabetes-related emotional stress (effect size 1.06)<sup>49</sup> in depressed patients; and a telemedicine strategy improved cognition in patients with [HF + COPD] (p = 0.006)<sup>50</sup>. Telemedicine did not improve health status among two studies of patients with [diabetes + heart failure]<sup>39,40</sup>. Another study that added an integrated nursing and rehabilitation program at home to telemedicine (n = 112)<sup>52</sup> significantly improved QOL in patients with [HF + COPD] (p = 0.0000); as did a care coordination strategy involving nurse-



administered case management (n = 1001)<sup>45</sup> for [DEP + AT] (p = 0.005); no effect estimates reported. Two care coordination strategies significantly reduced dyspnea-related disability in patients with [DEP + COPD] (p = 0.044)<sup>33</sup> or [DM + DEP] (p = 0.022)<sup>60</sup>; as did home-based telemonitoring in patients with [COPD + HF] (p = 0.0015)<sup>38</sup>; no effect estimates reported.

**Antidepressant use:** In two pre-planned sub-group analyses of the IMPACT trial<sup>45,60</sup> evaluating a care coordination intervention with the components of care pathways, disease management and education found that patients with [DEP + (AT or DM)] were significantly more likely to take antidepressants or partake in psychotherapy than usual care (66% vs 52%; p<0.001<sup>45</sup>; 82% vs. 61%; p<0.001<sup>60</sup>; respectively).

**Mental health service use:** Meta-analysis of two RCTs (n = 688)<sup>48,60</sup> showed increased use of mental health services with care coordination interventions that included at least education + care pathways compared with controls among patients with [DM + (CVD or DEP)] (RR 2.57; CI 1.90 to 3.49; I<sup>2</sup> = 0%) (Figure 3; Table 1).

**Physical activity:** Four studies investigated physical activity in patients with [DM + another disease]<sup>35,48,56,60</sup>. In particular, a nurse-led collaborative care strategy (n = 317) significantly increased the number of patients who exercised 30 min/day compared with controls (60% vs. 29%; p < 0.001)<sup>48</sup> as did patients who received care coordination (BGD 0.50; CI 0.12 to 0.89; p = 0.001)<sup>60</sup>.

**Health care utilization:** Of three studies investigating hospitalization (n = 465)<sup>39,46,50</sup>, home telemonitoring (n = 58) targeting patients with [HF + COPD] reduced the risk for at least one all-cause hospital admission compared with controls (RR 0.66; CI 0.44 to 0.99; p = 0.033)<sup>46</sup>.

**Cost:** Of two studies investigating costs, neither found a difference between groups with telemedicine in patients with [COPD + DM + HF] (58% vs. 47%; p > 0.05)<sup>50</sup>; and with care coordination in patients with [DM + DEP]<sup>60</sup>; no effect estimates reported.

## INTERPRETATION

Overall, our findings showed that care coordination interventions (i.e., changes in how, when and where healthcare is organized and delivered, and who delivers healthcare<sup>62</sup>) appear to have the greatest potential for improving primary and secondary outcomes in older adults with multimorbidity. More specifically, our subgroup analyses showed that: 1) the intervention

combination of case management + education + self-management significantly reduced depressive symptoms in older adults with [DEP + COPD] or [DM + CVD]; and reduced HbA1c levels in those with [DM + another disease]; 2) care coordination or telemedicine interventions that included at least education as a component, significantly reduced dyspnea related disability and improved cognitive functioning in patients with [DM + DEP] or [COPD + HF]; and 3) the intervention combination of care pathways + education significantly increased mental health service use in those with [DM + (DEP or CVD)]. These findings support previous studies that collaborative care is a promising approach for chronic disease management<sup>63</sup>, particularly for improving outcomes in depressed patients with other coexisting chronic conditions<sup>4,46,64</sup>. Of note, 92% of our meta-analyses included older adults with at least depression as part of the disease cluster, highlighting that depression is prevalent among co-existing conditions, most often occurring in combination with diabetes in our study. We therefore suggest that older adults with [DEP + DM] can benefit from care coordination strategies with or without education (targeting patients and providers) to lower HbA1c, reduce depressive symptoms, and to increase the use of mental health services.

### **Strengths and limitations**

We contributed to the current limited knowledge of which interventions are effective for multimorbid older adults. A Cochrane review investigated health service or patient-oriented interventions in multimorbid patients of any age, and found mixed results<sup>65</sup>, but suggested that those targeting specific risk factors or focusing on difficulties with daily functioning may be more effective<sup>65</sup>. Our review builds on this work in several respects. We included a larger number of articles (n = 25) and older adults (n = 12,579) and identified interventions that were designed for specific chronic disease combinations (rather than for an index disease with co-existing conditions). To our knowledge, we are the first to elucidate this in an older adult population. We deconstructed interventions to help identify which studies were the *most* appropriate to pool in a meta-analysis and performed targeted searches for each chronic disease (embedded within our overall search strategy) to capture a *broader perspective* of multimorbidity. As such, we included a wider spectrum of disease clusters, intervention types,

outcomes and settings, thereby making our systematic review among the most comprehensive of those investigating multimorbidity, and the only one targeting older adults specifically.

Our study had some limitations. As with any systematic review, it is possible that we may not have captured all potentially relevant articles, particularly since we had a very large yield at both levels of screening. However, we conducted five (title/abstract) and two (full-text) calibration exercises with six reviewer pairs to attain our screening reliability goal. Additionally, our search strategy was developed by an experienced information specialist and validated by another using the PRESS checklist<sup>17</sup>. This approach increases the overall quality of the evidentiary base of systematic reviews by enhancing the comprehensiveness of database searches and reducing the potential for errors<sup>66</sup>. Second, six RCTs had missing data on certain outcomes that precluded meta-analyses; two authors provided missing data. Third, few studies defined multimorbidity, and fourth, studies ranged widely in the outcomes they considered and how they measured them. As such, there was potential for their misclassification. However, we used established Cochrane classification systems<sup>25,26,62</sup>, and pilot tested all our systematic review tools at all stages of screening and abstraction to optimise reliability. These processes also helped us to elucidate clinically relevant messages from high-quality trials. Lastly, we acknowledge that mid-aged adults also have a high prevalence of multimorbidity, but we focused on older adults because they represent a relatively unstudied population, and given their projected population growth, they urgently need our attention to optimize their care.

### **Implications for future study**

Our study highlights the paucity of interventions specifically created to address multimorbidity in older adults, particularly for chronic diseases that most frequently occur in clusters (diabetes, depression, heart failure, CVD and COPD). In particular, depression in diabetes is common, and since each can be a risk factor for the other, self-care and medication adherence are often significant obstacles to improving outcomes<sup>67</sup>. Future studies should investigate the potential impact of interventions that consider commonly occurring disease dyads: [DM + DEP], [DM + CVD], [COPD + HF]. Stepped-care models of care (i.e., care that is adjusted in stages) have potential to effectively treat common disease dyads such as depression in diabetes<sup>51,68,69</sup> but require further evidence of effectiveness on patient relevant outcomes for their routine use. The

lack of optimized strategies for managing multimorbidity (and common disease dyads) is also an indication that clinical practice guidelines focusing on the clinical assessment and management of multimorbidity are lacking. The UK National Institute for Health and Care Excellence (NICE) guideline is one of the first to tackle this<sup>70</sup>. In Canada, despite having good quality guidelines, most are single disease focused, and therefore have limited relevance and applicability to multimorbidity management<sup>71</sup>. Second, multimorbidity management can be confusing for patients and overwhelming for providers due to the heterogeneous nature of multimorbidity<sup>72</sup> disease and treatment interactions and possible conflicts<sup>73,74</sup>, and the difficulty of attributing symptoms to conditions<sup>72</sup>. Therefore, optimized multimorbidity management requires a better understanding of health priorities both from the patient and provider perspectives. We conducted a realist review alongside our systematic review (to understand the underlying mechanisms of our findings), which confirmed this. When mitigating the complexities of multimorbidity management, patients tend to focus on reducing their undesired symptoms and preserving their quality of life, while providers focus on the condition that most threaten a patient's morbidity and mortality<sup>75</sup>. As such, interventions need to consider not only the clinical aspects of care, but patients' health priorities and goals as well as their social and emotional vulnerabilities. Lastly, the mean follow-up period of our included studies was relatively short (mean 26.3 weeks), which highlights an important gap in the literature – complex interventions are not designed for sustained use. This is consistent with our recent scoping review, which found that very few studies focus on the sustainability of implemented interventions<sup>76</sup>. If interventions don't have sustainability capacity, they are less likely to achieve desired outcomes and can even be harmful, and contribute to research waste<sup>77</sup>. Future multi-CDM interventions should be sustainable to optimize their impact, be designed and implemented to meet the specialized needs of older adults, and ensure a good balance between clinical and patient priorities.

## **Conclusions**

Care coordination interventions with one or a combination of case management, care pathways, self-management, and education, appear to have the greatest potential for impact. In particular, older adults with [diabetes + (depression or cardiovascular disease)] or [COPD + heart failure] can benefit from care coordination or telemedicine strategies with or without education to lower

HbA1c, reduce depressive symptoms, improve health-related functional status, and to increase the use of mental health services.

### **Competing interests**

None declared.

### **Contributors**

MK conceived the study; MK, JH, GW, NMI, and SS developed the study design and all authors contributed to the drafting of the manuscript; LP and BS developed the search strategy; JH conducted the meta-analyses. All authors read and approved the final manuscript.

### **Funding**

This research was supported by an Ontario, Canada Ministry of Health and Long-term Care (MOHLTC) Health Systems Research Fund (HSRF) Capacity Award. The MOHLTC had no role in the study's design, conduct and reporting. MK is funded by a Canadian Institutes of Health Research (CIHR) New Investigator Award. NMI is funded by a CIHR New Investigator Award from the Department of Family and Community Medicine, University of Toronto. SES is funded by a Tier 1 Canada Research Chair in Knowledge Translation.

### **Acknowledgements**

In addition to our core research team, we would like to thank the following research staff who helped throughout the screening and data abstraction phases of our systematic review: Chamila Adhihetty, Arnav Agarwal, Ronak Brahmabhatt, Ryan Kealey, Fissan Lau, Lori Wheelan, Lisa Ye. We also thank Laure Perrier, Becky Skidmore and Alissa Epworth for helping to develop and execute the search strategy.

### **Abbreviations**

CDM (chronic disease management); RCT (randomized controlled trial); SMD (standardized mean difference); COPD (chronic obstructive pulmonary disease); PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis); CADTH (Canadian Agency for

Drugs and Technologies in Health); QOL (quality of life); CASP (Critical Appraisal Skills Program (CASP); MMAT (Mixed Method Appraisal (MMAT); RR (relative risk); CI (confidence interval); HbA1c (glycated hemoglobin); DMC (difference in mean change).

## **Ethics approval**

This research study did not involve humans, and therefore it did not require ethics approval.

## **References**

1. Chatterji S, Byles J, Cutler D, Seeman T, Verdes E. Health, functioning, and disability in older adults--present status and future implications. *Lancet*. 2015;385(9967):563-575.
2. Statistics\_Canada. Canada Yearbook. Seniors. 2012; <http://www.statcan.gc.ca/pub/11-402-x/2012000/chap/seniors-aines/seniors-aines-eng.htm>. Accessed May 8, 2017.
3. World Health Organization: Major non-communicable diseases and their risk factors. Available at: <http://www.who.int/ncds/en/>. Accessed in April 2018.
4. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev*. 2011;10(4):430-439.
5. World Health Organization: Multimorbidity. Available at: <http://apps.who.int/iris/bitstream/handle/10665/252275/9789241511650-eng.pdf?sequence=1>. Accessed in April 2018.
6. Roberts KC, Rao DP, Bennett TL, Loukine L, Jayaraman GC. Prevalence and patterns of chronic disease multimorbidity and associated determinants in Canada. *Health Promote Chronic Dis Prev Can*. 2015;35(6):87-94.
7. Moore EG, Rosenberg MW, Fitzgibbon SH. Activity limitation and chronic conditions in Canada's elderly, 1986-2011. *Disabil Rehabil*. 1999;21(5-6):196-210.
8. Ward BW, Schiller JS. Prevalence of multiple chronic conditions among US adults: estimates from the National Health Interview Survey, 2010. *Prev Chronic Dis*. 2013;10:E65.
9. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380(9836):37-43.
10. Boyd C, Fortin M. Future of multimorbidity research: How should understanding of multimorbidity inform health system design? *Public Health Reviews*. 2011;33(2):451-474.
11. Weingarten SR, Henning JM, Badamgarav E, et al. Interventions used in disease management programmes for patients with chronic illness-which ones work? Meta-analysis of published reports. *BMJ*. 2002;325(7370):925.
12. Wenger NS, Solomon DH, Roth CP, et al. The quality of medical care provided to vulnerable community-dwelling older patients. *Ann Intern Med*. 2003;139(9):740-747.
13. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the Chronic Care Model in the new millennium. *Health Aff (Millwood)*. 2009;28(1):75-85.
14. Fortin 2018

15. Kastner M, Perrier L, Hamid J, et al. Effectiveness of knowledge translation tools addressing multiple high-burden chronic diseases affecting older adults: protocol for a systematic review alongside a realist review. 2015.
16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-34.
17. Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C. An evidence-based practice guideline for the peer review of electronic search strategies. *J Clin Epidemiol*. 2009;62(9):944-952.
18. Smith SM, Soubhi H, Fortin M, Hudon C, O'Dowd T. Managing patients with multimorbidity: systematic review of interventions in primary care and community settings. *BMJ*. 2012;345:e5205.
19. Kastner M, Wilczynski NL, Walker-Dilks C, McKibbin KA, Haynes B. Age-specific search strategies for Medline. *J Med Internet Res*. 2006;8(4):e25.
20. CADTH. Grey Matters: a practical tool for searching health-related grey literature | CADTH.ca. 2015; <https://www.cadth.ca/resources/finding-evidence/grey-matters>. Accessed May 8, 2017.
21. Stone PW. Popping the (PICO) question in research and evidence-based practice. *Appl Nurs Res*. 2002;15(3):197-198.
22. PHAC. Preventing chronic disease strategic plan 2013–2016. Ottawa: Public Health Agency of Canada;2013.
23. Aging No. Live Long and Well in the 21st Century: Strategic Directions for Research on Aging. Bethesda: National Institutes of Health;2007.
24. Lefevre T, Ivernois J.-F., De Andrade V, Crozet C, Lombrail P, Gagnayre R. What do we mean by multimorbidity? An analysis of the literature on multimorbidity measures, associated factors, and impact on health services organization. *Epidemiology and Public Health* 2014;62:305-14.
25. EPOC. EPOC (Effective Practice and Organization of Care) Taxonomy. 2015; <http://epoc.cochrane.org/epoc-taxonomy>. Accessed May 8, 2017.
26. Shojania KG, Ranji SR, Shaw LK, et al. AHRQ Technical Reviews. In: Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies (Vol. 2: Diabetes Care). Rockville (MD): Agency for Healthcare Research and Quality (US); 2004.
27. Cochrane. Taxonomy of outcomes of interest to the Cochrane Consumers & Communication Group. 2012; Available at: <https://cccr.org.cochrane.org/sites/cccr.org.cochrane.org/files/public/uploads/Outcomes.pdf> Accessed April 2018.
28. Hill S, Lowe D, McKenzie J. Identifying outcomes of importance to communication and participation. In: Hill S, ed. *The Knowledgeable Patient: Communication And Participation in Health*. London, UK: Wiley Blackwell; 2011:40-53.
29. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.
30. Pace R, Pluye P, Bartlett G, et al. Testing the reliability and efficiency of the pilot Mixed Methods Appraisal Tool (MMAT) for systematic mixed studies review. *Int J Nurs Stud*. 2012;49(1):47-53.

31. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011;64(4):401-406.
32. Elo S and Kyngas H. The qualitative content analysis process. *Journal of Advanced Nursing* 2008;62(1):107-115.
33. Alexopoulos GS, Kiosses DN, Sirey JA, et al. Untangling therapeutic ingredients of a personalized intervention for patients with depression and severe COPD. *Am J Geriatr Psychiatry.* 2014;22(11):1316-1324.
34. Alexopoulos GS, Sirey JA, Banerjee S, Kiosses DN, Pollari C, Novitch RS, Artis A, Raue P. Two behavioural interventions for patients with major depression and severe COPD. *Am J Geriatr Psychiatry* 2016;24(11):964-974.
35. Becker A, Herzberg D, Marsden N, Thomanek S, Jung H, Leonhardt C. A new computer-based counselling system for the promotion of physical activity in patients with chronic diseases--results from a pilot study. *Patient Educ Couns.* 2011;83(2):195-202.
36. Begrambekova Y, Mareev V, Lomonosov M. Role of depression in effectiveness of disease management programs. In. *European Journal of Heart Failure Abstracts Supplement.* Vol 17 2015.
37. Begrambekova Y, Mareev V, Drobizhev M. Influence of psychoemotional disorders on the effectiveness of education and active outpatient control in heart failure patients. In. *Russian Journal of Cardiology.* Moscow, Russia 2016:48-52.
38. Bernocchi P, Vitacca M, La Rovere MT, Baratti D, Paneroni M, Campolongo G, , 2018, Sposato B, Scalvini S. Home-based telerehabilitation in older patients with chronic obstructive pulmonary disease and heart failure: a randomised controlled trial. *Age and Ageing* 2018;47(1):82-88.
39. Bowles KH, Holland DE, Horowitz DA. A comparison of in-person home care, home care with telephone contact and home care with telemonitoring for disease management. *J Telemed Telecare.* 2009;15(7):344-350.
40. Brodaty H, Draper BM, Millar J, et al. Randomized controlled trial of different models of care for nursing home residents with dementia complicated by depression or psychosis. *J Clin Psychiatry.* 2003;64(1):63-72.
41. Doyle C, Bhar S, Fearn M, Ames D, Osborne D, You E, Gorelik A, Dunt D. The impact of telephone-delivered cognitive behaviour therapy and befriending on mood disorders in people with chronic obstructive pulmonary disease: A randomized controlled trial. *British Journal of Health Psychology* 2017;22:542-556.
42. Katon W, Unützer J, Fan MY, et al. Cost-effectiveness and net benefit of enhanced treatment of depression for older adults with diabetes and depression. *Diabetes Care.* 2006;29(2):265-270. COMPANION
43. Kiosses DN, Rosenberg PB, McGovern A, Fonzetti P, Zaydens H, Alexopoulos GS. Depression and Suicidal Ideation During Two Psychosocial Treatments in Older Adults with Major Depression and Dementia. *J Alzheimers Dis.* 2015;48(2):453-462.
44. Lamers F, Jonkers CC, Bosma H, et al. A minimal psychological intervention in chronically ill elderly patients with depression: a randomized trial. *Psychother Psychosom.* 2010;79(4):217-226.



45. Lin EH, Katon W, Von Korff M, et al. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA*. 2003;290(18):2428-2429.
46. Martín-Lesende I, Orruño E, Bilbao A, et al. Impact of telemonitoring home care patients with heart failure or chronic lung disease from primary care on healthcare resource use (the TELBIL study randomised controlled trial). *BMC Health Serv Res*. 2013;13:118.
47. McSweeney K, Jeffreys A, Griffith J, Plakiotis C, Kharsas R, O'Connor DW. Specialist mental health consultation for depression in Australian aged care residents with dementia: a cluster randomized trial. *Int J Geriatr Psychiatry*. 2012;27(11):1163-1171.
48. Morgan MA, Coates MJ, Dunbar JA, Reddy P, Schlicht K, Fuller J. The TrueBlue model of collaborative care using practice nurses as case managers for depression alongside diabetes or heart disease: a randomised trial. *BMJ Open*. 2013;3(1).
49. Naik AD, White CD, Robertson SM, et al. Behavioral health coaching for rural-living older adults with diabetes and depression: an open pilot of the HOPE Study. *BMC Geriatr*. 2012;12:37.
50. Noel HC, Vogel DC, Erdos JJ, Cornwall D, Levin F. Home telehealth reduces healthcare costs. *Telemed J E Health*. 2004;10(2):170-183.
51. Pols AD, van Dijk SE, Bosmans JE, Hoekstra T, Harm W, van Marwijk J, van Tulder MW, Adriaanse MC. Effectiveness of a stepped-care intervention to prevent major depression in patients with type 2 diabetes mellitus and/or coronary heart disease and subthreshold depression: A pragmatic cluster randomized controlled trial. *PLoS One* 2017;12(8):e0181023.
52. Scalvini S, Bernocchi P, Baratti D, et al. Multidisciplinary telehealth program for patients affected by chronic heart failure and chronic obstructive pulmonary disease. In. *European Journal of Heart Failure Abstracts Supplement*. Vol 18 2016.
53. Schnipper JL, Linder JA, Palchuk MB, et al. Effects of documentation-based decision support on chronic disease management. *Am J Manag Care*. 2010;16(12 Suppl HIT):SP72-81.
54. Sran, M, Mercier J, Wilson P, Lieblisch P, Dumoulin C. Physical therapy for urinary incontinence in postmenopausal women with osteoporosis or low bone density: a randomized controlled trial. *Menopause: The Journal of the North American Menopause Society* 2016;23(3):286-293.
55. Unützer J, Hantke M, Powers D, et al. Care management for depression and osteoarthritis pain in older primary care patients: a pilot study. *Int J Geriatr Psychiatry*. 2008;23(11):1166-1171.
56. White KM, Terry DJ, Troup C, et al. An extended theory of planned behavior intervention for older adults with type 2 diabetes and cardiovascular disease. *J Aging Phys Act*. 2012;20(3):281-299.
57. Whitten P, Mickus M. Home telecare for COPD/CHF patients: outcomes and perceptions. *J Telemed Telecare*. 2007;13(2):69-73.
58. Williams A, Manias E, Walker R, Gorelik A. A multifactorial intervention to improve blood pressure control in co-existing diabetes and kidney disease: a feasibility randomized controlled trial. *J Adv Nurs*. 2012;68(11):2515-2525.

59. Williams A, Manias E, Liew D, Gock H, Gorelik A. Working with CALD groups: testing the feasibility of an intervention to improve medication self management in people with kidney disease, diabetes, and cardiovascular disease. *Renal Society of Australasia Journal*. 2012;8(2):62-69. - COMPANION
60. Williams JW, Katon W, Lin EH, et al. The effectiveness of depression care management on diabetes-related outcomes in older patients. *Ann Intern Med*. 2004;140(12):1015-1024.
61. Wu CJ, Chang AM, Courtney M, Kostner K. Peer supporters for cardiac patients with diabetes: a randomized controlled trial. *Int Nurs Rev*. 2012;59(3):345-352.
62. Cochrane. Taxonomy of outcomes of interest to the Cochrane Consumers & Communication Group. 2012; Available at: <https://cccrgrg.cochrane.org/sites/cccrgrg.cochrane.org/files/public/uploads/Outcomes.pdf> Accessed May 8, 2017.
63. Luijks H, Lucassen P, van Weel C, Loeffen M, Lagro-Janssen A, Schermer T. How GPs value guidelines applied to patients with multimorbidity: a qualitative study. *BMJ Open*. 2015;5(10):e007905.
64. Maly RC, Leake B, Frank JC, DiMatteo MR, Reuben DB. Implementation of consultative geriatric recommendations: the role of patient-primary care physician concordance. *J Am Geriatr Soc*. 2002;50(8):1372-1380.
65. Smith SM, Wallace E, O'Dowd T, Fortin M. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database Syst Rev*. 2016;3:CD006560.
66. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *JCE* 2016;75:40-46.
67. Lin EHB, Katon W, Von Korff M, Rutter C, Simon GE, Oliver M, et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care*. 2004; 27: 2154-2160.
68. Hermanns N, Caputo S, Dzida G, Khunti K, Meneghini LF, Snoek F. Screening, evaluation and management of depression in people with diabetes in primary care. *Primary Care Diabetes* 2013(7):1-10.
69. Firth N, Markham M, Kellett S. The clinical effectiveness of stepped care systems for depression in working age adults: A systematic review. *Journal of Affective Disorders* 2015;170:119-130.
70. Farmer C, Fenu E, O'Flynn N, Guthrie B. Clinical assessment and management of multimorbidity: summary of NICE guidance. *BMJ* 2016;354:i4843.
71. Fortin M, Contant E, Savard C, Hudon C, Poitras ME, Almirall J. Canadian guidelines for clinical practice: an analysis of their quality and relevance to the care of adults with comorbidity. *BMC Fam Prac* 2011;12:74.
72. Sinnige J, Korevaar JC, Westert GP, Spreeuwenberg P, Schellevis FG, Braspenning JC. Multimorbidity patterns in a primary care population aged 55 years and over. *Fam Pract*. 2015;32(5):505-513.
73. Luijks HD, Loeffen MJ, Lagro-Janssen AL, van Weel C, Lucassen PL, Schermer TR. GPs' considerations in multimorbidity management: a qualitative study. *Br J Gen Pract*. 2012;62(600):e503-510.

74. Harris MF, Dennis S, Pillay M. Multimorbidity: negotiating priorities and making progress. *Aust Fam Physician*. 2013;42(12):850-854.
75. Kastner M, Hayden L, Wong G, Lai Y, Makarski J, Treister V, Chan J, Lee J, Ivers NM, Holroyd-Leduc J, Straus SE. Underlying mechanisms of complex interventions addressing the care of older adults with multimorbidity: A realist review. *Age and Ageing* 2018 (in press).
76. Tricco AC, Ashoor HM, Cardoso R, MacDonald H, Cogo E, Kastner M, Perrier L, McKibbin A, Grimshaw JM, Straus SE. Sustainability of knowledge translation interventions in healthcare decision-making: a scoping review. *Implementation Science* 2016;11:55.
77. Moher D, Glasziou P, Chalmers I, Nasser M, Bossuyt PMM, Korevaar DA, Graham ID, Ravaud P, Boutron I. Increasing value and reducing waste in biomedical research: who's listening? *Lancet* 2016;387: 1573-86.